Development of Orally Active Oxytocin Antagonists: Studies on 1-(1-{4-[1-(2-Methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]-2-methoxybenzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (L-372,662) and Related Pyridines

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The previously reported oxytocin antagonist L-371,257 (**2**) has been modified at its acetylpiperidine terminus to incorporate various pyridine *N*-oxide groups. This modification has led to the identification of compounds with improved pharmacokinetics and excellent oral bioavailability. The pyridine *N*-oxide series is exemplified by L-372,662 (**30**), which possessed good potency in vitro (K_i = 4.1 nM, cloned human oxytocin receptor) and in vivo (intravenous AD_{50} = 0.71 mg/kg in the rat), excellent oral bioavailability (90% in the rat, 96% in the dog), good aqueous solubility (>8.5 mg/mL at pH 5.2) which should facilitate formulation for iv administration, and excellent selectivity against the human arginine vasopressin receptors. Incorporation of a 5-fluoro substituent on the central benzoyl ring of this class of oxytocin antagonists enhanced in vitro and in vivo potency but was detrimental to the pharmacokinetic profiles of these compounds. Although lipophilic substitution around the pyridine ring of compound **30** gave higher affinity in vitro, such substituents were a metabolic liability and caused shortfalls in vivo. Two approaches to prevent this metabolism, addition of a cyclic constraint and incorporation of trifluoromethyl groups, were examined. The former approach was ineffective because of metabolic hydroxylation on the constrained ring system, whereas the latter showed improvement in plasma pharmacokinetics in some cases.

Introduction

Preterm labor continues to be a serious problem in industrialized nations. Premature birth can have grave consequences for the newborn, with rates of morbidity and mortality increasing rapidly as gestational age decreases.[1−3] Furthermore, the perinatal care required for preterm babies is extremely expensive, and they often incur additional medical costs resulting from long-term health complications.[2−4] The only approved therapeutic treatment for premature labor in the United States is the β-agonist ritodrine, and it has clear limitations,[5] in terms of both efficacy and maternal safety. Thus, it is of considerable interest to investigate new approaches to tocolytic therapy. One such approach is the development of selective antagonists for the oxytocin receptor, following the observation that the nonapeptide hormone oxytocin (OT; Figure 1) plays a key role in the initiation and maintenance of labor.[6−9] Recently, the utility of such agents has been demonstrated clinically by using intravenously administered atosiban (ORF 22164; Figure 1).[10] This peptidyl antagonist was shown to inhibit uterine contractions in women with threatened and established preterm labor and displayed an improved safety profile compared with ritodrine. We have been interested in developing an OT antagonist which could be administered by either an intravenous (iv) or an oral route. Such a compound

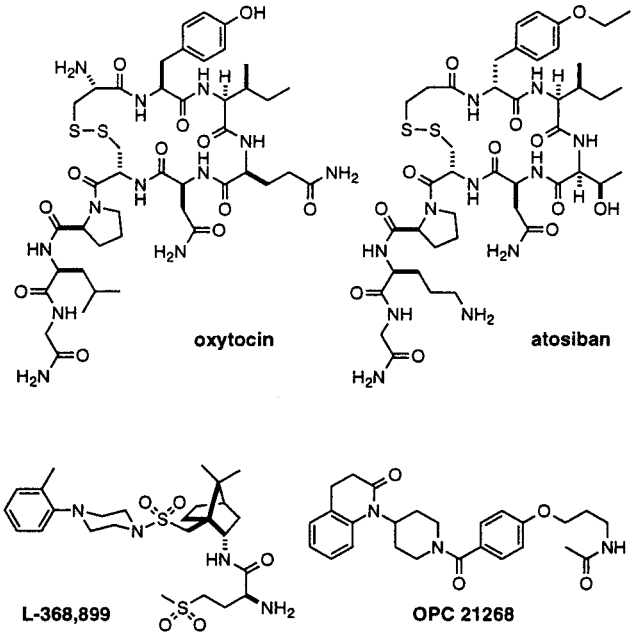

Figure 1. Structures of oxytocin, the oxytocin antagonists atosiban (ORF 22164) and L-368,899, and the arginine V_{1a} vasopressin antagonist OPC 21268.

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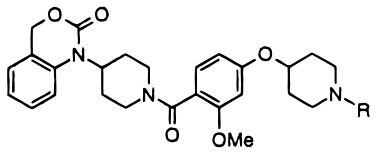


	Compound	R	K_i (nM)
L-371,209	1	H	82
L-371,257	2		4.8
L-371,377	3		10

Figure 2. Structures of the oxytocin antagonists L-371,209, L-371,257, and L-371,377 with K_i values shown for the cloned human oxytocin receptor.

would allow iv use for acute management of uterine contractions in a clinical setting, coupled with the potential for oral dosing on an outpatient basis. A number of structurally distinct classes of peptidyl OT antagonists have been identified,[11] but as a group, they have been hampered by poor oral bioavailability. Our laboratory has therefore focused on the design of non-peptide antagonists of OT.

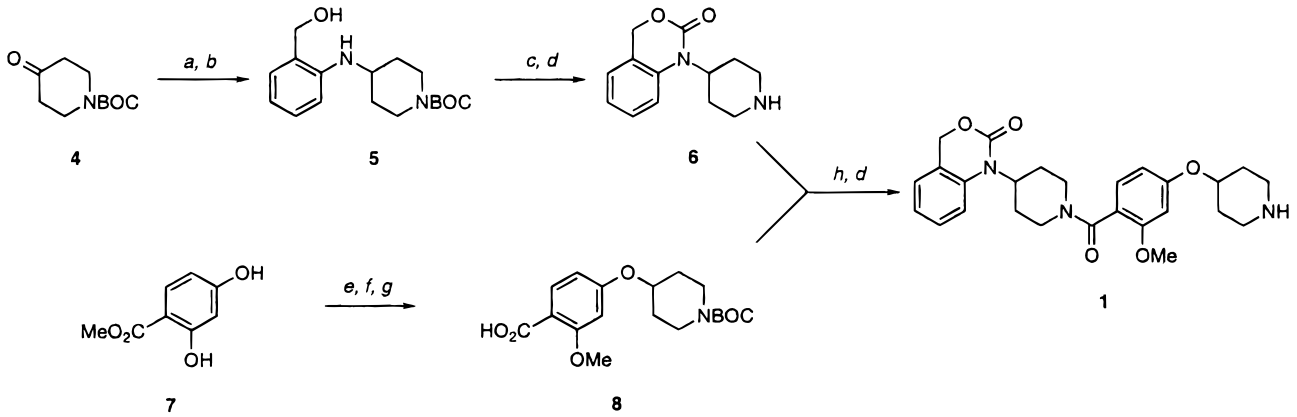
We have previously described the identification of a potent, orally bioavailable non-peptide OT antagonist (L-371,257; Figure 2),[12] which was developed from the Otsuka arginine vasopressin (AVP) antagonist OPC 21268 (Figure 1).[13] While the overall properties of L-371,257 (**2**) were encouraging, modifications that would enhance its pharmacokinetic half-life, bioavailability, potency, and aqueous solubility were sought. Improved solubility was required to allow formulation for intravenous administration. It had been observed in systematic structure−activity studies that alteration of the piperidinylbenzoxazinone or benzoyl moieties usually caused decreases in OT receptor affinity. The piperidinyl ether terminus, on the other hand, was relatively tolerant to change and was therefore chosen as the focus for efforts to introduce solubilizing groups. It was discovered that a variety of acidic or basic groups could be appended to the acetyl group with little effect on OT receptor affinity,[14] suggesting that these groups were protruding from the receptor into solvent. Simple removal of the acetyl group led to L-371,209 (**1**; Figure 2) which possessed improved aqueous solubility but reduced affinity for the OT receptor. Presumably the charged nature of the piperidine nitrogen is not tolerated at this relatively short distance from the benzoyl group. Thus, a pyridylmethyl substituent was employed to simultaneously place a polar heterocycle at a suitable distance from the benzoyl ring and attenuate the pK_a of the terminal piperidine nitrogen. These considerations led to L-371,377 (**3**; Figure 2), which possessed excellent aqueous solubility and even greater oral plasma levels than its progenitor compound, **2**. We now report the further development of such compounds to give highly potent OT antagonists with improved pharmacokinetic properties.

Chemical Methods

The pyridine derivatives described herein were generally synthesized via the piperidinyl ether **1** (Figure 2) or its fluorinated analogue **12** (Scheme 2). Scheme 1 details the synthesis of **1**, starting from commercially available *N*-(*tert*-butyloxycarbonyl)-4-piperidinone (**4**), which was used to reductively alkylate 2-aminobenzyl alcohol. Ring closure with triphosgene gave the benzoxazinone derivative, and deprotection afforded compound **6**. Methyl 2,4-dihydroxybenzoate (**7**) was selectively alkylated at the 4-hydroxy group to give its *N*-(*tert*-butyloxycarbonyl)-4-piperidinyl ether under Mitsunobu conditions.[15] Alkylation of the 2-hydroxyl moiety with iodomethane followed by saponification gave the carboxylic acid **8**, which was coupled with **6** to give, after removal of the Boc group, the desired intermediate.

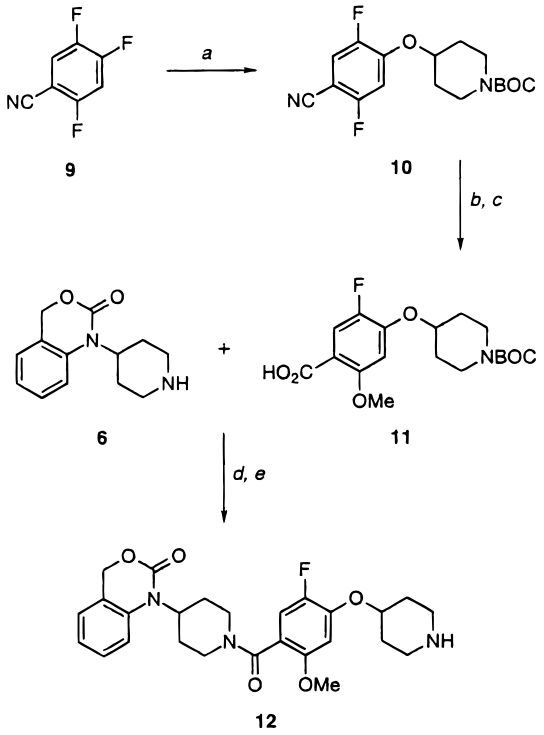
Upon discovery that a 5-fluoro substituent on the benzoyl ring of **1** was desirable for OT receptor affinity, a route to this alternative key intermediate was developed (see Scheme 2). This started from 2,4,5-trifluorobenzonitrile, which was reacted at low temperature with the anion of *N*-(*tert*-butyloxycarbonyl)-4-piperidinol in THF to give **10** using methods described by Wells et al.[16] A similar fluoride displacement at the 2-position of the benzonitrile by potassium methoxide, followed by saponification, gave acid **11**. Activation of **11** with EDC and 1-hydroxybenzotriazole (HOBT) allowed acylation of the piperidinylbenzoxazinone **6**, and deprotection of

Scheme 1[a]



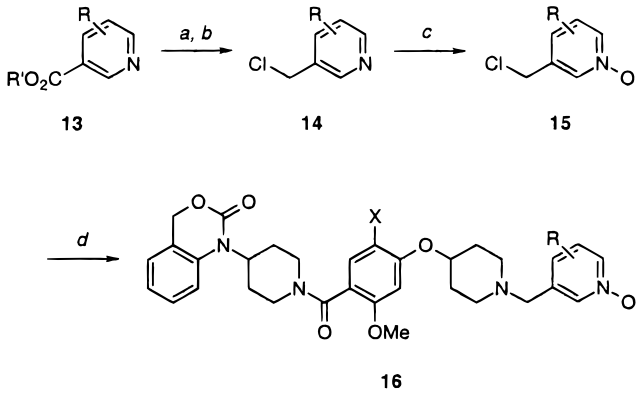
[a] Reagents: (a) 2-aminobenzyl alcohol, AcOH, toluene, reflux; (b) $NaCNBH_3$, AcOH, toluene, THF; (c) triphosgene, DIEA, THF; (d) HCl, EtOAc; (e) *N*-(*tert*-butyloxycarbonyl)piperidin-4-ol, Ph_3P, DEAD, THF; (f) NaH, MeI, DMF; (g) NaOH, MeOH, H_2O; (h) EDC, HOBT, DIEA, DMF.

Scheme 2[a]



[a] Reagents: (a) *N*-(*tert*-butyloxycarbonyl)piperidin-4-ol, *t*-BuOK, THF; (b) MeOH, *t*-BuOK, THF; (c) NaOH, EtOH, H_2O; (d) EDC, HOBT, DIEA, DMF; (e) HCl, EtOAc.

Scheme 3[a]



[a] Reagents: (a) DIBAL, THF; (b) $SOCl_2$, CH_2Cl_2; (c) mCPBA, $CHCl_3$; (d) **1** (X = H) or **12** (X = F), DIEA, DMF.

the resulting amide afforded the desired piperidine intermediate **12**.

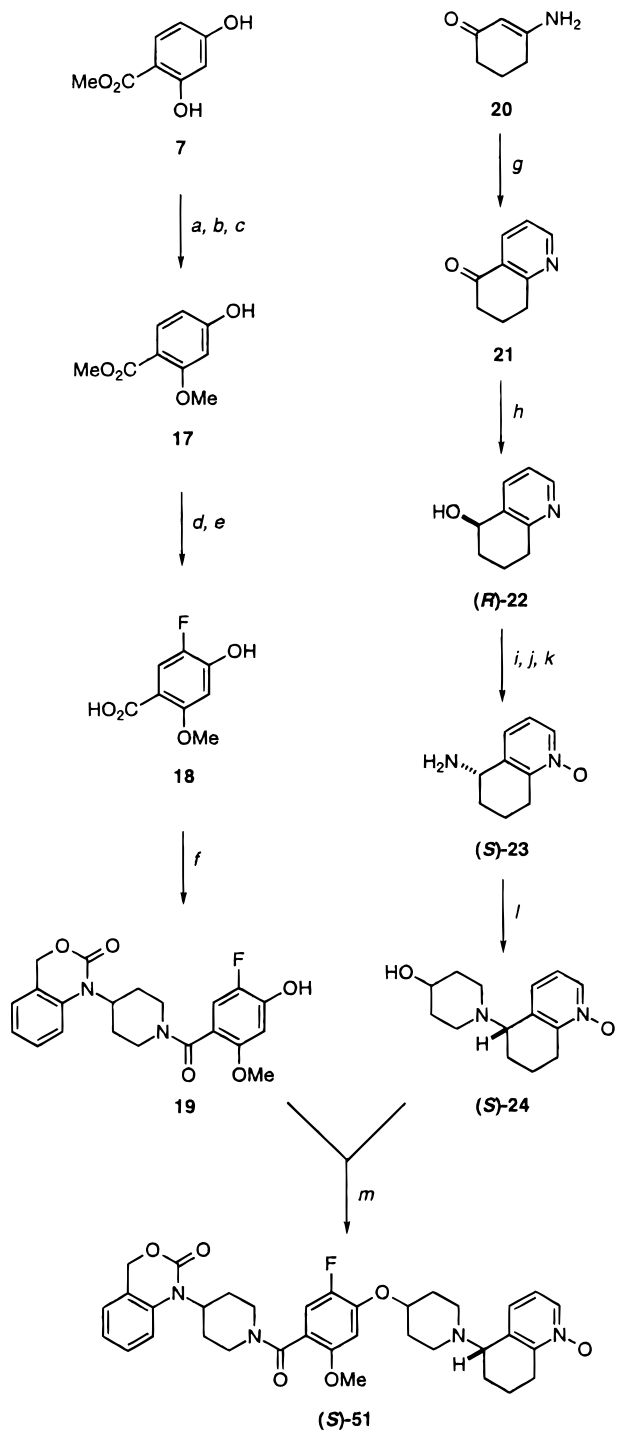
The general route to the pyridine *N*-oxide OT antagonists, utilizing either piperidine **1** or **12**, is shown in Scheme 3. Most of the pyridines were obtained from a nicotinate ester derivative **13** which was either commercially available or described in the literature. The nicotinate was subjected to reduction with diisobutylaluminum hydride (DIBAL) at 0 °C to give the corresponding carbinol, which was chlorinated with thionyl chloride to yield **14** as its hydrochloride salt. These salts were quite stable, but the corresponding free bases were prone to self-alkylation. Those containing multiple alkyl substituents were found to decompose more slowly, presumably due to steric hindrance of the chloride and pyridine functionalities. As a consequence of the instability of their free bases, the pyridine salts were deprotonated immediately before reaction with 3-chloroperoxybenzoic acid (mCPBA), and the resulting *N*-oxides were found to be relatively stable: most could be stored for several months under anhydrous conditions without significant decomposition. The final alkylation step of the piperidine with the chloride **15** in DMF at 50 °C usually proceeded smoothly and in good yield. It was found that degassing of the DMF reduced the incidence of side products and improved yields. For more sterically hindered chlorides, such as those used to provide the trialkylated pyridines in Table 2 and the tetrahydroquinolines in Table 3, addition of sodium iodide to the alkylation mixture improved reaction rates and yields.

Some of the pyridines were obtained directly as the alcohol or chloride intermediate for use in the above route, as described in the Experimental Section. The 2-(trifluoromethyl)pyridine derivatives **44** and **45** (Table 2) were synthesized via 3-(trifluoroacetyl)-2-(trifluoromethyl)pyridine, which has been described by Hojo and co-workers.[17−19] This trifluoromethyl ketone was converted to the corresponding ethyl ester by the method of Delgado and Clardy,[20] and the ester was carried forward in the standard route. The ethylpyridine derivative **48** (Table 3) was provided by reductive alkylation of piperidine **1** with 3-acetylpyridine. Standard EDC-mediated coupling of **1** with 2-methylnicotinic acid followed by oxidation with mCPBA gave the pyridine *N*-oxide **49** (Table 3).

The quinoline compound **55** (Table 3) was derived from alkylation of 5-aminoquinoline with 1,5-dichloropentan-3-ol in analogy with work by Reese and Thompson.[21,22] The resulting 5-(4-hydroxypiperidin-1-yl)-quinoline was coupled to the requisite phenol under Mitsunobu conditions[15] to give the desired product. The other bicyclic systems in Table 3 were realized via condensation of propynal[23] with the appropriate β-amino enone system. For example, 3-amino-2-cyclohexen-1-one (**20**) was reacted with propynal to give 7,8-dihydro-6*H*-quinolin-5-one[24] (**21**) (see Scheme 4). Reduction of this ketone with $NaBH_4$ gave the corresponding racemic alcohol, which was converted to the corresponding chloride and thence to the desired compounds **50** and **51** via the standard route described above. Alkylation of the piperidine **1** with this chloride gave the tetrahydroquinoline **54**. In analogy with the syntheses of these tetrahydroquinolines, condensation of propynal with 3-amino-2-cyclopenten-1-one[25] ultimately afforded the ring-contracted analogues **52** and **53**.

Because of the interesting activities of the racemic tetrahydroquinoline derivative **51**, it was necessary to have an asymmetric synthesis which could provide multigram quantities of its individual enantiomers for future study. The synthetic route is outlined in Scheme 4. Methyl dihydroxybenzoate (**7**) was converted to methyl 4-hydroxy-2-methoxybenzoate (**17**) using a benzyl protecting group for the 4-hydroxy group. Fluorination of phenol **17** with 3,5-dichloro-1-fluoropyridinium triflate[26] followed by saponification gave the carboxylic acid **18**, which was coupled with the piperidinyl benzoxazinone **6** to give the key phenolic intermediate **19**. The other key fragment was synthesized from the same ketone **21** that was used to make the racemic compounds. In this case, however, the oxazaborolidine (OAB) catalyst derived from α,α-diphenyl-2-pyrroli-

Scheme 4[a]



[a] Reagents: (a) $PhCH_2Br$, K_2CO_3, acetone; (b) NaH, MeI, DMF; (c) H_2, Pd−C, MeOH, AcOH; (d) 3,5-dichloro-1-fluoropyridinium triflate, CH_2Cl_2; (e) NaOH, MeOH, H_2O; (f) **6**, EDC, HOBT, DIEA, DMF; (g) propynal, DMF; (h) (*S*)-OAB-BH_3, CH_2Cl_2; (i) DPPA, DBU, toluene, THF; (j) mCPBA, $CHCl_3$; (k) H_2, Pd−C, EtOH; (l) 1,5-dichloropentan-3-ol, K_2CO_3, NaI, 1-BuOH; (m) Ph_3P, DEAD, THF.

dinemethanol was used to effect the asymmetric reduction of the ketone.[27] In Scheme 4, the (*S*)-OAB catalyst was used stoichiometrically to yield the tetrahydroquinolinol **(*R*)-22**. In this procedure, an extra equivalent of borane was used to complex with the pyridine nitrogen, and **(*R*)-22** was obtained in excellent yield and >99% ee. The absolute stereochemistry of this alcohol was predicted based upon chemical precedent and confirmed by comparison of its optical rotation with the reported value of **(*S*)-22**.[28] Treatment of **(*R*)-22** with diphenyl phosphorazidate (DPPA) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in toluene, with THF added to aid solubility, provided the corresponding azide with clean stereochemical inversion, in analogy with work by Thompson et al.[29] The pyridine was converted to its *N*-oxide with mCPBA, and catalytic hydrogenation of the 5-azidotetrahydroquinoline *N*-oxide over Pd−C yielded the desired amine **(*S*)-23** but caused a slight loss in stereochemical integrity, giving **(*S*)-23** in 97% ee. Alkylation of the amine with 1,5-dichloropentan-3-ol[22] in butanol with catalytic NaI provided piperidinol **(*S*)-24** in 41% yield which, while disappointing compared with the near-quantitative yields of the preceding steps, allowed access to the necessary intermediate in one transformation from amine **(*S*)-23**. The final Mitsunobu coupling proceeded smoothly, giving the desired **(*S*)-51** in good overall yield and 97% ee.

Biological Methods

The radioligand binding assays and the in vivo functional assay measuring blockade of OT-induced uterine contractions have been described in detail previously.[30,31]

Radioligand competition experiments with the test compounds of interest were used to determine their receptor affinities. The high-affinity binding of [^{3}H]OT to uterine tissue (OT site) taken from DES-treated rats or pregnant rats (days 22−23 of gestation) and that of [^{3}H]AVP to rat liver (V_{1a} site) and rat kidney medulla (V_2 site) taken from male rats were used to determine affinities for these rat receptors.[30] Similar competition experiments were also performed using uterine, liver, or kidney tissue taken from human surgical or early postmortem donors.[31] The human OT receptor was stably expressed in 293 embryonic kidney cells (293/OTR),[32] and plasma membrane fractions prepared from these cells were used for competition experiments with [^{3}H]OT to determine affinities for the cloned human OT receptor. Results are reported as K_i values for the test compounds to inhibit binding of the radioligand. Most of the K_i values are reported as the mean of several independent experiments with the standard error from the mean (SEM) being reported for at least three determinations; typical variation was less than 50% between experiments.

The in vivo functional assay measured the ability of test compounds to antagonize OT-stimulated contractions of the in situ rat uterus[31] and was performed on anesthetized, DES-pretreated rats prepared for recording of isometric uterine contractions. An approximate ED_{50} dose of OT (1 μg/kg) was administered intravenously at 35-min intervals. The uterine contraction in response to the third injection of OT was set at 100%, and a solution of the test compound (in saline, saline−2% DMSO, or saline−15% DMSO−15% emulphor) was infused intravenously over 10 min or a suspension (in saline−1% methocel) was injected intraduodenally (id). A fourth injection of OT was then administered, and the dose of compound which reduced the contractile response of the uterus to OT by 50%, compared to the vehicle-treated group, was determined to be the AD_{50} value. The reported numbers are the mean values for

4−6 animals per dose group; typical SEM was less than 20% of the mean for individual dose−response data points.

Pharmacokinetic studies in rats and dogs were performed as previously described.[31] Compounds were dosed at 3 mg/kg intravenously and 10 mg/kg per os (po), except as noted. For rats, a solution of the test compound (in saline, saline−2% DMSO, or saline−15% DMSO−15% emulphor) was administered to conscious adult female rats intravenously via the tail vein, or a suspension (in saline−1% methocel) was given orally. Blood samples were collected ($n = 3$ rats/time point) and analyzed by either radioreceptor assay or HPLC with UV or MS detection. For the radioreceptor assay, plasma samples were subjected to methanol extraction and dilution prior to assaying for ability to inhibit [^{3}H]-OT binding to the OT receptor. A standard curve was generated by spiking untreated plasma with known concentrations of the test compound and working these samples up identically to the experimental plasma isolates. HPLC analysis of plasma samples was performed analogously. To correlate bioactivity with parent compound, plasma samples were pooled across the sampling time course, extracted, and subjected to reversed-phase HPLC fractionation. Collected fractions were analyzed by radioreceptor assay for bioactivity, and the bioactivity profile was compared with the HPLC (UV detection) profile. For dog studies, adult female dogs with implanted arterial catheters were administered a solution of the test compound (in saline) intravenously or a suspension of the test compound (in saline−0.5% methocel) orally. Blood samples were collected from the arterial catheter and analyzed as described above. Pharmacokinetic data was analyzed by using the noncompartmental analysis program NCOMP.[33]

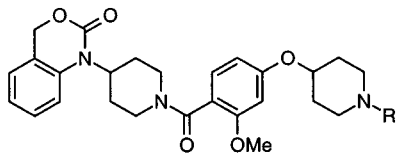
Results and Discussion

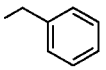
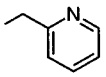
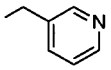
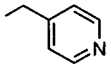
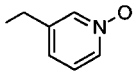
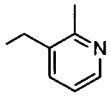
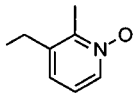
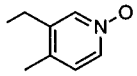
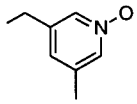
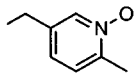
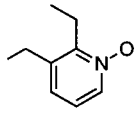
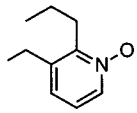
L-371,377 (**3**; see Table 1) was targeted as an attractive structure for further study because of its good aqueous solubility (11.5 mg/mL at pH 5.2) and promising absorption profile. The related pyridyl isomers **26** and **27** were synthesized, in addition to the phenyl analogue **25** (see Table 1). The 3- and 4-pyridyl derivatives (**3** and **27**, respectively) had some advantage in terms of receptor affinity and had similar absorption properties in the rat. A number of analogues of each were investigated, and these preliminary studies indicated that the 3-pyridyl analogues were more promising with respect to OTr affinity.[14] Moreover, following intraduodenal (id) administration in the rat, **3** blocked OT-induced uterine contractions with an $AD_{50} = 13$ mg/kg, compared with an intravenous (iv) $AD_{50} = 5.7$ mg/kg. This id/iv ratio of 2.3 for the AD_{50} values suggested that the compound was well-absorbed from the gut and compared very favorably with previous lead compounds such as the camphorsulfonamide L-368,899 (see Figure 1). This sulfonamide, which had entered phase I clinical studies, had an id/iv ratio of 20.[34] However, compound **3** had two major liabilities: first its receptor affinity was suboptimal ($K_i = 10$ nM at the cloned human OT receptor (chOTr)); second it had a short half-life in rats as judged by the rapid decrease in plasma bioactivity following po administration. Nonetheless, because of the attractive features of L-371,377 (**3**), we decided to focus on such 3-picolyl-containing structures and specifically sought to address the latter two issues.

As part of a structure−activity exploration of compound **3**, the 2-methyl analogue (**29**) was synthesized and plasma bioactivity was examined following oral administration to rats. This indicated a superior plasma half-life for analogue **29**, and it was also found to have improved duration of action and a 2-fold improvement in potency for inhibiting OT-induced uterine contractions in the rat, compared with compound **3**. Interestingly, in vitro binding assays did not reproduce this increased in vivo potency but showed **29** to be essentially equipotent with pyridine **3** (see Table 1). Examination of the pharmacokinetics of compound **29** in rats using HPLC analysis revealed it to have a shorter half-life and lower plasma levels than the bioassay experiments had indicated and thus implied the presence of one or more active metabolites. Pooled rat plasma samples were fractionated by HPLC, and the bioactivity in the fractions was assayed to reveal two major metabolites, the less active piperidine **1** ($K_i = 82$ nM at the chOTr), resulting from loss of the terminal 2-methylpyridin-3-ylmethyl group, and the more active pyridine *N*-oxide of **29**, the metabolite responsible for the pharmacodynamic disparity, L-372,662 (**30**, chOTr $K_i = 4.1$ nM; see Table 1).

The identity of L-372,662 (**30**) was independently verified by resynthesis, and more detailed examination of this *N*-oxide showed it to have an interesting overall profile. Although its affinity for the rat OT receptor ($K_i = 15$ nM) was only twice that of pyridine **3** ($K_i = 28$ nM), it was 8 times more potent at blocking OT-induced uterine contractions in the rat (iv $AD_{50} = 0.71$ mg/kg compared with 5.7 mg/kg for **3**). This disparity between intrinsic receptor affinity and efficacy in the rat for these two compounds may be due to differences in clearance (CL) or volume of distribution (V_d), or perhaps availability of the antagonist at the site of action. A difference in clearance could be explained by differential rates of metabolism for the compounds, and the *N*-oxide **30** did indeed exhibit greater resistance to metabolism than free pyridines such as **29** as judged by in vitro microsome studies. Following a 60-min incubation with rat liver microsomes, only 2% of compound **30** was metabolized compared with 24% of **29**. Both incubations produced piperidine **1** as the major metabolite, but the pyridine **29** also gave a significant amount of *N*-oxide **30**. Moreover, HPLC fractionation of plasma samples after administration of **30** to rats showed that almost all the bioactivity was associated with the parent compound, in contrast to analogue **29** (vide supra). Therefore, the *N*-oxide **30** has increased metabolic stability in rats compared with compound **29**, and based on the close structural similarity between pyridines **29** and **3**, this may partially explain the disparity between the in vitro and in vivo data above. L-372,662 (**30**) had good pharmacokinetic properties in rats ($C_{max} = 8$ μg/mL following a 10 mpk po dose, iv $t_{1/2} = 112$ min, $F = 90\%$) and dogs ($C_{max} = 11$ μg/mL following a 10 mpk po dose, iv $t_{1/2} = 107$ min, $F = 96\%$). The high oral bioavailabilities are notable for OT antagonists: L-368,-899, for example, had oral bioavailabilities of 35% in the rat and 25% in the dog. Compound **30** also

Table 1



Compound	R	K_i (nM)[a] rat OTr chOTr	rat AD_{50} iv (mg/kg) id (mg/kg)	rat PK (bioassay)[b] po C_{max} (μg eq/mL) iv $t_{1/2}$ (min)	rat PK (HPLC)[b] po C_{max} (μg/mL) iv $t_{1/2}$ (min)
25		65 (1) 29 (1)[c]			
26		36 (1) 23 (1)[c]			
3		28 ± 12 10 (1)	5.7 13	C_{max} = 5.5 (14 mpk) $t_{1/2}$ = nd[d]	
27		29 ± 16 7.8 (2)[c]		C_{max} = 7.4 (20 mpk) $t_{1/2}$ = nd	
28		29 (2) 11 (1)			
29		25 ± 7.3 11 ± 2.3	2.4 8.0	C_{max} = 4.3 $t_{1/2}$ = 93	C_{max} = 0.84 $t_{1/2}$ = 40 F = 44%
30		15 ± 3.7 4.1 ± 0.98	0.71 5.2	C_{max} = 4.8 $t_{1/2}$ = 81	C_{max} = 8.0 $t_{1/2}$ = 112 F = 90%
31		12 (2) 3.5 ± 0.76		C_{max} = 1.7 $t_{1/2}$ = 19	
32		nd 13 (1)			
33		nd 14 (1)			
34		11 ± 2.4 2.1 ± 0.67	0.87 4.2	C_{max} = 11.0 $t_{1/2}$ = 66	
35		8.5 (1) 2.5 (1)			

[a] K_i values are reported as mean value ± SEM for three or more determinations. If number of experiments was less than three, it is shown in parentheses. [b] Rat pharmacokinetic parameters as determined by bioassay or HPLC. Unless otherwise stated, dosing was 10 mpk po and 3 mpk iv. [c] Binding data obtained using human uterine tissue. [d] nd = not determined.

maintained a favorable id/iv ratio of 7 for its AD_{50} values in the rat, as may be expected for a highly bioavailable compound, and had good solubility in water at pH 5.2 (>8.5 mg/mL). Selectivity against the related AVP

receptors (V_{1a} and V_2) has often been an issue for OT antagonists, but *N*-oxide **30** represented a significant improvement over L-368,899 in this regard. For compound **30** at the human V_{1a} receptor, $K_i = 2\ 500 \pm 620$ nM (selectivity vs the chOTr = 600-fold), while at the human V_2 receptor, $K_i = 28\ 000 \pm 9\ 100$ nM (selectivity vs the chOTr = 6800-fold). For L-368,899 the corresponding selectivities vs the chOTr were 20-fold (V_{1a} receptor) and 70-fold (V_2 receptor). Moreover, all the compounds in this *N*-oxide class of OT antagonists exhibited excellent (>100-fold) selectivity for the human OT receptor vs the human V_{1a} and V_2 receptors. A more complete description of the pharmacology of L-372,662 (**30**) will be presented in a separate publication.

Overall, compound **30** had an impressive profile, maintaining the attractive features of L-371,377 (**3**) while demonstrating excellent oral bioavailability with significantly improved plasma half-life and having increased potency in vitro and in vivo. It became the focus of continued structure−activity exploration with the aim of further enhancing potency. One of the first areas of study was simple alkyl substitution on the pyridine ring. The various monomethyl isomers were prepared (see Table 1), and examination of the binding data at the chOTr revealed a preference for 2- and 4-substitution (compare compounds **30** and **31** with **32** and **33** in Table 1). Elongation of the 2-methyl group to ethyl (compound **34**; Table 1) or propyl (compound **35**; Table 1) gave little improvement in chOTr affinity. Table 2 details analogues in which the pyridine ring was substituted with two or three alkyl groups. Based on the observations with monomethyl compounds, effort was concentrated on 2- and 4-substitution, and gratifyingly, it was found that the enhancements seen in receptor affinity with these individual modifications were additive. Thus, the 2,4-dimethyl analogue (**37**; Table 2) had a $K_i = 1.0$ nM at the chOTr, an improvement of 4-fold compared with compound **30**. Other dimethylated pyridines offered no advantage over **30** (see analogues **38** and **39**; Table 2), and in general, alkyl substitution at the 6-position of the pyridine ring caused some reduction in affinity for the OT receptor. Concomitant with these studies on alkylated pyridines, a systematic exploration of substitution of the central benzoyl moiety was undertaken. This aromatic ring was found to be quite intolerant of modification in terms of OT receptor affinity, and the only advantageous change discovered was the addition of a 5-fluoro substituent, which usually provided a 3−5-fold improvement in K_i. Substitution at the benzoyl 5-position with other halogens, such as chloro or bromo, caused a marked decrease in affinity for the OT receptor.[14] Tables 2 and 3 detail a number of compounds which illustrate the advantage of this fluorine atom in terms of intrinsic potency.

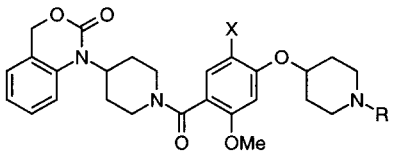
Thus, addition of simple alkyl groups and incorporation of a fluoro substituent on the benzoyl ring demonstrated improvements in intrinsic potency at the OT receptor, and the effects of such modifications on in vivo properties were investigated. The dimethyl analogue **37**, for example, exhibited a 4-fold improvement in K_i at the chOTr compared with *N*-oxide **30** and had a similarly enhanced affinity for the rat OT receptor. However, it showed an improvement of only about 2-fold at the rat uterus in vivo (iv $AD_{50} = 0.31$ mg/kg compared with 0.71 mg/kg for **30**), and this somewhat disappointing performance led to speculation that the additional methyl group may have introduced a metabolic liability.

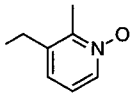
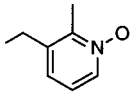
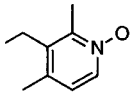
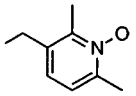
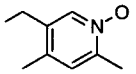
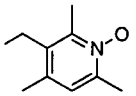
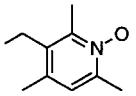
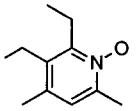
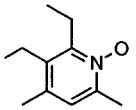
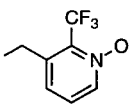
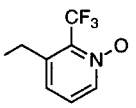
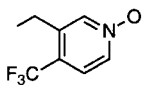
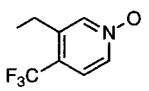
As noted above, alkyl substitution at the 6-position of the pyridine ring led to small losses in intrinsic potency. Such 6-substituted derivatives, however, exhibited an improved duration of action for in vivo blockade of OT-induced contractions in the rat uterus. This could be rationalized in terms of the increased steric hindrance around the pyridine *N*-oxide moiety which may help block metabolic conjugation reactions with this potentially labile group. The 2,4,6-trisubstituted analogues (entries **40**−**43** in Table 2) were made in an effort to combine this enhanced duration with the improved OT receptor affinity of the 2,4-disubstituted pyridines.

An example of such a structure is analogue **43** (Table 2), in which a 2-ethyl substituent on the pyridine ring appears to give some advantage over methyl in terms of receptor affinity (compare with compound **41**; Table 2). Examination of bioactivity in plasma following administration of this compound to rats revealed a good iv half-life (142 min) and reasonable plasma levels (C_{max} = 2.6 μg equiv/mL following a 10 mpk dose po). However, the in vivo AD_{50} values were again disappointing: while compound **43** was more than 4 times as potent as L-372,662 (**30**) at the rat OT receptor in vitro, the iv AD_{50} in the rat only improved fractionally, from 0.71 to 0.50 mg/kg. It seemed possible that either high plasma protein binding or more rapid clearance of these trisubstituted pyridine compounds might account for their relatively poor performance in vivo. To address the latter possibility, **43** was administered to rats, and HPLC-fractionated plasma samples were examined for binding to the OT receptor. The bioactivity was clearly distributed through several fractions which did not correspond to the parent antagonist, demonstrating the formation of active metabolites. Indeed, examination of the rat plasma pharmacokinetics by HPLC revealed that *N*-oxide **43** had only a 43-min iv half-life (see Table 2), and therefore the 142-min half-life seen by radioreceptor assay reflects the presence of such active metabolites. This difference between compound **43** and its monosubstituted analogue **36** (Table 2) is illustrated in Figure 3 which compares their plasma profiles in terms of bioactivity and actual concentration of the parent compound. It was concluded, therefore, that although additional alkyl groups on the pyridine moiety had effected an improvement in intrinsic receptor affinity with respect to compound **30**, they had introduced a serious metabolic liability, presumably involving oxidative metabolism of the substituted pyridine ring.

This realization led to a reexamination of a more simple alkylpyridine, the 4-methyl derivative **31** (Table 1). While this compound had similar in vitro binding affinities to its regioisomer **30**, it had a much poorer in vivo profile. The two analogues differed only in the position of a methyl group on the terminal pyridine ring and had similar physical properties: their log *P* coefficients, for example, were 1.95 (**30**) and 1.85 (**31**). Despite being so closely related, they exhibited very different pharmacokinetic profiles in the rat (see Table 1) with analogue **31** having less than a 20-min plasma

Table 2



Compound	X	R	K_i (nM)[a] rat OTr chOTr	rat AD_{50} iv (mg/kg) id (mg/kg)	rat PK (bioassay)[b] po C_{max} (μg eq/mL) iv $t_{1/2}$ (min)	rat PK (HPLC)[b] po C_{max} (μg/mL) iv $t_{1/2}$ (min)
30	H		15 ± 3.7 4.1 ± 0.98	0.71 5.2	C_{max} = 4.8 $t_{1/2}$ = 81	C_{max} = 8.0 $t_{1/2}$ = 112 F = 90%
36	F		5.1 (1) 1.1 ± 0.23	0.32 2.6	C_{max} = 4.2 $t_{1/2}$ = 66	C_{max} = 3.7 $t_{1/2}$ = 71 F = 84%
37	H		4.3 ± 1.6 1.0 ± 0.20	0.31 3.7	C_{max} = 4.1 $t_{1/2}$ = 85	
38	H		27 (2) 5.3 ± 1.1		C_{max} = 8.8 $t_{1/2}$ = 68	
39	H		30 (1) 5.1 (1)			
40	H		12 (2) 4.2 (2)	0.83 5.0	C_{max} = 8.3 $t_{1/2}$ = 79	
41	F		4.1 (2) 1.0 (2)	0.60 4.5		
42	H		8.0 (2) 1.5 ± 0.24	1.2 3.3	C_{max} = 6.9 $t_{1/2}$ = 65	
43	F		3.4 (2) 0.81 ± 0.38	0.50 2.2	C_{max} = 2.6 $t_{1/2}$ = 142	C_{max} = 1.2 $t_{1/2}$ = 43 F = 52%
44	H		nd[c] 1.4 (2)			C_{max} = 2.6 (3 mpk) $t_{1/2}$ = 86 (1 mpk) F = 82%
45	F		3.2 (1) 0.82 (2)	0.34 2.7	C_{max} = 6.2 $t_{1/2}$ = 80	C_{max} = 3.3 $t_{1/2}$ = 66 F = 66%
46	H		16 (1) 6.7 ± 2.4	2.4 nd	C_{max} = 9.6 $t_{1/2}$ = 113	
47	F		13 (1) 1.2 (2)	0.92 5.1		C_{max} = 2.3 $t_{1/2}$ = 62 F = 70%

[a] K_i values are reported as mean value ± SEM for three or more determinations. If number of experiments was less than three, it is shown in parentheses. [b] Rat pharmacokinetic parameters as determined by bioassay or HPLC. Unless otherwise stated, dosing was 10 mpk po and 3 mpk iv. [c] nd = not determined.

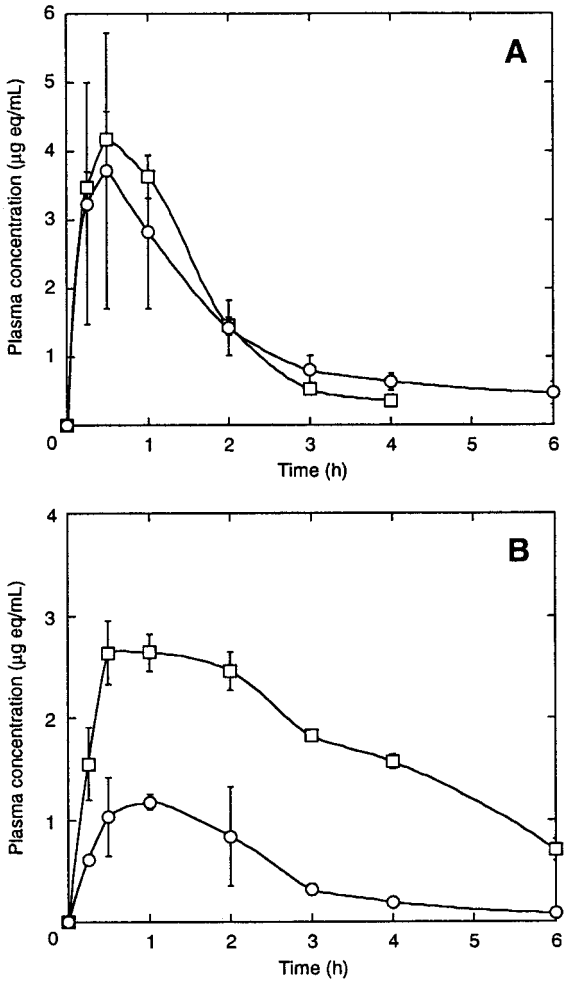


Figure 3. Comparison of plasma levels of (A) **36** and (B) **43** following po administration (10 mpk) in rats, as determined by bioassay (□) and HPLC (○).

half-life by bioassay. Since $t_{1/2} = (0.693V_d)/CL$ and it is improbable that there is a significant difference in V_d between the two compounds, this observation seemed most likely due to a high rate of clearance for compound **31**, and a metabolic explanation for this was sought. Two possibilities in which the position of the methyl group may play a role are either a conjugation reaction involving the *N*-oxide or direct oxidation of the methyl substituent. In the former example, it is conceivable that a 2-methyl substituent affords the *N*-oxide better protection than a 4-methyl group and hence shields compound **30** from such metabolism. In the latter case, it is possible that a methyl group at the 4-position of such a pyridine ring is a preferential site for oxidative attack by cytochrome P-450 enzymes and that a methyl substituent at the 2-position is relatively inert to such a process. To examine these possibilities, trifluoromethyl-containing analogues of **30** and **31** were synthesized (see Table 2, structures **44** and **46**). Presumably, such compounds would be protected from P-450-mediated hydroxylation of the alkyl substituents on the pyridine ring and would therefore allow the importance of such processes for these analogues to be examined.

The trifluoromethyl-containing analogues detailed in Table 2 (entries **44**−**47**) exhibit in vitro binding affinities that are broadly similar to their methyl-containing counterparts. The more important issue was an examination of their pharmacokinetic properties in rats. Gratifyingly, the first analogue tested, **46**, exhibited a much improved profile over its nonfluorinated counterpart, **31**, as analyzed by bioassay. The plasma levels following oral dosing of these two compounds in rats are shown in Figure 4 (C and F) which clearly illustrates a significantly higher C_{max} (9.6 μg equiv/mL) and longer half-life (113 min) for analogue **46**. These data suggest that oxidative metabolism of the 4-methyl group on the terminal pyridine ring of compound **31** is responsible for its poor pharmacokinetic profile and that perfluorination of this methyl group alleviates this problem. It is not possible to be certain, however, since the conversion of methyl to trifluoromethyl alters the electronic properties of the pyridine ring. It is possible that this would perturb metabolic conjugation reactions involving the pyridine *N*-oxide and hence offer protection from such metabolism. The electronic change in the pyridine ring also causes the fluoroalkyl compounds to become more lipophilic than their alkyl analogues: compare, for example, compound **44** (log $P = 2.75$) with compound **30** (log $P = 1.95$). Such a change in physical properties could account for changes in clearance or absorption of the compounds which might affect their pharmacokinetic properties.

An argument against a role for physical properties, or a change in pyridine electronics reducing metabolism of the *N*-oxide, is that the trifluoromethyl analogues **44** and **45** exhibit similar pharmacokinetic profiles to their methylated counterparts **30** and **36**, respectively (compare A with D and B with E in Figure 4). If protection of the *N*-oxide or increased lipophilicity were responsible for the enhanced profile of compound **46**, it would be expected that these 2-(trifluoromethyl)pyridyl analogues would have a similar advantage over the 2-methylpyridyl compounds, since they would presumably also benefit from such an effect. In conclusion, then, it appears that the 2-methyl group is not a primary site for oxidative metabolism in such molecules and hence that perfluorination of this substituent has little effect on the plasma profiles of such compounds. A 4-methyl substituent, on the other hand, seems to be a serious liability, and conversion of such a group to trifluoromethyl apparently offers substantial protection from such metabolism.

Addition of a fluorine atom to the central benzoyl ring of such trifluoromethylated antagonists affords some improvement in affinity for the OT receptor, as seen in the change from analogue **46** (chOTr $K_i = 6.6$ nM) to **47** (chOTr $K_i = 1.1$ nM). Unfortunately, this improvement in intrinsic potency seems to be accompanied by some losses in the pharmacokinetic profiles of these structures. The 5-fluorobenzoyl compound **45**, for instance, appears to have an inferior profile (iv $t_{1/2} = 66$ min, $F = 66\%$) when compared to the corresponding analogue **44** (iv $t_{1/2} = 86$ min, $F = 82\%$), and this is illustrated in Figure 4 (D and E). A similar trend is seen in the comparison of compounds **30** and **36** (see Table 2 and Figure 4A,B), and this, to some extent, undermines the advantages of the substituent in terms of affinity. It is possible that the 5-fluoro substituent leads to more rapid elimination of the molecules, either due to slightly increasing their overall lipophilicity and hence propensity to be good substrates for metabolizing enzymes (for reference, log P (**30**) = 1.95, log P (**36**) =

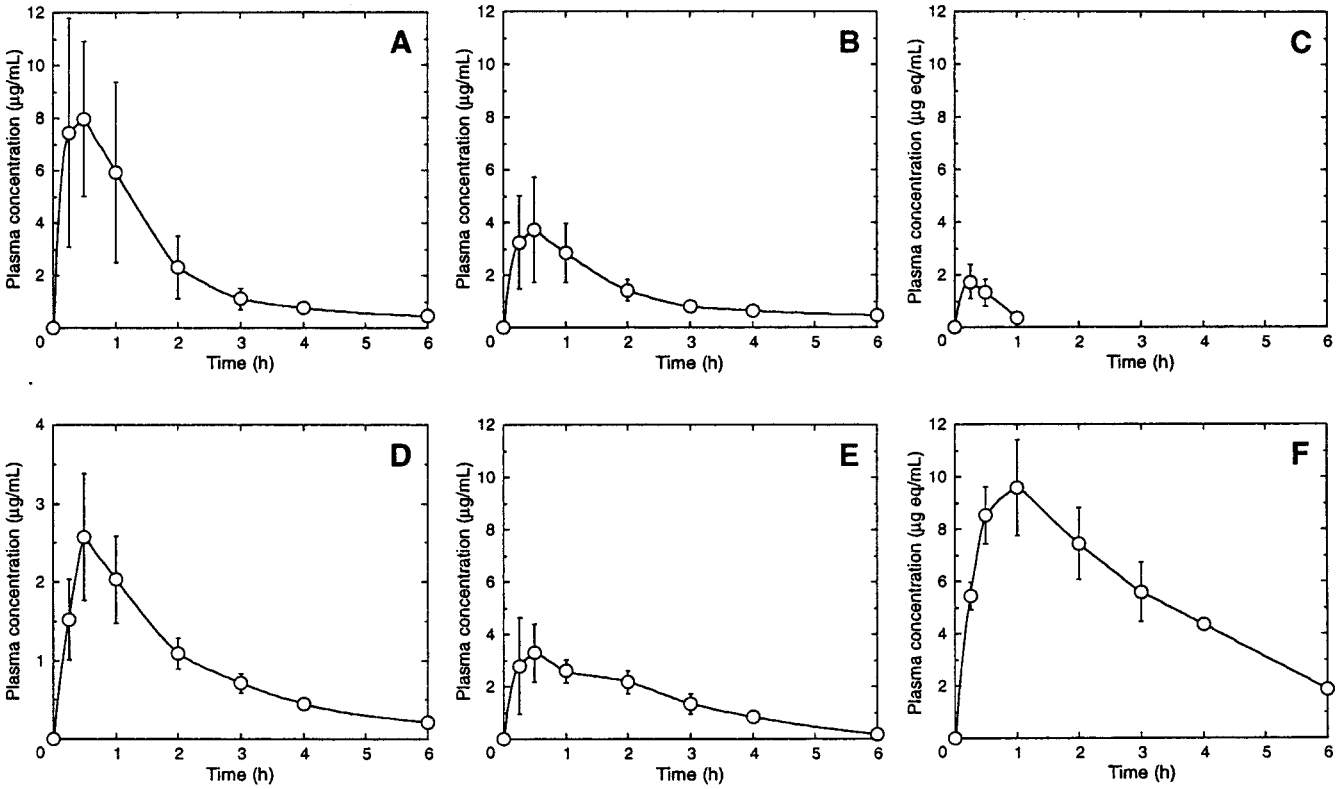


Figure 4. Plasma profiles following po dosing in rats, as analyzed by HPLC or radioreceptor assay for (A) **30** (10 mpk, HPLC), (B) **36** (10 mpk, HPLC), (C) **31** (10 mpk, bioassay), (D) **44** (3 mpk, HPLC), (E) **45** (10 mpk, HPLC), (F) **46** (10 mpk, bioassay). Plasma concentration axis for **44** is normalized to compensate for lower dose (3 mpk vs 10 mpk).

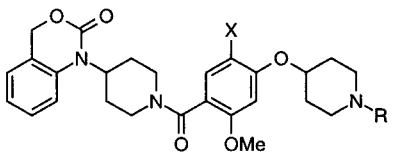
2.16) or by specifically enhancing some metabolic process such as demethylation of the aryl methyl ether.

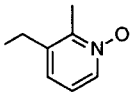
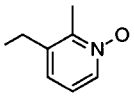
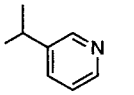
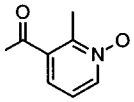
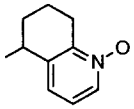
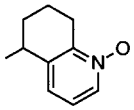
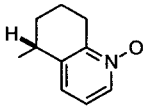
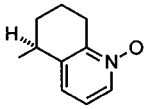
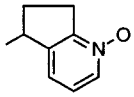
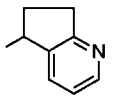
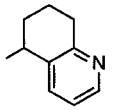
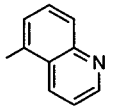
As described above, it was discovered that addition of a pyridine *N*-oxide end group to the piperidinylbenzoxazinone class of oxytocin antagonists led to potent, orally bioavailable compounds. The OT receptor affinity could be modulated by substitution around the pyridine ring, although some of the structures with the highest in vitro affinity did not manifest this in vivo due to metabolic liabilities. In the case of analogue **31**, replacement of the pyridine methyl substituent with a trifluoromethyl group offered a solution to its apparent metabolic problems. In addition to oxidation of alkyl substituents on the pyridine ring, a major metabolic pathway for this class of OT antagonists was N-dealkylation at the (pyridylmethyl)piperidine, as observed in the in vitro metabolism studies on compounds **29** and **30** (vide supra). To address this mode of metabolism, modification of the linker between the piperidinyl ether and the terminal pyridine moiety and incorporation of cyclic constraints into this region of the molecule were explored.

The first linker modification investigated was simple conversion of the pyridylmethyl group to a nicotinamide, to give structure **49** (Table 3). While receptor binding affinity is almost unaffected by this substitution, the duration of action in rats following iv administration of a 3 mpk dose was much shorter (falling to 50% of the initial response after 0.5 h) than that observed with compound **30** (50% at 2 h), suggesting that the amide linker gave rise to higher rates of clearance in vivo. This observation was not surprising since a number of similar amides, such as L-371,257 (**1**; Figure 2), had been investigated previously and found to have short duration in the rat. Therefore, the effects of blocking the pseudobenzylic position with a methyl group were investigated with compound **48** (Table 3), the methylated analogue of pyridine **3**. The modification caused a modest loss of receptor binding affinity and offered no advantage in terms of plasma half-life. Nonetheless, this result demonstrated that branching at this linker carbon was not very deleterious for potency at the OT receptor, and it encouraged the study of molecules in which the 2-methyl substituent on the pyridine ring of L-372,662 (**30**) was attached to this linker via a 1- or 2-atom tether.

The racemic tetrahydroquinolines **50** and **51** (see Table 3) were initially investigated, to determine whether such a cyclic constraint might imbue these molecules with a pharmacokinetic advantage by hindering metabolism at the pseudobenzylic position. The addition of the ethylene linker to compound **36** (Table 3) to give **51** caused a slight reduction in receptor affinity (from $K_i = 1.1$ nM to $K_i = 2.0$ nM at the chOTr) and also a reduction in potency in the rat (from iv $AD_{50} = 0.32$ mg/kg to iv $AD_{50} = 0.91$ mg/kg). A similar trend can be seen in the comparison of analogues **30** and **50**. Examination of the metabolic stability of such compounds in vitro by incubation of compound **30** or **51** with rat liver microsomes revealed essentially no metabolism (<5%) after 60 min in both cases. The initial pharmacokinetic results on **51** were also encouraging, revealing a po $C_{max} = 8.1$ μg equiv/mL (10 mpk) and iv $t_{1/2} = 158$ min, as analyzed by plasma bioactivity in rats (for comparison, the analogous data for compound **36** are po $C_{max} = 4.2$ μg equiv/mL and iv $t_{1/2} = 66$ min), and it was decided to investigate the individual enantiomers in more detail.

Table 3



Compound	X	R	K_i (nM)[a] rat OTr chOTr	rat AD_{50} iv (mg/kg) id (mg/kg)	rat PK (bioassay)[b] po C_{max} (μg eq/mL) iv $t_{1/2}$ (min)	rat PK (HPLC)[b] po C_{max} (μg/mL) iv $t_{1/2}$ (min)
30	H		15 ± 3.7 4.1 ± 0.98	0.71 5.2	C_{max} = 4.8 $t_{1/2}$ = 81	C_{max} = 8.0 $t_{1/2}$ = 112 F = 90%
36	F		5.1 (1) 1.1 ± 0.23	0.32 2.6	C_{max} = 4.2 $t_{1/2}$ = 66	C_{max} = 3.7 $t_{1/2}$ = 71 F = 84%
48	H		53 (1) 16 (2)			
49	H		14 (2) 5.6 (1)	1.1 nd[c]		
50	H		20 ± 0.23 7.0 (2)	2.6 10		
51	F		7.7 ± 1.1 2.0 ± 0.97	0.91 3.6	C_{max} = 8.1 $t_{1/2}$ = 158	
(*R*)-51	F		16 (1) 2.3 ± 0.48	1.1 4.0	C_{max} = 6.6 $t_{1/2}$ = 103	
(*S*)-51	F		8.5 ± 5.8 1.7 ± 0.86	0.41 3.1	C_{max} = 8.3 $t_{1/2}$ = 114	C_{max} = 6.9 $t_{1/2}$ = 57 F = 65%
52	F		nd 3.3 (2)			
53	F		nd 4.8 (2)			
54	F		nd 2.5 (1)			
55	F		nd 2.3 (1)			

[a] K_i values are reported as mean value ± SEM for three or more determinations. If number of experiments was less than three, it is shown in parentheses. [b] Rat pharmacokinetic parameters as determined by bioassay or HPLC. Unless otherwise stated, dosing was 10 mpk po and 3 mpk iv. [c] nd = not determined.

The enantiomers, **(*R*)-51** and **(*S*)-51** (Table 3), were found to be quite similar in terms of intrinsic potency: at the chOTr, for example, K_i = 2.3 and 1.7 nM, respectively. Other related analogues were also very similar in affinity at the cloned human receptor (see Table 3). Reduction of the *N*-oxide in analogue **51** gave

the racemic tetrahydroquinoline **54**, $K_i = 2.5$ nM, while aromatization of this ring system provided the quinoline **55**, $K_i = 2.3$ nM. Contraction of the cyclohexenyl ring in compound **51** to give analogue **52**, $K_i = 3.3$ nM, caused less than a 2-fold drop in receptor affinity. The lack of variation in intrinsic potency for the enantiomers of **51** as well as for these other analogues was in agreement with the hypothesis that this pyridine ring system is close to the mouth of the receptor in the bound state, rather than being buried deep in the binding site where such changes would be expected to have a more pronounced effect on affinity.

Examination of **(*R*)-51** and **(*S*)-51** in the rat revealed the latter compound was slightly more potent (iv $AD_{50} = 1.1$ and 0.41 mg/kg, respectively), and monitoring of plasma bioactivity following administration of the isomers to rats suggested that **(*S*)-51** had a small advantage in terms of half-life (iv $t_{1/2} = 114$ min vs 103 min for **(*R*)-51**) and plasma levels (po $C_{max} = 8.3$ μg equiv/mL vs 6.6 μg equiv/mL for **(*R*)-51**). Further studies on **(*S*)-51** examined its pharmacokinetic profile in rats (see Table 3) and dogs (iv $t_{1/2} = 246$ min, po $C_{max} = 2.2$ μg/mL) by HPLC. Unfortunately, although previous in vitro metabolism studies on compound **51** had indicated no significant metabolism by rat or dog liver microsomes, comparison of the HPLC plasma profiles with those obtained by bioassay indicated the presence of significant amounts of at least one active metabolite in both rats and dogs. The major metabolite identified was shown to be hydroxylated on the tetrahydroquinoline ring by LCMS studies, and since its UV absorption spectrum was very similar to that of **51**, the hydroxyl group was inferred to be on the alkyl portion of this heterocycle. This was apparently responsible for the promising appearance of the bioassay plasma profiles, and it was concluded that the concentrations of parent compound in rat plasma following po administration of either analogue **36** or the tetrahydroquinoline **(*S*)-51** were similar (see Table 3) and, as such, the cyclic constraint had not offered a significant advantage from a metabolic standpoint. It seems that the methyl group on the pyridyl ring of compound **30** is protected from metabolism, perhaps by the neighboring *N*-oxide moiety, but elongation of this alkyl group adds sites for metabolism even if the side chain is constrained in the form of a ring. Equally, addition of alkyl groups at other positions on the pyridine ring apparently provides metabolizing enzymes with prime sites for oxidation to give both active and inactive metabolites. Therefore, from a pharmacokinetic viewpoint, L-372,662 (**30**) and the trifluoromethyl-substituted pyridine *N*-oxides represent the optimal compounds discovered in this class of OT antagonists, and they exhibit the best plasma half-lives.

Conclusion

The introduction of a pyridine *N*-oxide group to the benzoxazinone class of oxytocin antagonists developed from L-371,257 (**2**) has provided potent compounds with an excellent overall profile, as exemplified by L-372,662 (**30**). As a class, these pyridine *N*-oxides exhibit a number of advantages over camphorsulfonamide compounds such as L-368,899, including improved affinity for the human oxytocin receptor, higher oral bioavailability, superior aqueous solubility, and very high selectivity for the human OT receptor vs human AVP receptors. Incorporation of a 5-fluoro substituent on the central benzoyl ring routinely offered an enhancement in terms of in vitro and in vivo potency, but it appeared to be somewhat detrimental to the pharmacokinetic profiles of these compounds. While increased lipophilic substitution around the pyridine ring gave higher affinity compounds in vitro, such substituents were a metabolic liability and caused shortfalls in vivo. Two approaches to prevent this metabolism, addition of a cyclic constraint and incorporation of trifluoromethyl groups, were examined. The former approach was ineffective due to metabolic hydroxylation on the constrained ring system, in a manner similar to that observed with other substituted pyridines. The latter showed improvement in plasma pharmacokinetics for a 4-substituted pyridyl group, apparently by blocking oxidative metabolism.

Experimental Section

General Methods. Proton NMR spectra were run at 300 MHz on a Varian VXR-300 or at 400 MHz on a Varian Unity 400 or VXR-400 spectrometer, and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. Fast atom bombardment mass spectra were recorded on a VG-ZAB-HF spectrometer using glycerol as matrix. Elemental analyses were performed using a Perkin-Elmer 2400 model II elemental analyzer. Silica gel 60 (230−400 mesh) from EM Science was used for column chromatography, and analytical or preparative thin-layer chromatography was conducted using EM Science Kieselgel 60 F_{254} plates. Thermoseparations HPLC equipment with a Vydac C18 reversed-phase column was used for analytical or preparative HPLC. The elution used either a gradient of 95/5 to 0/100 A/B, A = H_2O−0.1% TFA, B = CH_3CN−0.1% TFA (method A), or a gradient of 95/5 to 5/95 A/B, A = H_2O−0.1% H_3PO_4, B = CH_3CN (method B). Enantiomeric purity was established by HPLC on a Chiralpak AD column. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Melting points are uncorrected. For reactions performed under anhydrous conditions, glassware was either oven- or flame-dried and the reaction was run under a positive pressure of argon. Tetrahydrofuran was freshly distilled from sodium/benzophenone; all other anhydrous solvents were used as purchased from Aldrich. Except where noted, reagents were purchased from Aldrich and used without further purification. The reported yields are the actual isolated yields of purified material and are not optimized.

1-{1-[2-Methoxy-4-(piperidin-4-yloxy)benzoyl]piperidin-4-yl}-1,4-dihydrobenz[*d*][1,3]oxazin-2-one Hydrochloride (1). 1-(*tert*-Butyloxycarbonyl)-4-((2-hydroxymethyl)phenylamino)piperidine (5). 1-(*tert*-Butyloxycarbonyl)-4-piperidinone (**4**) (20 g, 0.10 mol), 2-aminobenzyl alcohol (13 g, 0.11 mol), and acetic acid (14 mL, 0.22 mol) were dissolved in dry toluene (500 mL). The solution was refluxed with azeotropic removal of water for 6 h, then cooled to ambient temperature, and concentrated under reduced pressure to about one-half of the original volume. To the solution were added $NaBH_3CN$ (20 g, 0.32 mol) and dry THF (300 mL). Acetic acid (10 mL, 0.17 mol) was added dropwise over a period of about 1 h. The reaction was stirred at ambient temperature for 24 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc (750 mL). The EtOAc layer was washed with saturated aqueous $NaHCO_3$ (4 × 250 mL) and brine (250 mL). The EtOAc layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using a gradient elution of 15−30% EtOAc in hexanes. The title compound was obtained as a gum (24 g, 78%): ^{1}H NMR ($CDCl_3$) δ 7.22 (1H, t, $J = 7$ Hz), 7.09 (1H, d, $J = 7$ Hz), 6.80−

6.60 (2H, m), 4.68 (2H, s), 4.00 (2H, m), 3.50 (1H, m), 3.00 (2H, m), 2.05 (2H, m), 1.47 (9H, s).

1-(4-Piperidinyl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one Hydrochloride (6). Aniline **5** (24 g, 78 mmol) was dissolved in dry THF (250 mL) and cooled to 0 °C. To the solution were added *N*,*N*-diisopropylethylamine (DIEA) (41 mL, 0.24 mol) and triphosgene (8.54 g, 28.8 mmol). The reaction was stirred at 0 °C for 1 h and then at ambient temperature for 72 h. Ether (250 mL) was added, the mixture was cooled to 0 °C for 3 h, and the hydrochloride salt of DIEA was removed by filtration. The filtrate solvents were removed under reduced pressure, and the residue was dissolved in EtOAc (750 mL). The EtOAc solution was washed with 5% aqueous citric acid (2 × 500 mL), water (250 mL), and saturated aqueous $NaHCO_3$ (2 × 500 mL). The EtOAc layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was boiled in ether (ca. 200 mL) until the solid had dissolved. Cooling overnight gave 1-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyl)-1,4-dihydrobenz[*d*]-[1,3]oxazin-2-one as off-white crystals (mp 143−145 °C; 19 g, 75%): ^{1}H NMR ($CDCl_3$) δ 7.34 (1H, t, J = 7 Hz), 7.16 (1H, d, J = 7 Hz), 7.10−7.00 (2H, m), 5.09 (2H, s), 4.30 (2H, br s), 4.02 (1H, tt, J = 12, 3 Hz), 2.80 (2H, m), 2.61 (2H, qd, J = 12, 4 Hz), 1.83 (2H, m), 1.48 (9H, s).

A stirred solution of 1-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (19 g, 57 mmol) in EtOAc (500 mL) was cooled to 0 °C. HCl gas was bubbled through the solution for 30 min. Stirring was continued at 0 °C for 1 h, during which time a precipitate had formed, and the reaction was warmed to ambient temperature for 1 h. The stirred suspension was cooled to 0 °C, and cold ether (250 mL) was added. After 1 h at 0 °C, the solid was collected by filtration and washed with ether. The solid was dried in vacuo for 18 h, giving the title compound as a white amorphous solid (14.5 g, 95%): ^{1}H NMR (CD_3OD) δ 7.42 (1H, t, J = 7 Hz), 7.51 (1H, d, J = 7 Hz), 7.47 (1H, d, J = 7 Hz), 7.18 (1H, t, J = 7 Hz), 5.19 (2H, s), 4.30 (1H, m), 3.60 (2H, m), 3.45 (2H, m, J = 12 Hz), 2.90 (2H, qd, J = 12, 4 Hz), 2.25 (2H, m).

4-(*N*-(*tert*-Butyloxycarbonyl)-4-piperidinyloxy)-2-methoxybenzoic Acid (8). Methyl 2,4-dihydroxybenzoate (**7**) (41.6 g, 248 mmol) and triphenylphosphine (84.4 g, 322 mmol) were dissolved in 800 mL of dry THF at 0 °C. To the stirred mixture was added dropwise, over a period of 2 h, a solution of *N*-(*tert*-butyloxycarbonyl)piperidin-4-ol (64.8 g, 322 mmol) and diethyl azodicarboxylate (56 g, 322 mmol) in THF (600 mL). The reaction mixture was stirred for 6 h at 0 °C and then warmed to ambient temperature for 18 h. The reaction mixture was diluted with 1 L of EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 200 mL), dried (Na_2SO_4), and concentrated to give 300 g of a semisolid. This material was suspended in 1 L of hexanes−EtOAc (9:1 v/v), stirred, and filtered to remove triphenylphosphine oxide. Evaporation of the filtrate solvents under reduced pressure yielded 125 g of a yellow oil which was purified by flash chromatography using 10% EtOAc in hexanes as eluant. The product-containing fractions were concentrated under reduced pressure to give methyl 4-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyloxy)-2-hydroxybenzoate as an oil which solidified on standing (68.6 g, 79%): ^{1}H NMR ($CDCl_3$) δ 10.96 (1H, s), 7.75 (1H, d, J = 7 Hz), 6.42 (2H, m), 4.50 (1H, m), 3.90 (3H, s), 3.70 (2H, m), 3.35 (2H, m), 1.95 (2H, m), 1.75 (2H, m), 1.45 (9H, s).

To a solution of methyl 4-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyloxy)-2-hydroxybenzoate (50 g, 0.14 mol) and iodomethane (17.4 mL, 0.28 mol) in DMF (400 mL) at 0 °C was added NaH (6.55 g of a 60% suspension in mineral oil, 0.164 mol) in several portions over a period of 2 h. The resulting suspension was warmed to ambient temperature and stirred for 18 h. The reaction was quenched with MeOH (5 mL), and the mixture was concentrated under reduced pressure. The residue was suspended in EtOAc (500 mL) and washed with water (2 × 250 mL) and brine (250 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a gradient elution of 20−40% EtOAc in hexanes. Methyl 4-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyloxy)-2-methoxybenzoate was obtained as a gum that solidified on standing (43 g, 89%): ^{1}H NMR ($CDCl_3$) δ 7.83 (1H, d, J = 7 Hz), 6.50 (2H, m), 4.56 (1H, m), 3.90 (3H, s), 3.87 (3H, s), 3.70 (2H, m), 3.35 (2H, m), 1.95 (2H, m), 1.78 (2H, m), 1.45 (9H, s).

Methyl 4-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyloxy)-2-methoxybenzoate (35 g, 96 mmol) was dissolved in MeOH (250 mL), and to the solution was added 2 N NaOH (100 mL, 0.20 mol). The mixture was warmed to 70 °C for 3 h. The solution was cooled to ambient temperature, concentrated under reduced pressure, and cooled to 0 °C, and 0.5 M aqueous citric acid solution (300 mL) was added. To the suspension were added EtOAc (500 mL) and water (300 mL). The EtOAc layer was separated, and the aqueous phase was washed with EtOAc (200 mL). The combined EtOAc layers were washed with brine (250 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure to give the title compound as a gum that solidified on standing (30.7 g, 95%): ^{1}H NMR ($CDCl_3$) δ 8.12 (1H, d, J = 7 Hz), 6.65 (1H, dd, J = 7, 2 Hz), 6.55 (1H, d, J = 2 Hz), 4.60 (1H, m), 4.05 (3H, s), 3.70 (2H, m), 3.35 (2H, m), 1.95 (2H, m), 1.78 (2H, m), 1.48 (9H, s).

1-{1-[2-Methoxy-4-(piperidin-4-yloxy)benzoyl]piperidin-4-yl}-1,4-dihydrobenz[*d*][1,3]oxazin-2-one Hydrochloride (1). The acid **8** (5.00 g, 14.2 mmol), piperidine **6** (4.02 g, 15.0 mmol), HOBT (2.52 g, 16.5 mmol), and EDC (3.27 g, 17.0 mmol) were combined in DMF (75 mL). DIEA (2.87 mL, 16.5 mmol) was added dropwise to the stirred solution. After 1 h, more DIEA (approximately 1 mL) was added to bring the mixture to pH 6−7 (wetted E. Merck pH 0−14 "colorpHast" indicator strips). The reaction was stirred at ambient temperature for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (150 mL) and washed with 5% aqueous citric acid solution (2 × 100 mL), water (100 mL), and saturated aqueous $NaHCO_3$ solution (2 × 100 mL). The EtOAc layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a gradient elution of 1−3% MeOH in CH_2Cl_2. 1-(1-(4-(*N*-(*tert*-Butyloxycarbonyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one was obtained as a white foam by evaporation of a CH_2Cl_2 solution under reduced pressure (7.22 g, 90%): ^{1}H NMR ($CDCl_3$) δ 7.35 (1H, t, J = 7 Hz), 7.20−7.05 (4H, m), 6.50 (2H, m), 5.10 (2H, s), 4.97 (1H, br d), 4.50 (1H, m), 4.20−4.10 (1H, m), 3.88−3.81 (3H, m), 3.70 (4H, m), 3.35 (3H, m), 3.20−3.00 (2H, m), 2.80−2.50 (2H, m), 1.95 (2H, m), 1.75 (2H, m), 1.48 (9H, s).

1-(1-(4-(*N*-(*tert*-Butyloxycarbonyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (5.0 g, 8.8 mmol) was dissolved in EtOAc (125 mL) and cooled to 0 °C. HCl gas was bubbled through the stirred solution for 20 min. A gummy precipitate formed. Excess HCl was purged by bubbling nitrogen through the solution, and the reaction was warmed to ambient temperature with stirring for 1 h. The solvent was removed under reduced pressure, and the residue was dried in vacuo for 24 h at 50 °C to give the title compound as an amorphous solid (4.37 g, 99%): ^{1}H NMR ($CDCl_3$) δ 7.37 (1H, t, J = 7 Hz), 7.20−7.05 (4H, m), 6.53 (1H, br s), 6.48 (1H, s), 5.10 (2H, s), 4.98 (1H, br d), 4.42 (1H, m), 4.20−4.10 (1H, m), 3.88−3.81 (3H, m), 3.70 (1H, br d), 3.20 (3H, m), 3.20−3.00 (3H, m), 2.80−2.50 (5H, m), 1.95 (3H, m), 1.75 (3H, m); MS (FAB) m/z = 466 (M^+ + H); HPLC purity = 99.0% (method A; 215 nm). Anal. ($C_{26}H_{31}N_3O_5$·HCl·0.6H_2O) C, H, N.

1-{1-[5-Fluoro-2-methoxy-4-(piperidin-4-yloxy)benzoyl]-piperidin-4-yl}-1,4-dihydrobenz[*d*][1,3]oxazin-2-one Hydrochloride (12). 4-(*N*-(*tert*-Butyloxycarbonyl)-4-piperidinyloxy)-2,5-difluorobenzonitrile (10). A solution of *t*-BuOK in THF (1.0 M, 25 mL, 25 mmol) was slowly added to a solution of *N*-(*tert*-butyloxycarbonyl)-4-piperidinol (5.0 g, 24.9 mmol) in THF (40 mL) at 0 °C. The resulting mixture was stirred for 0.5 h, then cannulated into a cold solution of 2,4,5-trifluorobenzonitrile (**9**) (4.7 g, 30 mmol) in THF (40 mL) at −65 °C. The reaction mixture was stirred at −65 °C for 3 h,

then warmed to ambient temperature over 2 h, and stirred for 18 h. Water (200 mL) and EtOAc (200 mL) were added. The organic layer was separated, washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography using 20% EtOAc in hexanes as eluant to give the title compound as a white solid (mp 120−121 °C; 7.1 g, 84%): ^{1}H NMR ($CDCl_3$) δ 7.31 (1H, dd, J = 9.1, 6.0 Hz), 6.80 (1H, dd, J = 10.1, 7.6 Hz), 4.56 (1H, m), 3.70 (2H, m), 3.40 (2H, m), 1.95 (2H, m), 1.80 (2H, m), 1.47 (9H, s).

4-(*N*-(*tert*-Butyloxycarbonyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoic Acid, Sodium Salt (11). MeOH (1.21 mL, 30 mmol) was added to a solution of *t*-BuOK in THF (1.0 M, 30 mL, 30 mmol) at 0 °C under an inert atmosphere to give a suspension. The suspension was stirred for 0.5 h and then cannulated into a cold solution of nitrile **10** (7.1 g, 21 mmol) in THF (100 mL) at −50 °C. The reaction mixture was stirred at −50 °C for 1 h, warmed to 0 °C over 0.5 h, and stirred at 0 °C for 6 h. Water (250 mL) and EtOAc (200 mL) were added, and the organic layer was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography using 50% EtOAc in hexanes as eluant to provide 4-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzonitrile as a white solid (mp 112−113 °C; 7.0 g, 92%): ^{1}H NMR ($CDCl_3$) δ 7.25 (1H, d, J = 10.4 Hz), 6.53 (1H, d, J = 6.6 Hz), 4.60 (1H, m), 3.90 (3H, s), 3.70 (2H, m), 3.40 (2H, m), 1.95 (2H, m), 1.80 (2H, m), 1.47 (9H, s).

To a solution of 4-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzonitrile (7.0 g, 20 mmol) in EtOH (50 mL) was added a solution of NaOH (3.2 g, 80 mmol, in 25 mL of water). The resulting slurry was heated to reflux for 18 h and then cooled to 0 °C. The precipitate was collected by filtration, washed with 5:1 EtOH−H_2O, and dried in vacuo to give the title compound as a flaky white solid (6.8 g, 87%): ^{1}H NMR (DMSO-d_6) δ 7.07 (1H, d, J = 11.7 Hz), 6.68 (1H, d, J = 7.0 Hz), 4.50 (1H, m), 3.70 (3H, s), 3.60 (3H, s), 3.20 (2H, m), 1.90 (2H, m), 1.55 (2H, m), 1.41 (9H, s).

1-{1-[5-Fluoro-2-methoxy-4-(piperidin-4-yloxy)benzoyl]-piperidin-4-yl}-1,4-dihydrobenz[*d*][1,3]oxazin-2-one Hydrochloride (12). To a solution of piperidine **6** (2.7 g, 10 mmol) in DMF (25 mL) were added acid **11** (3.9 g, 10 mmol), HOBT (1.5 g, 10 mmol), and EDC (3.8 g, 13 mmol). To the stirred solution was added DIEA (approximately 1.3 mL) until the reaction mixture was pH 7 (wetted E. Merck "colorpHast" pH 1−14 indicator strips). The reaction was stirred at ambient temperature for 18 h, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with 5% aqueous citric acid (75 mL), water (50 mL), and saturated aqueous $NaHCO_3$ (50 mL). The EtOAc layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using EtOAc as eluant to give 1-(1-(4-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one as an amorphous solid (5.4 g, 93%): ^{1}H NMR ($CDCl_3$) δ 7.37 (1H, t, J = 6 Hz), 7.20−7.00 (4H, m), 6.57 (1H, d, J = 6 Hz), 5.10 (2H, s), 4.96 (1H, d, J = 7 Hz), 4.48 (1H, m), 4.15 (1H, m), 3.86−3.79 (3H, m), 3.70 (4H, m), 3.35 (2H, m), 3.20−3.00 (1H, m), 3.80 (4H, m), 1.95 (2H, m), 1.80 (2H, m), 1.47 (9H, s).

Into a solution of 1-(1-(4-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (5.4 g, 9.3 mmol) in EtOAc (100 mL) was bubbled HCl gas for 20 min. The mixture was stirred at 0 °C for 1 h and then at ambient temperature for 1 h. The precipitate was collected by filtration, washed with EtOAc, and dried in vacuo to give the title compound as an amorphous solid (4.7 g, 97%): ^{1}H NMR (CD_3OD) δ 7.40 (1H, t, J = 7.0 Hz), 7.28 (1H, d, J = 8.2 Hz), 7.20−7.00 (3H, m), 6.91 (1H, d, J = 6.8 Hz), 5.14 (2H, s), 4.80 (1H, m), 4.22 (1H, m), 3.90−3.85 (3H, m), 3.62 (1H, m), 3.50−3.20 (6H, m), 3.00−2.50 (4H, m), 2.20−2.00 (4H, m), 2.00 (1H, m), 1.83 (1H, m); MS (FAB) m/z = 484 (M^+ + H); HPLC purity = 98.6% (method A; 215 nm). Anal. ($C_{26}H_{30}FN_3O_5 \cdot HCl \cdot 1.95H_2O$) C, H, N.

General Procedure for the Synthesis of Pyridine *N*-Oxide Derivatives: 1-(1-{2-Methoxy-4-[1-(2-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (30). To a stirred solution of ethyl 2-methylnicotinate (10.0 g, 60 mmol) in dry THF (180 mL) at 0 °C was added DIBAL (120 mL of a 1.0 M solution in THF, 120 mmol). The mixture was allowed to slowly warm to ambient temperature and stirred for 18 h. Saturated $NaHCO_3$ was added, the precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was partitioned between saturated $NaHCO_3$ (100 mL) and $CHCl_3$ (200 mL). The organic layer was removed and the aqueous layer extracted further with $CHCl_3$ (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 3-(hydroxymethyl)-2-methylpyridine (7.6 g, 100%): ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, d, J = 5 Hz), 7.70 (1H, d, J = 8 Hz), 7.15 (1H, dd, J = 8, 5 Hz), 4.73 (2H, s), 2.54 (3H, s).

To a stirred solution of 3-(hydroxymethyl)-2-methylpyridine (5.8 g, 47 mmol) in CH_2Cl_2 (250 mL) was added thionyl chloride (97.9 g, 0.823 mol), and the resulting mixture was stirred for 4 h at ambient temperature and then concentrated in vacuo. The residue was partitioned between saturated $NaHCO_3$ (150 mL) and CH_2Cl_2 (150 mL). The organic layer was removed and the aqueous layer extracted further with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 3-(chloromethyl)-2-methylpyridine (4.9 g, 74%). This compound could be stored as the hydrochloride salt: ^{1}H NMR (CD_3OD) δ 8.70 (1H, dd, J = 6, 2 Hz), 8.65 (1H, dd, J = 8, 2 Hz), 7.95 (1H, dd, J = 8, 6 Hz), 4.94 (2H, s), 2.88 (3H, s).

To a stirred solution of 3-(chloromethyl)-2-methylpyridine (500 mg, 3.53 mmol) in $CHCl_3$ (40 mL) was added mCPBA (1.11 g, 55 wt %, 3.53 mmol), and the resulting mixture was stirred for 2 h at ambient temperature. The reaction was quenched with saturated $NaHCO_3$ (25 mL), and the organic layer was washed with water (25 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with 3% MeOH in CH_2Cl_2 to give 3-(chloromethyl)-2-methylpyridine *N*-oxide (495 mg, 89%): ^{1}H NMR ($CDCl_3$) δ 8.27 (1H, d, J = 6.3 Hz), 7.26 (1H, d, J = 7.8 Hz), 7.15 (1H, t, J = 7.2 Hz), 4.59 (2H, s), 2.61 (3H, s).

To a solution of piperidine **1** (1.00 g, 2.15 mmol) and 3-(chloromethyl)-2-methylpyridine *N*-oxide (407 mg, 2.58 mmol) in dry, degassed DMF (25 mL) was added DIEA until the mixture was pH 7.5, as measured by moistened indicator paper. The reaction mixture was heated to 50 °C for 48 h; then the solvent was removed under reduced pressure. The residue was partitioned between saturated $NaHCO_3$ (100 mL) and $CHCl_3$ (100 mL). The organic layer was removed and the aqueous layer extracted further with $CHCl_3$ (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with 3% MeOH−0.3% NH_4OH in CH_2Cl_2 to give the title compound which was converted to the corresponding hydrochloride salt (880 mg, 59%): ^{1}H NMR (CD_3OD) δ 8.59 (1H, br s), 8.02 (1H, br s), 7.63 (1H, br s), 7.40 (1H, t, J = 7.8 Hz), 7.29−7.11 (4H, m), 6.80−6.64 (2H, m), 5.14 (2H, s), 4.80 (2H, m), 4.63 (2H, s), 4.23 (1H, m), 3.92−3.84 (3H, m), 3.75−3.16 (7H, m), 3.01−2.56 (5H, m), 2.53−2.20 (4H, m), 2.05−1.75 (2H, m); MS (FAB) m/z = 587 (M^+ + H); HPLC purity = 99.7% (method A; 215 nm). Anal. ($C_{33}H_{38}N_4O_6 \cdot HCl \cdot H_2O$) C, H, N.

The following compounds were made in analogy with pyridine *N*-oxide **30**, utilizing the appropriate ester,[35−38,40] alcohol,[39] or halide: **3**, **25**−**29**, **31**, **33**−**41**, **46**, and **47**. The following compounds were made by a similar method, with the exceptions as shown and yields quoted for the final step.

1-(1-{2-Methoxy-4-[1-(5-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (32). A mixture of 3,5-

lutidine (10.0 g, 93.3 mmol), *N*-chlorosuccinimide (15.0 g, 112 mmol), and 2,2′-azobis(isobutyronitrile) (AIBN) (187 mg, 1.1 mmol) was heated to reflux in CCl_4 (120 mL) for 18 h. The reaction mixture was poured into saturated $NaHCO_3$ (200 mL) and CH_2Cl_2 (500 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude sample of 3-(chloromethyl)-5-methylpyridine (2.5 g, 19%): ^{1}H NMR ($CDCl_3$) δ 8.43 (1H, s), 8.40 (1H, s), 7.56 (1H, s), 4.56 (2H, s), 2.37 (3H, s).

Using 3-(chloromethyl)-5-methylpyridine for the oxidation step gave the title compound (125 mg, 43%). For the hydrochloride salt: ^{1}H NMR (CD_3OD) δ 8.62 (1H, s), 8.53 (1H, s), 7.93 (1H, br s), 7.40 (1H, t, J = 7.9 Hz), 7.31−7.13 (4H, m), 6.79−6.64 (2H, m), 5.14 (2H, s), 4.81 (2H, m), 4.49 (2H, s), 4.22 (1H, m), 3.94−3.83 (3H, m), 3.68−3.14 (6H, m), 3.01−2.13 (7H, m), 2.48 (3H, s), 2.03−1.75 (2H, m); MS (FAB) m/z = 587 (M^+ + H); HPLC purity = 98.0% (method A; 215 nm). Anal. ($C_{33}H_{38}N_4O_6$·HCl·1.65H_2O·0.25CH_2Cl_2) C, H, N.

1-(1-{4-[1-(2-Ethyl-4,6-dimethyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]-2-methoxybenzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (42). A mixture of 2,4-pentanedione (15 g, 0.150 mol), ethyl 3-oxovalerate (25 g, 0.173 mol), and ammonium acetate (51 g, 0.662 mol) was heated at 110 °C for 96 h and then allowed to cool to ambient temperature. The crude product was purified by flash column chromatography, eluting with 5% EtOAc in hexane to give ethyl 2-ethyl-4,6-dimethylnicotinate as a yellow oil (6.5 g, 21%): ^{1}H NMR ($CDCl_3$) δ 6.86 (1H, s), 4.40 (2H, q, J = 7 Hz), 2.77 (2H, q, J = 7 Hz), 2.50 (3H, s), 2.28 (3H, s), 1.40 (3H, t, J = 7 Hz), 1.26 (3H, t, J = 7 Hz).

Using ethyl 2-ethyl-4,6-dimethylnicotinate for the reduction step gave the title compound (131 mg, 41%). For the hydrochloride salt: ^{1}H NMR (CD_3OD) δ 7.57 (1H, s), 7.40 (1H, t, J = 7.4 Hz), 7.31−7.11 (4H, m), 6.82−6.67 (2H, m), 5.14 (2H, s), 4.82 (2H, m), 4.61 (2H, br s), 4.22 (1H, tt, J = 11.8, 3.9 Hz), 3.94−3.83 (3H, m), 3.73−3.14 (8H, m), 3.00−2.20 (7H, m), 2.61 (3H, s), 2.61 (3H, s), 2.03−1.76 (2H, m), 1.28 (3H, t, J = 7.3 Hz); MS (FAB) m/z = 629 (M^+ + H); HPLC purity = 99.0% (method A; 215 nm). Anal. ($C_{36}H_{44}N_4O_6$·HCl·1.75H_2O·0.65CH_2Cl_2) C, H, N.

1-(1-{4-[1-(2-Ethyl-4,6-dimethyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]-5-fluoro-2-methoxybenzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (43). Using ethyl 2-ethyl-4,6-dimethylnicotinate for the reduction step and piperidine **12** in the alkylation reaction gave the title compound (108 mg, 34%). For the hydrochloride salt: ^{1}H NMR (CD_3OD) δ 7.61 (1H, s), 7.40 (1H, t, J = 7.2 Hz), 7.30−7.05 (4H, m), 6.95 (1H, m), 5.14 (2H, s), 4.80 (2H, m), 4.63 (2H, br s), 4.23 (1H, m), 3.94−3.84 (3H, m), 3.75−3.16 (8H, m), 3.01−2.23 (7H, m), 2.63 (3H, s), 2.62 (3H, s), 2.03−1.78 (2H, m), 1.29 (3H, t, J = 7.4 Hz); MS (FAB) m/z = 647 (M^+ + H); HPLC purity = 99.5% (method A; 215 nm). Anal. ($C_{36}H_{43}FN_4O_6$·HCl·1.4H_2O·0.85CH_2Cl_2) C, H, N.

1-(1-{2-Methoxy-4-[1-(1-oxido-2-(trifluoromethyl)pyridin-3-ylmethyl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (44). To a stirred suspension of NaH (1.97 g of a 60% dispersion in mineral oil, 49.4 mmol) in DMF (30 mL) was added 3-(trifluoroacetyl)-2-(trifluoromethyl)pyridine[19] (3.00 g, 12.3 mmol) in wet DMF (75 mL + 75 μL of H_2O), dropwise. The mixture was stirred at 60 °C for 45 min; then iodoethane (7.70 g, 49.4 mmol) was added. Stirring was continued at 60 °C for 1 h; then the mixture was cooled to ambient temperature, quenched with saturated $NaHCO_3$ (300 mL), and extracted with EtOAc (2 × 500 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with 20% EtOAc in hexane, to give ethyl 2-(trifluoromethyl)nicotinate (1.74 g, 65%): ^{1}H NMR ($CDCl_3$) δ 8.81 (1H, dd, J = 4.6, 1.2 Hz), 8.12 (1H, dd, J = 7.8, 1.2 Hz), 7.58 (1H, dd, J = 7.8, 4.6 Hz), 4.43 (2H, q, J = 7.2 Hz), 1.41 (3H, t, J = 7.2 Hz).

Using ethyl 2-(trifluoromethyl)nicotinate for the reduction step gave the title compound (124 mg, 57%). For the hydrochloride salt: ^{1}H NMR (CD_3OD) δ 8.55 (1H, dd, J = 5.0, 2.4 Hz), 7.83−7.76 (2H, m), 7.40 (1H, t, J = 7.3 Hz), 7.32−7.11 (4H, m), 6.81−6.65 (2H, m), 5.14 (2H, s), 4.82 (2H, m), 4.67 (2H, s), 4.22 (1H, tt, J = 11.9, 3.9 Hz), 3.95−3.83 (3H, m), 3.75−3.13 (6H, m), 3.01−2.14 (7H, m), 2.04−1.76 (2H, m); MS (FAB) m/z = 641 (M^+ + H); HPLC purity = 99.0% (method A; 215 nm). Anal. ($C_{33}H_{35}F_3N_4O_6$·0.9HCl·2.45H_2O) C, H, N.

1-(1-{5-Fluoro-2-methoxy-4-[1-(1-oxido-2-(trifluoromethyl)pyridin-3-ylmethyl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (45). Using ethyl 2-(trifluoromethyl)nicotinate for the reduction step and piperidine **12** in the alkylation reaction gave the title compound (227 mg, 79%). For the hydrochloride salt: ^{1}H NMR (CD_3OD) δ 8.55 (1H, dd, J = 5.1, 2.2 Hz), 7.83−7.76 (2H, m), 7.40 (1H, t, J = 7.2 Hz), 7.31−7.04 (4H, m), 6.95 (1H, d, J = 6.1 Hz), 5.14 (2H, s), 4.80 (2H, m), 4.66 (2H, s), 4.22 (1H, m), 3.94−3.83 (3H, m), 3.70−3.16 (6H, m), 3.01−2.15 (7H, m), 2.03−1.78 (2H, m); MS (FAB) m/z = 659 (M^+ + H); HPLC purity = 99.7% (method A; 215 nm). Anal. ($C_{33}H_{34}F_4N_4O_6$·HCl·2.25H_2O) C, H, N.

1-(1-{2-Methoxy-4-[1-(1-pyridin-3-ylethyl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]-oxazin-2-one (48). To a stirred solution of piperidine **1** (0.20 g, 0.43 mmol) in dichloroethane (2.2 mL) were added 3-acetylpyridine (94.5 mL, 0.86 mmol) and sodium triacetoxyborohydride (182 mg, 0.86 mmol). The solution was stirred at ambient temperature for 5 days. Everyday an additional 2 equiv each of the 3-acetylpyridine and sodium triacetoxyborohydride were added to the reaction mixture. The reaction solvent was removed under reduced pressure to afford a crude oil. The residue was purified by flash column chromatography using 5% MeOH−0.5% NH_4OH in CH_2Cl_2 and then further purified on a semipreparative HPLC column (method A). Removal of solvent gave the title compound as an amorphous powder. The sample was taken up in CH_3CN with 5 equiv of aqueous HCl and lyophilized to afford the hydrochloride salt of the title compound (240 mg, 82% yield): ^{1}H NMR ($CDCl_3$) δ 8.54 (1H, d, J = 1.7 Hz), 8.48 (1H, dd, J = 6.3, 1.6 Hz), 7.66 (1H, dt, J = 7.7, 1.9 Hz), 7.32 (1H, t, J = 7.4 Hz), 7.27−7.22 (2H, m), 7.14 (1H, t, J = 7.1 Hz), 7.10−7.03 (2H, m), 6.46−6.42 (1H, m), 6.42 (1H, s), 5.06 (2H, s), 4.95 (1H, d, J = 11.1 Hz), 4.29−4.25 (1H, m), 4.17−4.06 (1H, m), 3.85−3.76 (3H, m), 3.67 (1H, d, J = 12.8 Hz), 3.52 (1H, q, J = 7.0 Hz), 3.15−2.99 (1H, m), 2.83−2.67 (4H, m), 2.55−2.50 (1H, m), 2.34−2.22 (2H, m), 2.10−1.80 (4H, m), 1.80−1.74 (4H, m), 1.38 (3H, d, J = 7.0 Hz); MS (FAB) m/z = 571 (M^+ + H); HPLC purity = 98.8% (method A; 215 nm). Anal. ($C_{33}H_{38}F_4N_4O_5$·2HCl·1.95H_2O) C, H, N.

1-(1-{2-Methoxy-4-[1-(2-methyl-1-oxidopyridin-3-ylcarbonyl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (49). A solution of 2-methylnicotinic acid (118 mg, 0.86 mmol), piperidine **1** (431 mg, 0.86 mmol), HOBT (116 mg, 0.86 mmol), EDC (198 mg, 1.03 mmol), and DIEA (245 mg, 1.89 mmol) in dry, degassed DMF was stirred for 18 h at ambient temperature. The solvent was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (20 mL). The aqueous phase was extracted further with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 2% MeOH in CH_2Cl_2, to give 1-(1-{2-methoxy-4-[1-(2-methylpyridin-3-ylcarbonyl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (450 mg, 89%): ^{1}H NMR (CD_3OD) δ 8.68 (1H, dd, J = 5.5, 1.4 Hz), 8.24 (1H, d, J = 7.4 Hz), 7.76 (1H, dd, J = 7.4, 5.9 Hz), 7.40 (1H, t, J = 7.4 Hz), 7.30−7.11 (4H, m), 6.71−6.63 (2H, m), 5.14 (2H, s), 4.78 (2H, m), 4.22 (1H, m), 3.99 (1H, br s), 3.92−3.80 (3H, m), 3.67−3.52 (2H, m), 3.35−3.12 (2H, m), 3.00−2.42 (4H, m), 2.67 (3H, s), 2.17−1.74 (6H, m).

To a stirred solution of 1-(1-{2-methoxy-4-[1-(2-methylpyridin-3-ylcarbonyl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (225 mg, 0.385 mmol) in $CHCl_3$ (5 mL) was added mCPBA (275 mg, 55 wt %, 0.87 mmol), and the resulting mixture was stirred for 18 h at

ambient temperature. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with 5% MeOH in CH_2Cl_2. Further purification by semipreparative HPLC (method A) gave the title compound (88 mg, 38%): ^{1}H NMR ($CDCl_3$) δ 8.31 (1H, d, J = 6.2 Hz), 7.35 (1H, t, J = 7.2 Hz), 7.32−7.04 (6H, m), 6.55−6.46 (2H, m), 5.09 (2H, s), 4.99 (1H, d, J = 10.9 Hz), 4.64 (1H, d, J = 4.0 Hz), 4.23−3.79 (6H, m), 3.70 (1H, d, J = 13.1 Hz), 3.52 (1H, m), 3.26−2.98 (2H, m), 2.89−2.50 (6H, m), 2.10−1.73 (6H, m); MS (FAB) m/z = 601 (M^+ + H); HPLC purity = 99.8% (method A; 215 nm). Anal. ($C_{33}H_{36}N_4O_7$·EtOAc) C, H, N.

1-(1-{2-Methoxy-4-[1-(1-oxido-5,6,7,8-tetrahydroquinolin-5-yl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (50). 7,8-Dihydro-6*H*-quinolin-5-one (21). To a stirred solution of 3-amino-2-cyclohexen-1-one (Fluka) (12 g, 0.108 mol) in dry, degassed DMF (500 mL) was added propynal[23] (13.7 g, 0.25 mol) dropwise. The resulting mixture was stirred at ambient temperature for 48 h; then the solvent was removed under reduced pressure. The residual brown solid was heated to 140 °C for 5 min, and the cooled residue was purified by flash chromatography, eluting with 3% MeOH in CH_2Cl_2, to give the title compound as a dark oil (8.5 g, 53%): ^{1}H NMR ($CDCl_3$) δ 8.68 (1H, dd, J = 5, 2 Hz), 8.29 (1H, dd, J = 8, 2 Hz), 7.29 (1H, dd, J = 8, 5 Hz), 3.17 (2H, t, J = 6 Hz), 2.71 (2H, t, J = 7 Hz), 2.22 (2H, m).

5-Hydroxy-5,6,7,8-tetrahydroquinoline (22). Sodium borohydride (7.7 g, 0.204 mol) was added in portions, over 40 min, to a stirred solution of ketone **21** (10.0 g, 68 mmol) in MeOH (350 mL) at 0 °C. The reaction mixture was stirred for 18 h, allowing it to warm to ambient temperature. The solvent was evaporated under reduced pressure, and the residue was partitioned between saturated $NaHCO_3$ (450 mL) and EtOAc (500 mL). The organic layer was removed and the aqueous phase extracted further with EtOAc (2 × 500 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel, eluting with EtOAc, to give the title compound as a pale solid (9.20 g, 91%): ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, dd, J = 4.8, 1.6 Hz), 7.78 (1H, dd, J = 7.7, 1.3 Hz), 7.14 (1H, dd, J = 7.7, 4.8 Hz), 4.83 (1H, br s), 3.04−2.86 (2H, m), 2.15−2.00 (3H, m), 1.95−1.82 (2H, m).

1-(1-{2-Methoxy-4-[1-(1-oxido-5,6,7,8-tetrahydroquinolin-5-yl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (50). Using alcohol **22** for the chlorination step and adding sodium iodide in the alkylation reaction gave the title compound (131 mg, 36%). For the TFA salt: ^{1}H NMR (CD_3OD) δ 8.46 (1H, d, J = 6.4 Hz), 7.76 (1H, d, J = 8.1 Hz), 7.52 (1H, t, J = 7.2 Hz), 7.40 (1H, t, J = 7.6 Hz), 7.31−7.11 (4H, m), 6.77−6.66 (2H, m), 5.14 (2H, s), 4.81 (2H, m), 4.76 (1H, t, J = 4.2 Hz), 4.22 (1H, tt, J = 11.8, 3.8 Hz), 3.92−3.83 (3H, m), 3.64−3.12 (7H, m), 3.04 (2H, t, J = 6.4 Hz), 3.01−2.02 (10H, m), 2.02−1.75 (2H, m); MS (FAB) m/z = 613 (M^+ + H); HPLC purity = 99.8% (method A; 215 nm). Anal. ($C_{35}H_{40}N_4O_6$·1.9CF_3CO_2H·1.35H_2O) C, H, N.

The following compounds were made in analogy with pyridine *N*-oxide **50**, utilizing the appropriate ketone,[25] alcohol, or chloride: **51**−**54**.

(*S*)-1-(1-{5-Fluoro-2-methoxy-4-[1-(1-oxido-5,6,7,8-tetrahydroquinolin-5-yl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one [(*S*)-51]. Methyl 4-Hydroxy-2-methoxybenzoate (17). To a stirred, 0 °C solution of methyl 2,4-dihydroxybenzoate (**7**) (50 g, 0.30 mol) in acetone (1 L) were added K_2CO_3 (150 g, 1 mol) and benzyl bromide (56 g, 0.33 mol). The solution was allowed to warm to ambient temperature over 48 h. The reaction solution was filtered through Celite and the acetone solution stripped down under reduced pressure. The crude oil was dissolved in EtOAc (1 L) and washed with water (250 mL) and saturated $NaHCO_3$ (500 mL). The EtOAc layer was dried ($MgSO_4$) and filtered, and the EtOAc was removed under reduced pressure. The crude product was purified by flash column chromatography, eluting with 15% EtOAc in hexanes, to give methyl 4-(benzyloxy)-2-hydroxybenzoate as a white powder (44.5 g, 58%): ^{1}H NMR ($CDCl_3$) δ 7.75 (1H, d, J = 7.8 Hz), 7.44−7.30 (5H, m), 6.54−6.48 (2H, m), 5.08 (2H, s), 3.91 (3H, s).

To a stirred, 0 °C solution of methyl 4-(benzyloxy)-2-hydroxybenzoate (12 g, 46 mmol) in DMF (150 mL) were added NaH (2.76 g, 69 mmol) and methyl iodide (16.5 g, 116 mmol). The solution was allowed to warm to ambient temperature and stirred for 18 h. The reaction mixture was poured onto ice and the resulting aqueous solution extracted with Et_2O (3 × 200 mL). The organic phase was dried ($MgSO_4$) and filtered and the Et_2O removed under reduced pressure. The crude white solid was purified by flash column chromatography, eluting with 20% EtOAc in hexanes, to give methyl 4-(benzyloxy)-2-methoxybenzoate as a white powder (12 g, 96%): ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, d, J = 9.3 Hz), 7.46−7.32 (5H, m), 6.58−6.54 (2H, m), 5.10 (2H, s), 3.87 (3H, s), 3.85 (3H, s).

A solution of methyl 4-(benzyloxy)-2-methoxybenzoate (8.2 g, 30 mmol), palladium catalyst (10% Pd−C, 1 g), and AcOH (1 mL) in methanol (100 mL) was stirred under an atmosphere of hydrogen (ca. 1 atm) at ambient temperature for 18 h. The methanol solution was filtered through Celite and the crude reaction solution stripped down to afford an oil. The product was purified by flash column chromatography, eluting with 50% EtOAc in hexanes, to give the title compound as a white powder (4.7 g, 86%): ^{1}H NMR ($CDCl_3$) δ 7.79 (1H, d, J = 8.4 Hz), 6.47−6.42 (2H, m), 6.25 (1H, br s), 3.86 (3H, s), 3.82 (3H, s).

5-Fluoro-4-hydroxy-2-methoxybenzoic Acid (18). A mixture of ester **17** (3.7 g, 21 mmol) and 3,5-dichloro-1-fluoropyridinium triflate (8.4 g, 85 wt %, 23 mmol) in dry CH_2Cl_2 (80 mL) was heated to reflux for 18 h and then concentrated to dryness under reduced pressure. The residue was partially purified by flash column chromatography, eluting with a gradient of 0−2% MeOH in CH_2Cl_2, to give a solid which was recrystallized from hot Et_2O to give methyl 5-fluoro-4-hydroxy-2-methoxybenzoate (1.57 g, 38%): ^{1}H NMR ($CDCl_3$) δ 7.65 (1H, d, J = 11.0 Hz), 6.62 (1H, d, J = 7.3 Hz), 5.82 (1H, br s), 3.86 (6H, s).

To a stirred solution of methyl 5-fluoro-4-hydroxy-2-methoxybenzoate (500 mg, 2.50 mmol) in MeOH (5 mL) was added aqueous NaOH (2 N, 6.25 mL, 12.5 mmol). The resulting solution was heated to reflux for 3 h, then allowed to cool, and concentrated in vacuo. The residue was partitioned between 20% citric acid (20 mL) and EtOAc (50 mL). The organic layer was washed with water (2 × 20 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the title compound as a yellow solid (460 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 7.65 (1H, d, J = 10.7 Hz), 6.62 (1H, d, J = 7.1 Hz), 5.73 (1H, br s), 4.04 (3H, s).

1-(1-{5-Fluoro-4-hydroxy-2-methoxybenzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (19). A solution of acid **18** (460 mg, 2.47 mmol), piperidine **6** (730 mg, 2.72 mmol), EDC (947 mg, 4.94 mmol), HOBT (367 mg, 2.72 mmol), and DIEA (479 mg, 3.71 mmol) in dry, degassed DMF was stirred for 18 h at ambient temperature. The solvent was evaporated under reduced pressure and the residue partitioned between 10% citric acid (75 mL) and EtOAc (75 mL). The citric acid layer was extracted with a further portion of EtOAc (25 mL), and the combined organic extracts were washed with water (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with 3% MeOH in CH_2Cl_2, to yield the title compound (500 mg, 51%): ^{1}H NMR ($CDCl_3$) δ 7.35 (1H, t, J = 7.2 Hz), 7.18−6.92 (3H, m), 6.51 (1H, d, J = 7.0 Hz), 5.09 (2H, s), 4.95 (1H, d, J = 11.7 Hz), 4.13 (1H, m), 3.79−3.73 (3H, m), 3.72 (2H, m), 3.19−3.03 (1H, m), 2.89−2.56 (3H, m), 1.98−1.77 (2H, m).

(*R*)-5-Hydroxy-5,6,7,8-tetrahydroquinoline [(*R*)-22]. To a stirred solution of (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole−borane[41] (5.0 g, 17.1 mmol) and borane−methyl sulfide (10 M, 1.7 mL, 17 mmol) in dry CH_2Cl_2 (40 mL) at ambient temperature was added a solution of ketone **21** (2.5 g, 17 mmol) in CH_2Cl_2 (10 mL) over 5 min, during which time the temperature rose to 36 °C. The

reaction was carefully quenched into MeOH (250 mL), and the resulting solution was concentrated by distillation (1 atm) to remove volatile impurities. The MeOH addition/distillation was repeated (3×), and the crude residue was purified by flash column chromatography, eluting with 87:12:1 hexane−EtOH−triethylamine to remove diphenylprolinol and then with 40:47:12:1 hexane−CH_2Cl_2−EtOH−triethylamine to elute the product. Concentration of the product-containing fractions in vacuo followed by trituration with *tert*-butyl methyl ether gave the title compound as a white solid (2.2 g, 88%): ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, dd, J = 4.8, 1.6 Hz), 7.77 (1H, dd, J = 7.7, 1.3 Hz), 7.14 (1H, dd, J = 7.7, 4.8 Hz), 4.82 (1H, br s), 3.03−2.85 (2H, m), 2.15−2.02 (2H, m), 1.94−1.83 (3H, m); MS (FAB) m/z = 150 (M^+ + H); HPLC (Chiralpak) >99% ee; $[\alpha]^{20}_D = -40°$ (c = 0.8, MeOH).

(*S*)-5-Amino-1-oxido-5,6,7,8-tetrahydroquinoline [(*S*)-23]. A solution of alcohol **(*R*)-22** (1.00 g, 6.70 mmol), diphenyl phosphorazidate (2.77 g, 10.1 mmol), and DBU (1.53 g, 10.1 mmol) in dry toluene (10 mL) and dry THF (1 mL) was stirred at ambient temperature for 18 h. The solvent was evaporated under reduced pressure, and the residue was partitioned between saturated $NaHCO_3$ (75 mL) and CH_2Cl_2 (75 mL). The organic layer was removed and the aqueous phase extracted further with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a dark oil which was chromatographed on silica gel, eluting with 30% EtOAc in hexane, to give (*S*)-5-azido-5,6,7,8-tetrahydroquinoline as a colorless oil (1.05 g, 90%): ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, dd, J = 4.8, 1.7 Hz), 7.63 (1H, dd, J = 7.7, 1.1 Hz), 7.17 (1H, dd, J = 7.7, 4.8 Hz), 4.59 (1H, t, J = 4.7 Hz), 3.02 (1H, m), 2.91 (1H, m), 2.15−1.97 (3H, m), 1.93 (1H, m); MS (FAB) m/z = 175 (M^+ + H); HPLC (Chiralpak) 99.1% ee; $[\alpha]^{20}_D = -36°$ (c = 0.9, MeOH).

To a stirred solution of (*S*)-5-azido-5,6,7,8-tetrahydroquinoline (1.02 g, 5.86 mmol) in $CHCl_3$ (35 mL) was added mCPBA (1.19 g, 85 wt %, 5.86 mmol), and the resulting mixture was stirred at ambient temperature for 18 h. The reaction was quenched with saturated $NaHCO_3$ (75 mL) and the organic layer extracted. The aqueous phase was extracted further with $CHCl_3$ (2 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil which was chromatographed on silica gel, eluting with 5% MeOH in EtOAc, to give (*S*)-5-azido-1-oxido-5,6,7,8-tetrahydroquinoline as a colorless oil (1.11 g, 100%): ^{1}H NMR ($CDCl_3$) δ 8.25 (1H, d, J = 6.4 Hz), 7.28 (1H, dd, J = 7.7 Hz), 7.17 (1H, dd, J = 7.7, 6.4 Hz), 4.60 (1H, t, J = 4.9 Hz), 3.05 (1H, dt, J = 19.8, 5.8 Hz), 2.88 (1H, dt, J = 19.8, 6.8 Hz), 2.16−1.88 (4H, m); MS (FAB) m/z = 191 (M^+ + H); HRMS (FAB) m/z = 191.0957 (M^+ + H), $C_9H_{11}N_4O$ = 191.0933; HPLC (Chiralpak) 99.5% ee; $[\alpha]^{20}_D = -94°$ (c = 0.8, MeOH).

A mixture of (*S*)-5-azido-1-oxido-5,6,7,8-tetrahydroquinoline (1.00 g, 5.26 mmol) and 10% Pd−C (100 mg) in EtOH (50 mL) was stirred under an atmosphere of hydrogen (ca. 1 atm) at ambient temperature for 2 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to give a crude solid. Purification by flash column chromatography, eluting with 7% MeOH−0.5% NH_4OH in CH_2Cl_2, gave the title compound as a pale solid (820 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 8.18 (1H, d, J = 6.4 Hz), 7.43 (1H, dd, J = 8.1 Hz), 7.13 (1H, dd, J = 8.1, 6.4 Hz), 3.99 (1H, dd, J = 6.9, 4.7 Hz), 2.96 (2H, t, J = 6.4 Hz), 2.10−2.04 (2H, m), 1.87 (1H, m), 1.73−1.54 (3H, m); MS (FAB) m/z = 165 (M^+ + H); HRMS (FAB) m/z = 165.1009 (M^+ + H), $C_9H_{13}N_2O$ = 165.1009; HPLC (Chiralpak) 96.7% ee; $[\alpha]^{20}_D = -4.0°$ (c = 0.8, MeOH).

(*S*)-5-(4-Hydroxypiperidin-1-yl)-1-oxido-5,6,7,8-tetrahydroquinoline [(*S*)-24]. To a stirred solution of amine **(*S*)-23** (300 mg, 1.83 mmol) in 1-butanol were added 1,5-dichloropentan-3-ol[22] (260 mg, 1.66 mmol), anhydrous K_2CO_3 (505 mg, 3.65 mmol), and anhydrous NaI (274 mg, 1.83 mmol). The reaction mixture was stirred at 75 °C for 18 h, then additional portions of 1,5-dichloropentan-3-ol (57 mg, 0.37 mmol) and NaI (27 mg, 0.18 mmol) were added, and heating was continued for 8 h. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography, eluting with 5% MeOH−0.5% NH_4OH in CH_2Cl_2, to give the title compound as a pale solid (188 mg, 41%): ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, d, J = 6.4 Hz), 7.69 (1H, d, J = 8.1 Hz), 7.12 (1H, t, J = 7.1 Hz), 3.80 (1H, dd, J = 10.5, 4.7 Hz), 3.71 (1H, m), 3.15 (1H, dd, J = 19.1, 5.2 Hz), 2.79−2.67 (2H, m), 2.60−2.53 (2H, m), 2.27−2.13 (2H, m), 2.04−1.84 (3H, m), 1.73−1.46 (4H, m); MS (FAB) m/z = 249 (M^+ + H); HRMS (FAB) m/z = 249.1601 (M^+ + H), $C_{14}H_{21}N_2O_2$ = 249.1603; HPLC (Chiralpak) 96.4% ee; $[\alpha]^{20}_D = +84°$ (c = 0.8, MeOH).

(*S*)-1-(1-{5-Fluoro-2-methoxy-4-[1-(1-oxido-5,6,7,8-tetrahydroquinolin-5-yl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]oxazin-2-one [(*S*)-51]. To a stirred solution of phenol **19** (178 mg, 0.44 mmol) and triphenylphosphine (157 mg, 0.60 mmol) in dry THF (5 mL) at 0 °C was added a solution of alcohol **(*S*)-24** (100 mg, 0.40 mmol) and diethyl azodicarboxylate (77 mg, 0.44 mmol) in dry THF (5 mL), dropwise. The reaction mixture was stirred at ambient temperature for 18 h, the solvent was evaporated in vacuo, and the residue was partitioned between saturated $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL). The organic layer was removed and the aqueous phase extracted further with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a crude residue which was chromatographed on silica gel, eluting with 3% MeOH−0.3% NH_4OH in CH_2Cl_2, to give the title compound as a pale solid (175 mg, 69%). For the hydrochloride salt: ^{1}H NMR (CD_3OD) δ 8.60 (1H, d, J = 6.4 Hz), 8.16−8.00 (1H, m), 7.64 (1H, t, J = 7.2 Hz), 7.40 (1H, td, J = 7.8, 1.4 Hz), 7.31−7.23 (2H, m), 7.21−6.89 (2H, m), 7.14 (1H, t, J = 7.4 Hz), 5.14 (2H, s), 4.90−4.65 (3H, m), 4.23 (1H, m), 3.94−3.83 (3H, m), 3.61 (2H, m), 3.48 (2H, m), 3.33−3.04 (5H, m), 3.01−2.05 (10H, m), 2.03−1.77 (2H, m); MS (FAB) m/z = 631 (M^+ + H); HRMS (FAB) m/z = 631.2912 (M^+ + H), $C_{35}H_{40}FN_4O_6$ = 631.2926; HPLC purity = 99.6% (method A; 215 nm); HPLC (Chiralpak) 96.8% ee; $[\alpha]^{20}_D = -27°$ (c = 0.8, MeOH). Anal. ($C_{35}H_{39}FN_4O_6 \cdot HCl \cdot 2.25H_2O \cdot 0.2CH_2Cl_2$) C, H, N.

1-(1-{5-Fluoro-2-methoxy-4-[1-(quinolin-5-yl)piperidin-4-yloxy]benzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]-oxazin-2-one (55). To a stirred solution of 5-aminoquinoline (222 mg, 1.54 mmol) in dry DMF (1 mL) was added 1,5-dichloropentan-3-ol[22] (220 mg, 1.40 mmol), anhydrous K_2CO_3 (426 mg, 3.08 mmol), and anhydrous NaI (115 mg, 0.77 mmol). The reaction mixture was stirred at 100 °C for 4 h and then partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with a further portion of EtOAc (15 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with 40% hexane in EtOAc, to give 5-(4-hydroxypiperidin-1-yl)quinoline as a pale solid (67 mg, 21%): ^{1}H NMR ($CDCl_3$) δ 8.88 (1H, dd, J = 4.2, 1.7 Hz), 8.49 (1H, dt, J = 7.7, 0.8 Hz), 7.81 (1H, d, J = 8.4 Hz), 7.61 (1H, dd, J = 8.3, 7.6 Hz), 7.39 (1H, dd, J = 8.4, 4.2 Hz), 7.12 (1H, dd, J = 7.5, 0.7 Hz), 3.95 (1H, m), 3.32 (2H, dt, J = 11.9, 4.0 Hz), 2.90 (2H, td, J = 10.8, 2.3 Hz), 2.61 (1H, br s), 2.13 (2H, m), 1.91 (2H, m).

To a stirred solution of phenol **19** (58 mg, 0.145 mmol), 5-(4-hydroxypiperidin-1-yl)quinoline (30 mg, 0.13 mmol), and triphenylphosphine (52 mg, 0.197 mmol) in dry THF (2 mL) at 0 °C was added a solution of diethyl azodicarboxylate (25 mg, 0.145 mmol) in dry THF (2 mL), dropwise. The reaction mixture was stirred at ambient temperature for 18 h and then partitioned between saturated $NaHCO_3$ (10 mL) and EtOAc (10 mL). The organic layer was removed and the aqueous phase extracted further with EtOAc (10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give a crude residue which was purified by preparative TLC, eluting with EtOAc to give the title compound as a pale solid (38 mg, 48%): ^{1}H NMR ($CDCl_3$) δ 8.90 (1H, dd, J = 4.1, 1.6 Hz), 8.50 (1H, dd, J = 8.1, 0.7 Hz), 7.81 (1H, d, J = 8.4 Hz), 7.63 (1H, dd, J = 8.4, 7.5 Hz), 7.40 (1H, dd, J = 8.6, 4.2 Hz), 7.35 (1H, td, J = 7.8, 1.3 Hz), 7.20−7.03 (5H, m), 6.64 (1H, d, J = 6.4 Hz), 5.09 (2H, s), 4.97 (1H, d, J

= 10.1 Hz), 4.58 (1H, br s), 4.15 (1H, m), 3.93−3.78 (3H, m), 3.71 (1H, d, J = 13.2 Hz), 3.44−3.33 (2H, m), 3.24−2.53 (6H, m), 2.30−2.09 (4H, m), 2.02−1.75 (2H, m); MS (FAB) m/z = 611 ($M^+ + H$); HPLC purity = 98.0% (method B; 215 nm). Anal. ($C_{35}H_{35}FN_4O_5 \cdot 0.4H_2O$) C, H, N.

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Supporting Information Available: ^{1}H NMR and MS data for all final compounds which are not described in the Experimental Section of this paper (9 pages). Ordering information is given on any current masthead page.

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