Design, Synthesis, and SAR of Tachykinin Antagonists: Modulation of Balance in NK_1/NK_2 Receptor Antagonist Activity

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Through optimization of compounds based on the dual NK_1/NK_2 antagonist ZD6021, it was found that alteration of two key regions could modulate the balance of NK_1 and NK_2 potency. Substitution of the 2-naphthalene position in analogues of ZD6021 resulted in increased NK_1 potency and thus afforded NK_1 preferential antagonists. Alterations of the piperidine region could then increase NK_2 potency to restore dual NK_1/NK_2 selectivity. Through these efforts, three novel receptor antagonists from a single chemically related series were identified; two are dual NK_1/NK_2 antagonists, and the third is an NK_1 preferential antagonist. In this paper, the factors affecting the balance of NK_1 and NK_2 selectivity in this series are discussed and the in vitro and in vivo properties of the novel antagonists are described.

Introduction

In mammals, the tachykinins are a family of three neuropeptides: substance P (SP), neurokinin A (NKA), and neurokinin B (NKB). The preferred receptors for these are termed (respectively) NK_1, NK_2, and NK_3. NK_1 and NK_2 are widely distributed in the central nervous system (CNS) and peripheral tissue, and NK_3 appears to be more localized in the CNS.[1] Functioning as neurotransmitters or neuromodulatory agents, SP, NKA, and NKB may be involved in several pathophysiological conditions including asthma, arthritis, cough, emesis, anxiety, depression, pain, urinary incontinence, and inflammatory bowel disease.[2,3] The areas of neurokinin antagonist development have been extensively reviewed.[4−7]

In an earlier paper, we described the discovery of the potent, orally active NK_2 antagonist ZD7944 (**1**).[8] Evidence has suggested that both NK_1 and NK_2 are involved in pulmonary pathophysiology and other disorders.[9,10] Therefore, agents that simultaneously antagonize NK_1 and NK_2 may have therapeutic applications.

To explore these possibilities, we sought to introduce NK_1 activity while maintaining NK_2 activity in structures related to **1**. Approaches to the development of dual NK_1/NK_2 antagonists have been demonstrated by starting from other NK_2 selective agents[11−15] and by starting from NK_1 selective agents.[5]

Our subsequent efforts[16,17] led to the discovery of the NK_1/NK_2 dual antagonist ZD6021 (**2**). Ongoing work has focused on improving the properties of related compounds as antagonists and on better understanding the subtle factors relevant to neurokinin selectivity. By starting from compounds related to **2** and altering the piperidine and naphthamide regions (Figure 1), it has been possible to modulate the degree of NK_1 and NK_2 activity. Described here are structure−activity relationship (SAR) studies leading to the identification of the dual NK_1/NK_2 antagonist ZD2249 (**3**), the NK_1 preferential antagonist ZD4974 (**4**), and the dual NK_1/NK_2 antagonist **5** (Chart 1).

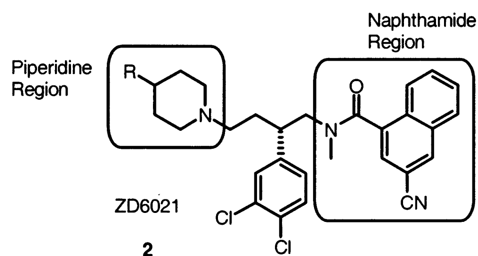

Figure 1. Structure of **2** indicating the "piperidine" and "naphthamide" regions.

Chemistry

Synthesis of 3. The synthesis of compound **3** is described in Scheme 1. 3-Methoxyphenol was reacted with bromine to give **6**. Bromophenol **6** was converted to thioether **9** utilizing the Newman−Kwart rearrangement.[18] Following lithiation with *n*-butyllithium, **9** underwent cerium-mediated reaction with N-Cbz-piperidone and was dehydroxylated using triethylsilane with trifluoroacetic acid. The resulting aryl methyl thioether (**11**) was stereoselectively oxidized using a method similar to that described by Kagan.[19] Deprotection of the Cbz group was then carried out using KOH to afford **13**. This material was then reductively alkylated with aldehyde **14**[16] in the presence of sodium cyanoborohydride to give **3**.

Synthesis of 4. The key naphthamide moiety in **4** was prepared according to Scheme 2. 3-Hydroxy-2-naphthoic acid (**15**) was iodinated using NaI with sodium hypochlorite/NaOH and then bis-methylated using dimethyl sulfate to give **17**. The methyl ester was

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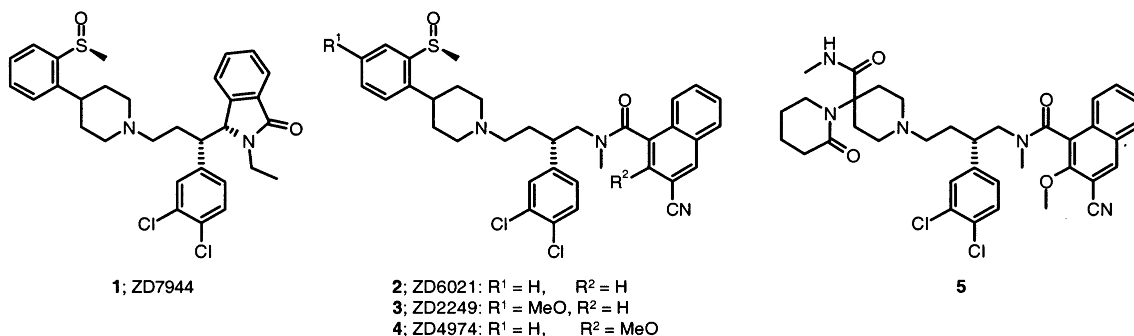
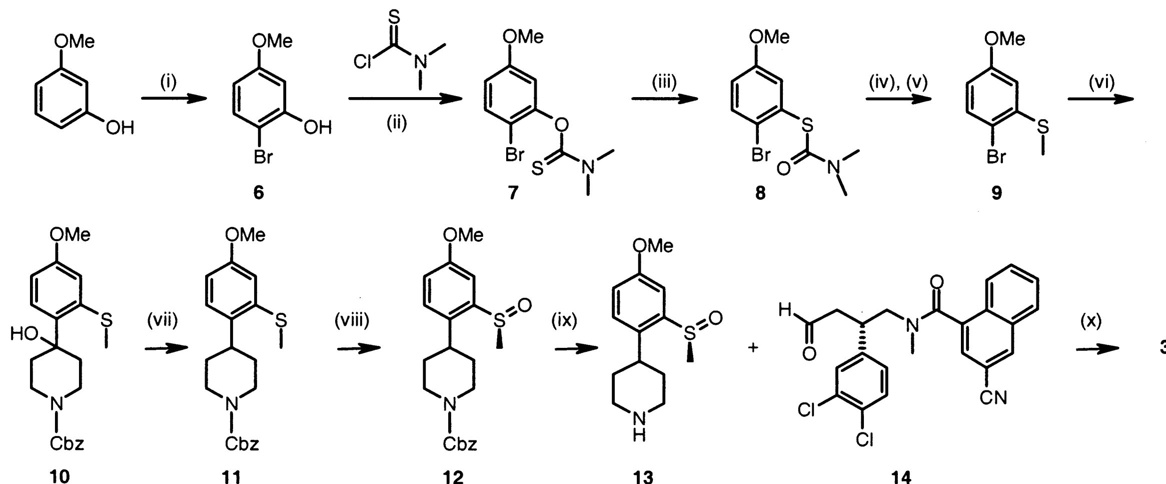
Chart 1

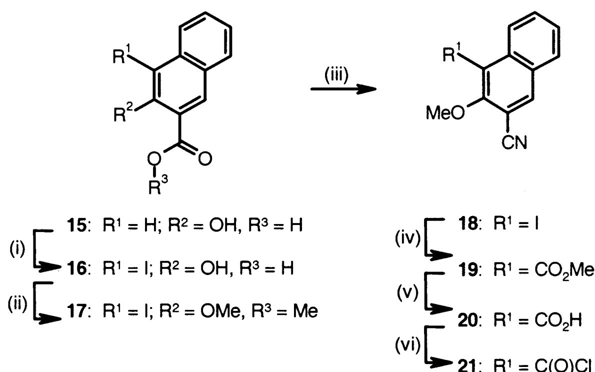


Scheme 1[a]



[a] Reagents: (i) Bromine, benzoyl peroxide, 1,1,1-trichloroethanol, 77%. (ii) 1,4-Diazabicyclo[2.2.2]octane, DMF, 60%. (iii) *N*,*N*-Diethylaniline, 230 °C, 59%. (iv) KOH, methanol. (v) MeI, K_2CO_3, 99% (overall iv and v). (vi) *n*-BuLi, $CeCl_3$, of N-Cbz-4-piperidone, 79%. (vii) Et_3SiH, TFA, 89%. (viii) Diethyl-D-tartrate, tBuOOH, $Ti(OiPr)_4$, 69%. (ix) KOH, methanol, 47%. (x) $NaBH_3CN$, AcOH, methanol, 70%.

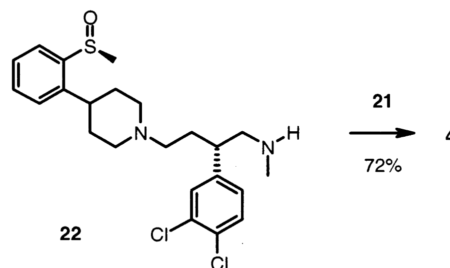
Scheme 2[a]



[a] Reagents: (i) NaOH, NaI, sodium hypochlorite, 75%. (ii) K_2CO_3, dimethyl sulfate, 64%. (iii) Dimethyl aluminum amide, 73%. (iv) $Pd(OAc)_2$, Et_3N, carbon monoxide (1 atm), methanol, 59%. (v) LiOH, water, THF, 89%. (vi) Oxalyl chloride, catalytic DMF.

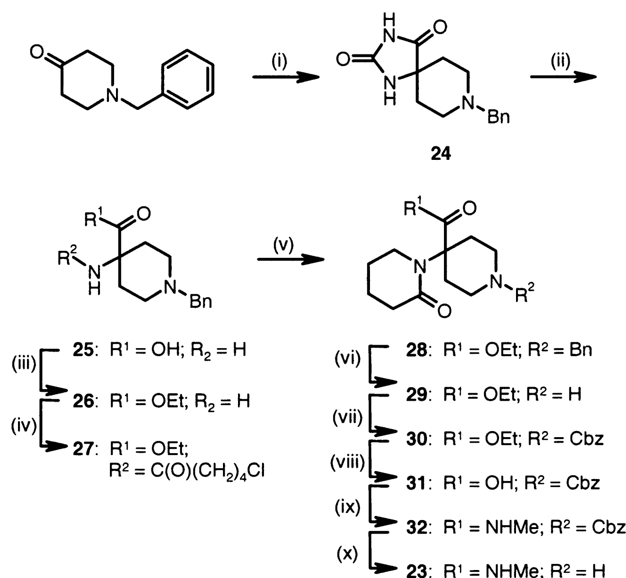
converted directly to the nitrile (**18**) using Wienreb conditions.[20] The resulting material was carbonylated using carbon monoxide in the presence of $Pd(OAc)_2$ and methanol to give **19**, the methyl ester was saponified using LiOH to give **20**, and then, the carboxylic acid was converted to the acid chloride using oxalyl chloride to afford **21**. Compound **4** was prepared by reaction of acid chloride **21** with **22**[16] using Schotten–Baumann conditions according to Scheme 3. Similarly, amine **22** could be reacted with a variety of other naphthoyl chlorides to prepare naphthamide analogues related to **2**.

Scheme 3



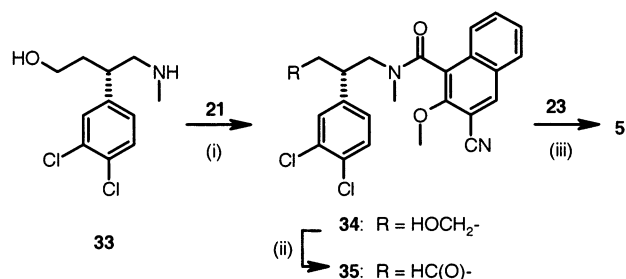
Synthesis of 5. The 4,4-disubstituted piperidine **23** was prepared according to Scheme 4. 1-Benzyl-4-piperidone was reacted with ammonium carbonate and sodium cyanide to give spirohydantoin **24**. This material was hydrolyzed (LiOH) to amino acid **25** and converted to ethyl ester **26** using thionyl chloride in ethanol. The amine was acylated with 5-chlorovaleryl chloride to give **27** and then cyclized by slow addition to a suspension containing NaH to give lactam **28**. A change in amine protecting groups was carried out by palladium hydroxide-catalyzed hydrogenolysis of the benzylamine (to **29**) and reaction with *N*-(benzyloxycarbonyloxy)succinimide to afford **30**. The ethyl ester (**30**) was saponified to **31**, reacted with methylamine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in the presence of 4-(dimethylamino)pyridine to give **32**, and then deprotected by catalytic hydrogenolysis to afford **23**.

Scheme 4[a]



[a] Reagents: (i) $(NH_4)_2CO_3$, NaCN, 89%. (ii) LiOH, reflux, 40 h, 66%. (iii) Thionyl chloride, ethanol, 84%. (iv) 5-Chlorovaleryl chloride, 57%. (v) NaH, 87%. (vi) $Pd(OH)_2$ (20%), H_2 (1 atm), 99%. (vii) *N*-(Benzyloxycarbonyloxy)succinimide, 86%. (viii) NaOH, THF, water, reflux, 10 h, 88%. (ix) Methylamine hydrochloride, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, DMAP, 80%. (x) $Pd(OH)_2$ (20%), H_2 (1 atm), 99%.

Scheme 5[a]



[a] Reagents: (i) NaOH, water, DCM (biphasic). (ii) Oxalyl chloride, DMSO, triethylamine, 91%. (iii) HOAc, $NaBH_3CN$, methanol, 88%.

As shown in Scheme 5, amino alcohol **33**[21] was acylated with **21** using Schotten−Baumann conditions. The resulting alcohol **34** was oxidized to aldehyde **35** using Swern[22] conditions and, finally, reductively aminated with the substituted piperidine **23** to afford **5**.

Results

(a) Substituted Aryl Sulfoxide Piperidine Analogues of 2; Identification of Dual NK_1/NK_2 Antagonist 3. We have previously described the identification of **2** as a dual NK_1/NK_2 antagonist.[16,17] With this as a starting point, we sought to further improve the activity and balance of NK_1/NK_2 potency through alterations in the piperidine region. A series of analogues were prepared, which contained the 2-methylsulfinylphenyl group and additional substitution in the aryl ring (Table 1).

In previous work, we investigated the preferences for the sulfoxide stereochemistry on NK_1 and NK_2 affinity. Briefly, in comparison to **2**, the (*R*)-sulfoxide diastereomer had moderately weaker NK_1 affinity ($pK_B = 8.36 \pm 0.21$) and essentially equivalent NK_2 affinity ($pK_B = 8.39 \pm 0.06$).[16] Therefore, aryl-substituted analogues were prepared as the (*S*)-sulfoxide diastereomer where practical; however, in some cases, (*R*,*S*)-sulfoxide mixtures were studied.

Table 1. Receptor Affinity (pK_B) for Substituted Aryl Sulfoxide Piperidine Analogues of **2**[a]

	R	config[b]	NK_1[c]	NK_2[d]
2		*S*	8.98 ± 0.17	8.26 ± 0.10
3	4-MeO	*S*	8.20 ± 0.08	8.70 ± 0.08
36a		*R*, *S*	8.43 ± 0.23	8.48 ± 0.04
36b	4-F	*S*	8.01 ± 0.04	8.38 ± 0.01
36c	4-Br	*S*	8.00 ± 0.10	8.12 ± 0.10
36d	4-HO	*R*, *S*	8.93 ± 0.24	8.34 ± 0.18
36e	4-HO_2C	*R*, *S*	7.87 ± 0.12	6.38 ± 0.22
36f	4-MeO_2C	*R*, *S*	7.92 ± 0.06	6.84 ± 0.28
36g	4-$H_2NC(O)$	*R*, *S*	8.53 ± 0.06	6.92 ± 0.07
36h	4-MeS(O)	*R*, *S*	7.33 ± 0.11	8.27 ± 0.18
36i	5-F	*R*, *S*	8.26 ± 0.10	8.34 ± 0.32
36j	5-Br	*R*, *S*	8.46 ± 0.11	8.55 ± 0.14
36k	6-F	*R*, *S*	7.25 ± 0.34	6.83 ± 0.03

[a] pK_B determinations using rabbit pulmonary artery tissue ($n = 2-6$). [b] Sulfoxide stereochemical configuration. [c] Agonist, ASMSP. [d] Agonist, BANK.

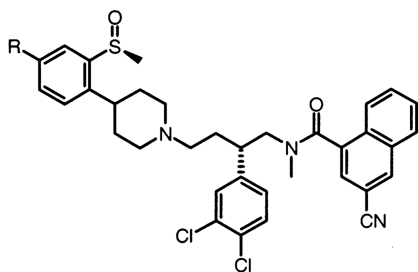
In general, NK_1 affinity remained similar or decreased slightly for most analogues containing additional aryl substituents (Table 1). Only the 4-methylsulfonyl (**36h**) and the 6-fluoro analogues (**36k**) showed substantially weaker affinity. NK_2 affinity was also quite tolerant to additional substitution in the aryl ring; however, the 4-carbonyl-containing analogues (**36e**−**g**) and the 6-fluoro analogue (**36k**) showed significantly weaker affinity.

Compounds showing strong affinity at both NK_1 and NK_2 (generally $pK_B > 8$) underwent in vivo testing in the guinea pig pulmonary mechanics model[23] (PMM). The PMM assay measures the ability of an antagonist to block the increase in airway resistance, which otherwise occurs in response to administration of the NK_1 selective agonist ASMSP (Ac-($Arg^6Sar^9Met(O_2)^{11}$) SP_{6-11}) or the NK_2 selective agonist BANK (β-ala^8NKA_{4-10}). Antagonist potency can be expressed as the dose ratio (dr), which is the ratio of the agonist ED_{50} value (for airway response) in the presence of antagonist divided by the ED_{50} value in the absence of antagonist.

For example, a compound with a dr of 50 would indicate that after it was dosed with a particular antagonist, 50 times more agonist (ASMSP for NK_1 or BANK for NK_2) would be required to induce an airway restriction response as compared to the agonist dose needed to generate the same response for a control animal where no antagonist is given. In Table 2, results are shown for compounds with significant activity in this assay.

Compounds were administered intravenously (generally with antagonist at 10 μmol/kg, 10 min prior to agonist challenge) or orally (generally with antagonist

Table 2. Comparison of the In Vivo Potency (dr) of **2** and Substituted Aryl Sulfoxide Piperidine Analogues in the Guinea Pig PMM[a]



	R	NK_1 iv[c]	NK_1 po[d]	NK_2 iv[c]	NK_2 po[d]
2	H	156	33	61	21
3	MeO	64	8	337	60
36b	F	126	4	153	5
36c	Br	11	nd[e]	30	nd[e]
4	na[b]	1365	610	14	2
5	na[b]	384	50	155	49

[a] Values given are dr (ED_{50} in the presence of antagonist divided by the ED_{50} in the absence of antagonist) based on $n \geq 3$ determinations; NK_1 agonist = ASMSP; NK_2 agonist = BANK. [b] na = not applicable; see structures in schemes. [c] Antagonist dosing, 10 μmol/kg 10 min prior to agonist challenge. [d] Antagonist dosing, 30 μmol/kg 120 min prior to agonist challenge. [e] nd = not determined.

at 30 μmol/kg, 2 h prior to agonist challenge). For a given compound, comparison between the intravenous and the oral potency can provide an indication of the relative bioavailability in guinea pig (ED_{50} iv/ED_{50} po). For example, antagonist potency of **2** decreased by (respectively) about 5- and 3-fold for NK_1 and NK_2 when administered orally in comparison to when administered intravenously.

As indicated in Table 2, the relative reduction in iv versus po activity for fluorine analogue **36b** was substantial (about 30-fold) at both NK_1 and NK_2; for the bromine analogue (**36c**), iv activity was much weaker. This was indicative of poor bioavailability, and these compounds were therefore dismissed from further consideration. For **3**, the relative activity differences (iv/po) were similar to those observed for **2**, suggesting that the distributional properties and in vivo potencies may also be similar. However, **3** has greater potency at NK_2 than NK_1 whereas **2** has greater NK_1 potency. As potential therapeutic agents, it is not known what the optimal balance of activity (NK_1 vs NK_2) would be for various disease states; therefore, it will be desirable to be able to compare antagonists with different relative potencies at each receptor.

Because of its good receptor affinity and in vivo activity, **3** was advanced for more detailed analysis. The binding affinity of **3** to human NK_1 and NK_2 receptors was high and similar to **2** (Table 3). As another assessment of NK_1 antagonist potency, an in vivo model was used to monitor the ability of the test compound to inhibit ASMSP-induced extravasation of plasma proteins in guinea pig lung.[24] The NK_1 potency of **3** (ED_{50} = 1 μmol/kg) was similar to **2** (Table 4). In comparison, the NK_2 potency for **3** (ED_{50} = 3 μmol/kg) was improved by about 4-fold relative to **2** in the PMM model. Therefore, the NK_1 and NK_2 activities are approximately balanced for **3** whereas **2** has greater potency at NK_1 than NK_2.

Table 3. Antagonist Binding to Human Tachykinin Receptors;[a] K_i (nM)

antagonist	NK_1[b]	NK_2[c]	NK_3[d]
1	1620 ± 670	0.92 ± 0.67	9190 ± 3960
2	0.12 ± 0.01	0.64 ± 0.08	74 ± 13
3	0.14 ± 0.06	0.34 ± 0.17	39 ± 12
4	0.17 ± 0.09	67 ± 27	220 ± 53
5	0.27 ± 0.14	35 ± 13	9.4 ± 5.5

[a] Human tachykinin receptor expressed in mouse erythroleukemia cells; $n \geq 2$ determinations. [b] Against ^{3}H-SP. [c] Against ^{3}H-NKA. [d] Against ^{125}I-MPNI.

Table 4. Guinea Pig In Vivo Activity in Pulmonary Models; ED_{50} (μmolg/kg)[a]

antagonist	NK_1[b]	NK_2[c]
2	0.6	13
3	1	3
4	0.07	nd[d]
5	0.5	9.3

[a] Determined 2 h after oral dosing of antagonist; reported as single E_{50} values, calculated from the dose response obtained from three to six animals at each dose for 4−5 dosing levels over the course of several days; on a given day, the full dose response is not possible; therefore, the doses are staggered for randomness. [b] Lung plasma extravasation assay; agonist, ASMSP. [c] Pulmonary mechanics assay; agonist, BANK. [d] nd = not determined.

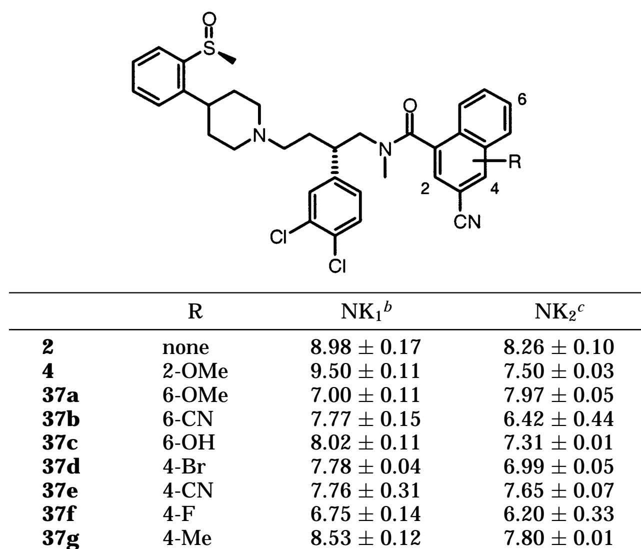
(b) Increasing NK_1 Selectivity. Substituted Cyanonaphthamide Analogues of 2; Identification of 4. As previously described,[16] antagonist **2** bound with high affinity to NK_1 and NK_2 in rabbit pulmonary artery tissue and showed potent in vivo activity in guinea pig following oral dosing. However, bioavailablity in rat and dog was relatively low (9 and 18%, respectively). Following administration to rat, the major metabolic transformations identified were oxidation of the sulfoxide to the sulfone and hydroxylation and glucuronidation of the naphthamide ring. As a strategy toward improving bioavailability, we sought to identify metabolically labile sites.

By further substituting the cyanonaphthamide ring, we attempted to alter the observed in vitro metabolic path. Substitution at the naphthalene 6-position by methoxy, cyano, or hydroxy groups (**37a−c**) reduced antagonist affinity at NK_1 (Table 5). Similarly, substitution at the 4-position with bromo, cyano, or fluoro groups (**37d−f**) also reduced NK_1 affinity. The 4-methyl-substituted adduct (**37g**) showed only slightly decreased NK_1 activity in comparison to **2**. However, NK_1 affinity was increased for the 2-methoxy-substituted analogue (**4**, pK_B = 9.5). NK_2 affinity was reduced for all additionally substituted analogues. Therefore, in comparison to **2**, addition of the 2-methoxy substitution to the naphthyl group (affording **4**) had the effect of increasing NK_1 affinity while reducing NK_2 affinity and thereby shifting the profile of the resulting compound from a dual NK_1/NK_2 antagonist to an NK_1 preferential antagonist.

As indicated in Table 3, **4** inhibited binding of [^{3}H]-SP to human NK_1 receptors with greater potency (K_i = 0.17 nM) than the binding of [^{3}H]NKA to NK_2 receptors (K_i = 67 nM). Inhibition of binding of ^{125}I-MPNKB to NK_3 receptors was substantially weaker (K_i = 220 nM).

Oral administration of **4** to guinea pigs dose-dependently attenuated NK_1-induced extravasation of plasma proteins (ED_{50} = 0.07 μmol/kg, 2 h postdose) with approximately 14 times greater potency than **3** (ED_{50} = 1.0 μmol/kg, Table 4). In the guinea pig PMM assay,

Table 5. Receptor Affinity (pK_B) for Substituted Cyanonaphthamide Analogues of **2**[a]



	R	NK$_1$[b]	NK$_2$[c]
2	none	8.98 ± 0.17	8.26 ± 0.10
4	2-OMe	9.50 ± 0.11	7.50 ± 0.03
37a	6-OMe	7.00 ± 0.11	7.97 ± 0.05
37b	6-CN	7.77 ± 0.15	6.42 ± 0.44
37c	6-OH	8.02 ± 0.11	7.31 ± 0.01
37d	4-Br	7.78 ± 0.04	6.99 ± 0.05
37e	4-CN	7.76 ± 0.31	7.65 ± 0.07
37f	4-F	6.75 ± 0.14	6.20 ± 0.33
37g	4-Me	8.53 ± 0.12	7.80 ± 0.01

[a] Tissue, rabbit pulmonary artery; $n = 2-6$. [b] Agonist, ASMSP. [c] Agonist, BANK.

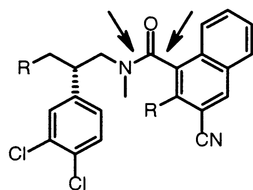


Figure 2. Bonds with restricted rotation (arrows) in the 2-substituted, 3-cyanonaphthamide series.

inhibition of airway restriction in response to the NK$_2$ agonist (BANK) showed 30-fold weaker potency (dr = 2) in comparison to **3** (dr = 60) when dosed orally at 30 μmol/kg, 2 h prior to agonist challenge (Table 2). The bioavailability in dog was nearly three times greater for **4** (51%) than for **3** (18%). However, differences were smaller for bioavailability in rat (12% for **4** and 7% for **3**).

Compounds that contain a 2-substituted cyanonaphthamide group (such as **4**) typically exist as an equilibrating mixture of four conformational isomers. This results from the restricted rotation about the amide and the carbonyl−aryl bonds (Figure 2). The kinetics and thermodynamics of atropisomer interconversion for related systems have been extensively studied.[25,26] NMR spectra for compound **4** show sets of resonances for each of the component atropisomers. For most compounds of this type, each of the four atropisomers can be resolved by analytical high-performance liquid chromatography (HPLC) at low temperatures. The atropisomeric properties and significance will be further discussed separately.[27]

(c) Effect of 2-Methoxynaphthalene Substituent on the Balance of NK$_1$/NK$_2$ Affinity. As described above, **2** showed approximately balanced affinity at NK$_1$ and NK$_2$; however, addition of a 2-methoxyl substituent to the naphthyl region (affording **4**) increases NK$_1$ affinity while decreasing NK$_2$ affinity. This effect can be seen in Table 6 by comparing receptor affinities for analogues containing R^2 = H with R^2 = OMe. For compounds where R^2 = OMe, NK$_1$ affinity (pK_B) was increased by about 0.5−1 log units (Table 6, entries 1 and 5) while NK$_2$ affinity was decreased by about 0.5−1 log units (e.g., Table 6, entries 1−4 and 6). While most compounds appeared to behave as purely competitive antagonists, this was not the case for some compounds containing the naphthalene methoxyl group (**38b**−**d**,**f**). These compounds continued to behave as high affinity antagonists, but they induced a suppression in the maximal response to added agonist.[28] Such behavior is often associated with noncompetitive or partially competitive antagonism.

For this series, it has been demonstrated that varying the naphthamide region influences the balance of NK$_1$/NK$_2$ affinity; the balance of affinity can be altered over a wide range to afford compounds that are essentially NK$_2$ selective (**1**), that have mixed NK$_1$/NK$_2$ selectivity (**2** and **3**), and that are NK$_1$ preferential (**4**).

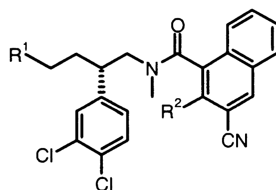
(d) Restoration of Dual NK$_1$/NK$_2$ Potency to Analogues of 4 Through Alteration of the Piperidine Region; Identification of NK$_1$/NK$_2$ Antagonist 5. As noted above, the 2-methoxynaphthalene substituent appeared to improve the dog bioavailability characteristics for **4** in comparison to **2** while simultaneously altering the balance of affinity to favor NK$_1$ over NK$_2$. Thus, returning to our interests in identifying dual NK$_1$/NK$_2$ antagonists, we tried to determine if the balance of NK$_1$/NK$_2$ activity could be restored by altering the piperidine component to increase NK$_2$ affinity while maintaining the potent NK$_1$ affinity and improved bioavailability characteristics associated with the 3-cyano-2-methoxynaphthalene unit.

We noted above that for compounds containing an aryl-substituted piperidine, addition of the naphthyl 2-methoxyl group tended to increase NK$_1$ affinity and reduce NK$_2$ affinity (Table 6, entries 1−6). However, NK$_2$ affinity was not reduced for the nonaryl-substituted piperidines in entry 7 (Table 6). In previous efforts, we had seen that related 4,4-disubstituted piperidine analogues of **2** were NK$_2$ preferential (unpublished results). Starting from such compounds, we sought to find if NK$_1$ affinity could be increased by addition of the naphthalene 2-methoxyl group.

As was observed for entry 7 (Table 6), changing from R^2 = H to R^2 = OMe increased NK$_1$ potency for the remaining nonaryl piperidines in entries 8−11. However, unlike the aryl piperidines, changing from R^2 = H to R^2 = OMe in the nonaryl piperidines did not necessarily reduce NK$_2$ potency.

In this series, the compound that retained the highest dual NK$_1$/NK$_2$ potency in rabbit pulmonary artery tissue was **5** (Table 6, entry 9). Activity in the PMM assay was also strong and evenly balanced (Table 2). However, binding affinity was not as balanced when determined for the human receptors expressed in MEL cells (Table 3); NK$_1$ affinity (K_i = 0.27 nM) was about 130-fold stronger than for NK$_2$ affinity (K_i = 35 nM). Oral administration of **5** to guinea pigs dose-dependently attenuated NK$_1$-induced extravasation of plasma proteins (ED$_{50}$ = 0.5 μmol/kg, 2 h postdose). In the guinea pig PMM assay, inhibition of airway restriction in response to the NK$_2$ agonist (BANK) showed 19-fold weaker potency (9.3 μmol/kg) when dosed orally at 30 μmol/kg, 2 h prior to agonist challenge (Table 4). The bioavailability of **5** in dog (15%) was essentially equivalent to the bioavailability of **2** and **3**.

Table 6. Comparison of Antagonist Affinity (pK_B) for 3-Cyano-2-naphthamides and 3-Cyano-2-methoxynaphthamides[a]



Entry	R^1	R^2 = H			R^2 = OMe		
			NK_1	NK_2		NK_1	NK_2
1		**2**	8.98±0.17	8.26±0.10	**4**	9.50±0.11[b]	7.50±0.03
2		**3**	8.20±0.08	8.70±0.08	**38b**	nc[c]	7.61±0.10
3		**36c**	8.00±0.10	8.12±0.10	**38c**	nc[c]	7.5±0.04
4		**36d**	8.93±0.24	8.34±0.18	**38d**	nc[c]	7.46±.26
5		**36f**	7.92±0.06	6.84±0.28	**38e**	8.85±0.02	<7
6		**36g**	8.53±0.06	6.92±0.07	**38f**	nc[c]	6.20±0.07
7		**39a**	8.18±0.07	7.86±0.12	**40a**	8.45±0.17	7.92±0.07
8		**39b**	7.60±0.23	8.22±0.31	**40b**	8.14±0.24	8.11±0.05
9		**39c**	7.33±0.07	8.44±0.06	**5**	8.70±0.11	8.20±0.10
10		**39d**	7.51±0.01	7.81±0.05	**40d**	8.55±0.28	7.79±0.05
11		**39e**	7.36±0.04	8.52±0.38	**40e**	7.88±0.11	7.70±0.07

[a] Tissue, rabbit pulmonary artery; $n = 2-6$. NK_1 = ASMSP, and NK_2 agonist = BANK. [b] Compound causes suppression of the maximum response to increasing concentration of agonist (ASMSP); therefore, by definition, it does not behave as a purely competitive antagonist. However, for purposes of comparison, the affinity (pK_B) could be determined at low antagonist concentration (1 nM) where suppression of response was minimal. [c] nc: Not a purely competitive antagonist; therefore, pK_B value could not be determined.[28]

Several compounds in this series exhibit significant NK_3 affinity (Table 3); this is particularly evident for **5** (K_i = 9.4 nM). For this compound, affinity at NK_3 is greater than at NK_2 (K_i = 35 nM). Other groups have also demonstrated structurally related compounds that have high NK_3 affinity. For example, SR142801 is a potent and selective NK_3 antagonist[29] (0.21 nM), which shares a similar structural core to that in the presently described series. Analysis of NK_3 SARs will require further investigation.

Discussion

The identification of the dual NK_1/NK_2 antagonist **2** has been previously described.[16] Although this compound had relatively high affinity and potent in vivo activity, it had low bioavailability in rat and dog (9 and 18%, respectively). To better understand the factors involved in NK_1/NK_2 activity and to develop further improved antagonists, we made a series of modifications to the piperidine and naphthamide regions of structures related to **2**.

Piperidine Aryl Ring Substitutions; Identification of Dual Antagonist 3. For most compounds, additional substitution of the piperidine aryl ring resulted in slightly to substantially reduced affinity (pK_B; rabbit pulmonary artery tissue) at both NK_1 and NK_2 (Table 1). However, the methoxyl-substituted compound **3** was an exception, which maintained good (albeit weaker) NK_1 activity and improved NK_2 activity. This compound and others that maintained good, dual NK_1/NK_2 activity were advanced for in vivo testing in guinea pig (Table 2). Among these analogues, **3** showed the greatest activity following oral dosing. When dosed orally as an NK_1 antagonist, **3** (dr = 8) was weaker than **2** (dr = 33). As an NK_2 antagonist, **3** (dr = 60) was about 3-fold more potent than **2** (dr = 21). Similar to **2**, high binding affinity was observed for **3** with cloned human NK_1 and NK_2 receptors; NK_3 affinity was substantially weaker (Table 3). As shown in Table 4, NK_1 in vivo potency was similar for **3** and **2** (ED_{50} = 1 and 0.6 μmol/kg, respectively), while NK_2 in vivo potency was about 4-fold greater for **3** than **2** (ED_{50} = 3 and 13 μmol/kg, respectively). However, despite this improvement in NK_2 potency, bioavailability of **3** (8% in rat, 18% in dog) was essentially identical to **2**.

Naphthyl Ring Substitutions; Identification of NK_1 Preferential Antagonist 4. In vitro metabolism studies of **2** indicated that a significant degradation pathway was oxidation/glucuronidation of the naphthamide ring. Analogues containing additional substitution of the cyanonaphthamide group were prepared to try to modulate metabolism in this region. In comparison to **2**, most additionally substituted analogues showed similar or reduced affinity at NK_1 and NK_2; however, addition of a 2-methoxy group (**4**) resulted in a substantial increase in NK_1 affinity and a substantial decrease in NK_2 affinity (Table 5). Thus, the effect of adding the naphthyl 2-methoxyl substitution was to alter the balance of NK_1/NK_2 affinity from approximately equivalent (**2** and **3**) to NK_1 preferential (**4**). Compound **4** showed high affinity and selectivity for the cloned human NK_1 receptor (Table 3) and had very potent activity following oral dosing in guinea pig (ED_{50} = 0.07 μmol/kg, Table 4). Furthermore, addition of the methoxyl group resulted in increased bioavailability in dog (51%) as compared to **2** and **3**. Further studies will be needed to determine if the improved bioavailability of **4** resulted directly from blocking naphthalene hydroxylation.

Piperidine Substitutions; Restoration of Dual Activity and of Identification of Antagonist 5. When introduced into aryl-substituted piperidine analogues of **4**, the effect of the naphthyl 2-methoxyl group was seen to be general (Table 6, entries 1−6); that is, NK_1 affinity was increased and NK_2 affinity was decreased. However, for several naphthyl 2-methoxyl analogues (**38b**−**d**,**f**), NK_1 binding was not purely competitive; such compounds were potent antagonists, but pK_B values could not be determined.[28] We had observed that certain nonaryl-substituted piperidines in the 3-cyanonaphthalene series tended to increase NK_2 affinity and decrease NK_1 affinity (unpublished results). With the assumption that the addition of the naphthyl 2-methoxyl group might enhance NK_1 affinity for other analogues (as for **4** vs **2**), we prepared a series of compounds that contained such nonaryl-substituted piperidines (Table 6, entries 7−11). Indeed, addition of the naphthyl 2-methoxyl group tended to increase NK_1 affinity while reducing NK_2 affinity to a smaller extent. The greatest difference was seen between compounds **39c** (an NK_2 preferential antagonist) and **5** (a dual NK_1/NK_2 antagonist; addition of the naphthyl 2-methoxyl group increased NK_1 affinity by 1.4 log units and essentially had no effect on NK_2 affinity (Table 6, entry 9). For compound **5**, binding to human cloned receptors (Table 3) was more NK_1 preferential than observed for the other dual antagonists **2** and **3**. However, compound **5** showed excellent, balanced, dual activity in oral dosing in the guinea pig PMM assay (Table 2), which was greater than that observed for **2** or **3**.

In summary, by trying to improve upon the potency of **2**, we found that subtle alterations in the piperidine and naphthamide regions could lead to substantial changes in affinity for NK_1 and NK_2. By adding a 4-methoxyl group to the aryl piperidine, the resulting compound (**3**) maintained good potency at NK_1 while increasing potency at NK_2. We demonstrated that addition of a naphthyl 2-methoxyl group increased NK_1 activity for a range of piperidine analogues. Therefore, starting from the dual NK_1/NK_2 antagonist **2** and adding a 2-methoxy substituent in the naphthamide region, the resulting compound, **4** (an NK_1 preferential antagonist), had increased NK_1 affinity and decreased NK_2 affinity. Furthermore, by starting from NK_1 preferential compounds based on **4**, NK_2 activity could be restored by complementary modifications in the piperidine region. By combining an NK_2-preferring piperidine with the NK_1-preferring naphthamide, the dual NK_1/NK_2 antagonist **5** was identified.

Experimental Section

Biological Studies. The cloning, heterologous expression, and scale-up growth of MEL cells transfected with either the NK_1, NK_2, or NK_3 receptor were conducted as previously described for the human NK_2 receptor.[30−33] The human NK_1 receptor was identical to that reported previously[34,35] whereas the human NK_3 receptor differed from the genomic sequence at AA439 (Cys vs Phe).[36,37] Ligand binding assays with ASMSP, BANK, and ^{125}I-MPNI and cloned NK_1, NK_2, and NK_3

receptors were conducted as published.[38] Isolated tissue response (pK_B), pulmonary mechanics, and plasma extravasation studies were carried out as previously described.[17] Compound potency in the guinea pig in vivo models (Table 4) was determined 2 h after oral dosing of antagonist and reported as a single ED_{50} value; this was calculated from the dose response obtained from three to six animals at each dose for 4−5 dosing levels over the course of several days; on a given day, the full dose response is not possible; therefore, the doses were staggered for randomness. Full details for the extravasation and mechanics models have been previously described.[17]

For pK_B determinations, different antagonist concentrations were used according to the affinity of the compound under study; concentrations ranged from 10 nM (for the highest affinity antagonists) to 10 mM (for lower affinity antagonists).

Bioavailability Analysis. Compounds were administered to rat ($n = 3$) or dog ($n = 1$) at 1−10 μmol/kg by iv bolus injection or at 10−100 μmol/kg orally as a solution in 75% poly(ethylene glycol) 400 in normal saline. Blood samples were taken via surgically implanted cannula or by venipuncture over a 24 h period, and plasma was analyzed for unchanged compound by liquid chromatography (LC)/mass spectrometry (MS).

Chemistry. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker DPX 300 spectrometer and were referenced to tetramethylsilane (TMS). Mass spectral data were obtained on a Micromass QTOF mass spectrometer. Silica gel chromatography was performed with ICN silica 32−63, 60 Å. Thin-layer chromatography was done on silica gel 60 F-254 (0.25 mm thickness) plates, and visualization was accomplished with UV light. Elemental analyses (C, H, N) were performed on an Exeter Analytical CE-440 elemental analyzer, and all compounds are within 0.4% of theory. All materials were obtained commercially and used without further purification. For compounds containing derivatives of 2-substituted-1-naphthoic acids, ^{1}H NMR spectra and HPLC chromatograms are complex because these compounds exist as a mixture of slowly interconverting conformational isomers (atropisomers). In these cases, ^{1}H NMR integrations are not given.

2-Bromo-5-methoxyphenol (6). To a solution of 3-methoxyphenol (129.03 g) and benzoyl peroxide (1.00 g) in 500 mL of 1,1,1-trichloroethane (TCE) was slowly added a solution of bromine (167.90 g in 150 mL in TCE) over 1 h. During the addition, the reaction flask was irradiated with a GE sunlamp (275 W, 120 V), which caused a gentle reflux to occur. The HBr released was trapped in a beaker containing a solution of 126.02 g of $NaHCO_3$ and 800 mL of water. When the addition of bromine was complete, the reaction mixture was purged with nitrogen for 20 min. The reaction mixture was extracted with saturated $NaHCO_3$ until the pH of the aqueous extract was neutral. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a reddish oil. The crude product was purified by vacuum distillation (150 °C, 150 mTorr) to give 161.78 g (77%) of a viscous liquid. ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3 H), 5.57 (s, 1 H), 6.42 (m, 1 H), 6.60 (d, 1 H, $J = 3.0$), 7.30 (d, 1 H, $J = 9.0$).

2-Bromo-5-methoxy-(*N,N*-dimethylthiocarbamoyloxy)-phenol (7). To a stirred solution **5** (161.78 g) and 1,4-diazabicyclo[2.2.2]octane (180.03 g) in dimethylformamide (DMF) (1 L) was slowly added dimethylthiocarbamoyl chloride (200 g) in four separate portions over 30 min. When the addition was complete, the mixture was stirred overnight (18 h) under a nitrogen atmosphere. At the end of this period, the mixture was poured into distilled water (4 L) with rapid stirring. The precipitated product was collected by filtration and washed with water. The crude product was air-dried for 4 h and crystallized from methanol to give white crystals (139.19 g, 60%). ^{1}H NMR ($CDCl_3$): δ 3.38 (s, 3 H), 3.47 (s, 3 H), 3.79 (s, 3 H), 6.71 (m, 2 H), 7.45 (m, 1 H). MS *m/z* 290 (M^+).

4-Bromo-3-(*N,N*-dimethylcarbamoylthio)methoxybenzene (8). A solution of **7** (139.19 g) and *N,N*-diethylaniline (350 mL) was vacuum-degassed (4 cycles, flask was backfilled with nitrogen) and then heated under reflux under nitrogen for 3.5 h. The resulting brown solution was concentrated (short path distillation) to approximately 100 mL, and the residue was poured into 500 mL of ice cold 6 N HCl with rapid stirring. The mixture was cooled to room temperature, 100 mL of diethyl ether was added, and a heavy precipitate was formed, which was collected by filtration. This tan precipitate (crude product) was briefly air-dried. The filtrate was extracted with diethyl ether. Diethyl ether extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a brownish solid (additional crude product). The crude product was purified by crystallization from methanol to give off-white crystals (82.04 g, 59%). ^{1}H NMR ($CDCl_3$): δ 3.05 (br s, 3 H), 3.12 (br s, 3 H), 3.79 (s, 3 H), 6.82 (dd, 1 H, $J = 8.7$, 3.0), 7.19 (d, 1 H, $J = 3.0$), 7.55 (d, 1 H, $J = 8.7$). MS *m/z* 290 (M^+).

4-Bromo-3-(methylthio)methoxybenzene (9). To a stirred solution of KOH (120.01 g) in 500 mL of methanol was added 82.04 g of **8**. The mixture was heated under reflux under a nitrogen atmosphere for 2 h, then cooled to 0 °C, and neutralized with 400 mL of 6 N HCl. The mixture was cooled to 0 °C and extracted with dichloromethane (DCM). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a light brown liquid. This liquid was dissolved in 600 mL of anhydrous DMF and treated with 80.90 g of anhydrous K_2CO_3. The resulting mixture was stirred for 20 min, and then, 68.40 g of methyl iodide was slowly added over 15 min. The resulting mixture was stirred at room temperature under a nitrogen atmosphere overnight (18 h). At the end of this period, the reaction mixture was poured into 2.8 L of distilled water and extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a pale yellow liquid (65.03 g, 99%). ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3 H), 3.80 (s, 3 H), 6.55 (dd, 1 H, $J = 8.7$, 3.0), 6.66 (d, 1 H, $J = 3.0$), 7.39 (d, 1 H, $J = 8.7$).

4-Hydroxy-4-(4-methoxy-2-methylthiophenyl)-N-Cbz-piperidine (10). Cerium(III) chloride heptahydrate (181.38 g) was heated under high vacuum at 100 °C for 2 days and then at 140 °C for 2 days. This material was transferred to a dry flask equipped with a mechanical stirrer, suspended in 700 mL of anhydrous tetrahydrofuran (THF), and stirred while cooling to −78 °C. A solution of **9** in 500 mL of anhydrous THF was cooled to −78 °C and treated dropwise with *n*-butyllithium (111.5 mL of a 2.5 M solution in hexane) over 1 h. The temperature of the reaction flask was kept below −70 °C during the addition. This mixture was stirred at −78 °C for 1.5 h and transferred via wide bore insulated cannula into the flask containing the stirred suspension of $CeCl_3$ at −78 °C. The resulting peach-colored suspension was stirred for 1.5 h at −78 °C, and then, a solution of 1-benzyloxycarbonyl-4-piperidone (65.10 g in 200 mL of anhydrous THF) was added via cannula over 30 min. When the addition was complete, the reaction mixture was warmed to room temperature and stirred overnight (18 h). At the end of this period, the reaction mixture was quenched with 500 mL of saturated NH_4Cl and stirred for 30 min. The organic layer was decanted, concentrated under reduced pressure, and set aside. The remaining grayish suspension was stirred with 1 L of DCM and filtered through Celite. The Celite filter cake was washed with DCM. All organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a viscous oil, which was purified by chromatography on silica (1:1, ethyl acetate:hexane) to give 85.00 g (79%) of an oil. ^{1}H NMR ($CDCl_3$): δ 1.99 (m, 2 H), 2.12 (m, 2 H), 2.52 (s, 3 H), 3.39 (m, 2 H), 3.81 (s, 3 H), 4.10 (m, 3 H), 5.15 (s, 2 H), 6.71 (dd, 1 H, $J = 8.7$, 2.7), 6.95 (d, 1 H, $J = 2.7$), 7.24 (d, 1 H, $J = 8.7$), 7.37 (m, 5 H). MS *m/e* 387 (M^+).

4-(4-Methoxy-2-methylthiophenyl)-N-Cbz-piperidine (11). To an ice-cooled, rapidly stirred slurry of **10** (50.09 g) in triethylsilane (29.12 g) was slowly added trifluoroacetic acid (29.60 g). When the addition was complete, the mixture was warmed to room temperature and stirred overnight (18 h). At the end of this period, the mixture was poured into 300 mL of

saturated $NaHCO_3$ and extracted with DCM. Extracts were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The product was purified by chromatography on silica (40:1 to 20:1 gradient, DCM:ethyl acetate) to give 42.50 g (89%) of an oil. ^{1}H NMR ($CDCl_3$): δ 1.57 (m, 2 H), 1.83 (d, 2 H, J = 12.3), 2.46 (s, 3 H), 2.91 (m, 2 H), 3.06 (tt, 1 H, J = 12.0, 3.3), 3.80 (s, 3 H), 4.33 (m, 2 H), 5.14 (s, 2 H), 6.68 (dd, 1 H, J = 8.7, 2.4), 6.76 (d, 1 H, J = 2.4), 7.04 (d, 1 H, J = 8.7), 7.36 (m, 5 H). MS *m/z* 394 (M + Na).

4-(4-Methoxy-2-(*S*)-methylsulfinylphenyl)-N-Cbz-piperidine (12). To a 500 mL flask was added 11.56 g of diethyl-D-tartrate, 140 mL of anhydrous DCM, 7.96 g of titanium(IV) isoproproxide, and 0.50 g of water. The pale yellow solution was stirred for 30 min and then treated with 10.78 g of **11** dissolved in 40 mL of DCM. The reaction mixture was then immersed in a water/glycol bath prechilled to −30 °C. After it was stirred for 30 min (bath temperature −36 °C), 5.6 mL of a 6 M solution of *tert*-butylhydroperoxide in nonane was slowly added to the reaction mixture and stirred for 6 days under nitrogen atmosphere (bath temperature −38 °C). At the end of this period, the reaction was quenched with 50 mL of water and stirred vigorously for 1 h while warming to room temperature. The mixture was then treated with 100 mL of 2.5 M NaOH, stirred for an additional 20 min, and filtered through Celite, and the layers were separated. The filter cake was washed with DCM twice, and each portion was used to extract the aqueous layer. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This gave a light yellow oil (7.76 g, 69%), which was purified by chromatography on silica (4:1, ethyl acetate:DCM). ^{1}H NMR ($CDCl_3$): δ 1.62 (m, 2 H), 1.79 (m, 2 H), 2.70 (s, 3 H), 2.86 (m, 3 H), 3.87 (s, 3 H), 4.34 (m, 2 H), 5.16 (s, 2 H), 7.00 (dd, 1 H, J = 8.4, 2.7), 7.18 (d, 1 H, J = 8.4), 7.36 (m, 5 H), 7.52 (d, 1 H, J = 2.7). MS *m/z* 410 (m + Na).

4-(4-Methoxy-2-(*S*)-methylsulfinylphenyl)piperidine (13). To a solution of KOH (1.50 g) in 20 mL of 1:1 ethanol: water was added 1.23 g of **12**. The resulting mixture was heated under reflux under nitrogen atmosphere for 18 h, evaporated, dissolved in 10 mL of water, and extracted with $CHCl_3$. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography on silica (19:1, DCM:methanol with 0.5% aqueous NH_4OH) to give 0.38 g (47%) of white solid. Chiral purity was >99% as determined by chiral HPLC using a Chiral-CBH 150 × 4 mm column (cellobiohydrolase immobilized onto 5 μm silica, Bodman) eluted with 2-propanol at a flow rate of 1.2 mL/min with UV detection at 220 nm. Under these conditions, the desired isomer (*S*) elutes with a retention time of 13.3 min and the alternate isomer (*R*) elutes with a retention time of 5.4 min. ^{1}H NMR ($CDCl_3$): δ 1.69 (m, 2 H), 1.82 (m, 2 H), 2.38 (m, 1 H), 2.70 (s, 3 H), 2.75 (m, 2 H), 3.22 (m, 2 H), 3.88 (s, 3 H), 7.01 (dd, 1 H, J = 8.7, 2.7), 7.28 (d, 1 H, J = 8.7), 7.51 (d, 1 H, J = 2.7). MS *m/z* 254 (M^+).

N-((*S*)-2-(3,4-Dichlorophenyl)-4-(4-(4-methoxy-(*S*)-2-methylsulfinylphenyl)-1-piperidinyl)butyl)-N-methyl-3-cyano-1-naphthamide Fumarate (3). A solution of **13** (0.61 g) in methanol (30 mL) was treated with **14**[16] (1.02 g), and the reaction mixture was acidified to pH 4.0 using acetic acid. Following addition of $NaBH_3CN$ (0.23 g), the reaction mixture was stirred for 18 h. The reaction mixture was then diluted with DCM and washed with 20% potassium carbonate solution. The aqueous layer was extracted with additional DCM, and the combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a foam, which was purified by chromatography. Elution with 9:1 DCM:methanol afforded the product as a foam (1.48 g, 93%). To a flask was added 0.87 g of **3** and 5 mL of absolute ethanol. In a separate flask, 0.15 g of fumaric acid was dissolved in 5 mL of absolute ethanol. Both flasks were heated to reflux with a heat gun, and the fumaric acid solution was added to the solution of **3**. The mixture was allowed to cool and was stirred overnight (18 h) under a N_2 atmosphere and filtered. The solid was washed with cold absolute ethanol and then dried under vacuum for 18 h at 50 °C to give a white solid (0.79 g, 78%). ^{1}H NMR (DMSO-d_6): δ 8.63 (m, 1 H), 8.10 (m, 1 H), 7.90−6.83 (m, 10 H), 6.59 (s, 2 H), 3.81 (s, 3 H), 3.70−2.85 (m, 6 H), 2.82−2.39 (m, 6 H), 2.38−1.42 (m, 11 H). MS *m/z* 662 (M^+); mp 239−243 °C. Anal. calcd for $C_{36}H_{36}N_3O_3SCl_2$, 1 fumaric acid, 0.5 water: C, 61.07; H, 5.25; N, 5.34. Found: C, 60.86; H, 5.27; N, 5.05.

3-Hydroxy-4-iodo-2-naphthoic Acid (16). A mixture of NaOH (2.12 g) in methanol (100 mL) was stirred until the solution was homogeneous. Sodium iodide (3.98 g) and **15** (5.00 g) were added and allowed to stir for 30 min. The resulting suspension was cooled to 0 °C, and a 5.25% (w/v) aqueous solution of sodium hypochlorite was added dropwise, and stirring was continued for 1 h. Saturated sodium thiosulfate (25 mL) was added, and after 5 min, the solution was acidified to pH 2 by addition of 6 N HCl resulting in the formation of a yellow precipitate, which was filtered and washed with water (50 mL). The precipitate was transferred to a round-bottomed flask, dissolved in methanol (70 mL) and toluene (100 mL), concentrated, redissolved in methanol (70 mL), concentrated, redissolved again in methanol (70 mL) and toluene (100 mL), and concentrated to afford the product as a yellow solid (6.26 g, 75%). ^{1}H NMR (DMSO-d_6): δ 12.41 (br s, 1 H), 8.63 (s, 1 H), 8.05−7.97 (m, 2 H), 7.70 (m, 1 H), 7.42 (m, 1 H). MS *m/z* 313 (M − 1).

Methyl 3-Methoxy-4-iodo-2-naphthoate (17). A solution of **16** (8.0 g), dimethyl sulfate (8.03 g), powdered potassium carbonate (8.80 g), and dry acetone (150 mL) was heated under reflux for 18 h. The solution was cooled to room temperature, triethylamine (15 mL) was added, and stirring was continued for 30 min. The solution was filtered through a pad of Celite and washed with dry acetone (50 mL). The filtrate was concentrated to a yellow oil, diluted with ethyl acetate, and washed successively with 1 N HCl (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL). The organic phase was dried (sodium sulfate), filtered, concentrated, and purified by chromatography (0−10% ethyl acetate in hexanes) to afford the product as a yellow oil (5.53 g, 64%). ^{1}H NMR (DMSO-d_6): δ 8.47 (s, 1 H), 8.09 (m, 2 H), 7.74 (m, 1 H), 7.61 (m, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H).

1-Iodo-2-methoxy-3-cyanonaphthalene (18). On the basis of the procedure of Weinreb,[20] **17** (5.0 g) was suspended in xylenes (100 mL) and cooled to 0 °C, dimethylaluminum amide solution (approximately 37 mmol) was added, and the solution was heated under reflux for 2.5 h. The solution was then cooled to 0 °C, and the solution was acidified to pH 2 by addition of 1 N HCl and extracted with ethyl acetate (3 × 100 mL). The combined ethyl acetate extracts were washed with saturated aqueous sodium bicarbonate (150 mL) and brine (150 mL), dried (sodium sulfate), filtered, concentrated, and purified by chromatography (1:1 ethyl acetate:DCM and then 10−20% ethyl acetate in DCM) to afford the product as a white solid (3.29 g, 73%). ^{1}H NMR (DMSO-d_6): δ 8.69 (s, 1 H), 8.24−8.04 (m, 2 H), 7.91−7.81 (m, 1 H), 7.76−7.65 (m, 1 H), 3.99 (s, 3 H). MS *m/z* 311 (M^+).

Methyl 2-Methoxy-3-cyano-1-naphthoate (19). Through a suspension of **18** (0.250 g), $Pd(OAc)_2$ (0.018 g), triethylamine (0.081 g), and methanol (20 mL) was bubbled carbon monoxide for 25 min and then stirred at 70 °C under carbon monoxide (1 atm) for 18 h. The cooled solution was filtered, rinsed with methanol (20 mL) and DCM (20 mL), concentrated, preadsorbed onto silica (1 g), and purified by chromatography (0−10% ethyl acetate in hexanes) to afford the product as a white solid (0.113 g, 59%). ^{1}H NMR (DMSO-d_6): δ 8.78 (s, 1 H), 8.12−8.09 (m, 1 H), 7.84−7.78 (m, 2 H), 7.70−7.63 (m, 1 H), 4.02−4.01 (m, 6 H). IR (cm^{-1}): 2228, 1724, 1296, 1236, 1208, 1017.

2-Methoxy-3-cyano-1-naphthoic Acid (20). A solution of **19** (0.113 g), LiOH (0.0196 g), THF (3 mL), water (1 mL), and methanol (1 mL) was stirred overnight at room temperature. The solution was diluted with saturated sodium bicarbonate and extracted with diethyl ether. The aqueous layer was acidified to pH 2 by addition of 1 N HCl and extracted with diethyl ether. The organic layer was washed with water (30 mL) and brine (40 mL), dried (sodium sulfate), filtered, and

concentrated to a white solid (96 mg, 89%). ^{1}H NMR (DMSO-d_6): δ 14.06 (broad, 1 H), 8.08−8.02 (m, 1 H), 7.83−7.76 (m, 2 H), 7.69−7.63 (m, 1 H), 4.02 (s, 3 H). MS *m*/*z* 226 (M − 1).

N-((*S*)-2-(3,4-Dichlorophenyl)-4-(4-((*S*)-2-methylsulfinylphenyl)-1-piperidinyl)butyl)-N-methyl-2-methoxy-3-cyano-1-naphthamide Citrate (4). A solution of **20** (0.065 g), oxalyl chloride (0.039 g), and DMF (approximately 5 mL) was stirred for 1.5 h and then concentrated to afford 2-methoxy-3-cyano-1-naphthoyl chloride as a white residue, which was used directly. 2-Methoxy-3-cyano-1-naphthoyl chloride (0.065 g) was reacted with **22**[16] (0.136 g), and the free base (0.170 g, 72%) was converted to the citrate salt. ^{1}H NMR (DMSO-d_6): δ 8.71−8.63 (m, 1 H), 8.08−8.00 (m, 1 H), 7.85−7.33 (m, 8.68, 1 H), 7.11−6.85 (m, 0.6 H), 6.31−6.28 (m, 0.47 1 H), 4.57−0.96 (m, 22 H). MS *m*/*z* 662 (M$^+$). Anal. calcd for $C_{36}H_{37}N_3O_3SCl_2$, 1.05 citric acid: C, 58.78; H, 5.29; N, 4.86. Found: C, 58.64; H, 5.28; N, 5.16.

8-Benzyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (24). 1-Benzyl-4-piperidone (100 g) was added in a single portion to a mechanically stirred suspension of ammonium carbonate (488.5 g) and sodium cyanide (70.0 g) in water (700 mL) and ethanol (700 mL). The reaction mixture was stirred at 60 °C for 12 h. The inorganic salts dissolved gradually in the solution, and spirohydantoin crystals formed. After they cooled to room temperature, the solids were collected by filtration, washed with warm water (2 L), recrystallized from 80% ethanol (2 L), washed with ethanol, and dried in a vacuum oven at 50 °C to give the hydantoin (122 g, 89%) as a white solid. NMR (DMSO-d_6): δ 10.64 (bs, l H), 8.45 (broad s, l H), 7.29 (m, 5 H), 3.48 (s, 2 H), 2.69 (m, 2 H), 2.28 (m, 2 H), 1.81 (m, 2 H), 1.51 (m, 2 H). MS *m*/*z* 260 (M$^+$).

4-Amino-1-benzyl-4-carboxypiperidine (25). A stirred solution of **24** (40.0 g) and lithium hydroxide monohydrate (32.4 g) in water (500 mL) was heated under reflux for 40 h. The mixture was cooled to room temperature and filtered to remove a white precipitate, and the filtrate was evaporated. The pH of the concentrate was adjusted from 12 to 5 with concentrated hydrochloric acid, and the solution was evaporated to dryness. The residue was suspended in methanol to provide a white precipitate that was filtered, washed with methanol, and air-dried to give the product (32.7 g, 66%) as a white solid. NMR (DMSO-d_6): δ 4.00 (m, 5 H), 3.89 (m, 2 H), 2.92 (m, 4 H), 2.12 (m, 2 H), 1.84 (m, 2 H). MS *m*/*z* 235 (M$^+$).

4-Amino-1-benzyl-4-ethoxycarbonylpiperidine (26). Thionyl chloride (43.0 mL) was added dropwise to a suspension of **25** (23.0 g) in ethanol (400 mL) at 0 °C to give a clear solution. The reaction mixture was warmed to room temperature, heated under reflux for 5 h, and stirred overnight at room temperature. The mixture was concentrated, redissolved in toluene, and concentrated again. The resulting oil was dissolved in water, adjusted to pH 3 with 1 N sodium hydroxide, neutralized with saturated aqueous sodium bicarbonate, and extracted with DCM. The organic extracts were dried and evaporated to give the product (21.5 g, 84%) as an oil. NMR ($CDCl_3$): δ 7.28 (m, 5 H), 4.17 (q, 2 H, *J* = 7.1), 3.52 (s, 2 H), 2.50 (m, 4 H), 2.13 (m, 2 H), 1.54 (m, 4 H), 1.27 (t, 3 H, *J* = 7.1). MS *m*/*z* 263 (M$^+$).

1-Benzyl-4-(5-chlorovaleramido)-4-ethoxycarbonylpiperidine (27). 5-Chlorovaleryl chloride (13.2 g) in DCM (50 mL) was added dropwise to a solution of **26** (20.3 g) and pyridine (13.1 mL) in DCM (250 mL) at 0 °C, resulting in the formation of a thick slurry within 20 min. After it was warmed to room temperature and stirred overnight, the slurry was diluted with aqueous sodium bicarbonate to give a clear, biphasic solution, which was extracted with DCM. The organic extracts were dried ($MgSO_4$) and evaporated to a light brown semisolid. Ether was added, and the mixture was filtered to give the product (16.8 g, 57%) as a white solid. ^{1}H NMR (CD_3-OD): δ 7.28 (m, 5 H), 4.11 (q, 2H, *J* = 7.1), 3.55 (m, 4 H), 2.68 (m, 2 H), 2.26 (m, 4 H), 2.05 (m, 4 H), 1.75 (m, 4 H), 1.21 (t, 3H, *J* = 7.1). MS *m*/*z* 381 (M$^+$).

1-Benzyl-4-ethoxycarbonyl-4-(2-oxopiperidino)piperidine (28). A solution **27** (16.8 g) in THF (50 mL) was transferred by cannula into a suspension of sodium hydride (2.1 g) in THF (150 mL). After it was stirred overnight, the reaction mixture was quenched with water, concentrated (to remove THF), diluted with water, and extracted with DCM. The combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography using DCM:methanol (gradient 97:3, 95:5) to give the product (13.2 g, 87%) as a solid. NMR (CD_3OD): δ 7.30 (m, 5 H), 4.11 (q, 2 H, *J* = 7.1), 3.54 (s, 2 H), 3.44 (m, 2 H), 2.66 (m, 2 H), 2.52 (m, 2 H), 2.32 (m, 2 H), 2.20 (m, 2 H), 2.01 (m, 2 H), 1.85 (m, 2 H), 1.74 (m, 2 H), 1.20 (t, 3 H, *J* = 7.1). MS *m*/*z* 345 (M$^+$).

4-Ethoxycarbonyl-4-(2-oxopiperidino)piperidine (29). A solution of **27** (12.4 g) and 20% palladium hydroxide on carbon (2.0 g) in ethanol (150 mL) was stirred overnight under hydrogen (1 atm). The reaction mixture was filtered through diatomaceous earth, and the filtrate was evaporated to give the product (9.1 g, 99%) as a viscous oil. NMR (CD_3OD): δ 4.13 (q, 2 H, *J* = 7.1), 3.44 (m, 2 H), 2.95 (m, 4 H), 2.32 (m, 2 H), 2.19 (m, 2 H), 1.88 (m, 4 H), 1.74 (m, 2 H), 1.23 (t, 3 H, *J* = 7.1). MS *m*/*z* 255 (M$^+$).

1-Benzyloxycarbonyl-4-(ethoxycarbonyl)-4-(2-oxopiperidino)piperidine (30). A solution of **29** (9.0 g) in DCM (25 mL) was added to a solution of N-(benzyloxy-carbonyloxy)-succinimide (8.8 g) and triethylamine (5.4 mL) in DCM (150 mL). After 1.5 h, the reaction mixture was washed successively with 1.0 N hydrochloric acid and saturated aqueous sodium bicarbonate. The separated organic layer was dried and evaporated to give the title compound (11.6 g, 86%) as a light yellow solid. NMR ($CDCl_3$): δ 7.37 (m, 5 H), 5.16 (s, 2 H), 4.28 (q, 2 H, *J* = 7.1), 4.09 (m, 2 H), 3.40 (m, 2 H), 3.28 (m, 2 H), 2.53 (m, 2 H), 2.34 (m, 2 H), 1.83 (m, 6 H), 1.30 (t, 3 H, *J* = 7.1). MS *m*/*z* 389 (M$^+$).

1-Benzyloxycarbonyl-4-carboxy-4-(2-oxopiperidino)piperidine (31). A solution of **30** (11.4 g) in THF (150 mL) and 1.0 N sodium hydroxide (50 mL) was heated under reflux for 10 h. The reaction mixture was evaporated, and the resulting aqueous solution was diluted with water and extracted with DCM to recover unreacted starting material (3.7 g). The aqueous phase was acidified to pH 3 with 1.0 N hydrochloric acid and extracted with DCM. The combined organic extracts were washed with water, dried, and evaporated to afford a light yellow solid. The material was suspended in ether and filtered to give the title compound (6.3 g, 88% based on reacted starting material) as a white solid. NMR ($CDC1_3$): δ 7.37 (m, 5 H), 5.17 (s, 2 H), 4.11 (m, 2 H), 3.45−3.32 (m, 4 H), 2.55 (m, 2 H), 2.37 (m, 2 H), 1.94−1.78 (m, 6 H). MS *m*/*z* 361 (H$^+$).

1-Benzyloxycarbonyl-4-methylaminocarbonyl-4-(2-oxopiperidino)piperidine (32). To a solution of **31** (45.0 g) in DCM was added methylamine hydrochloride (9.7 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (27.8 g), and then 4-(dimethylamino)pyridine (17.7 g). After it was stirred overnight, the mixture was washed with 1 N HCl (2 × 250 mL), 1 N NaOH (250 mL), and brine (250 mL), dried ($MgSO_4$), filtered, and concentrated. This material was purified by flash chromatography (gradient elution using 1−5% methanol in DCM) to afford the product as a dry, light pink foam (36.5 g, 80%). NMR: δ 7.35 (m, 5 H), 6.72 (m, l H), 5.12 (s, 2 H), 3.56 (m, 4 H), 3.30 (m, 2 H), 2.78 (d, 3H, *J* = 4.8), 2.43 (m, 2 H), 2.27 (m, 2 H), 2.20 (m, 2 H), 1.76 (m, 4 H).

4-Methylaminocarbonyl-4-(2-oxopiperidino)piperidine (23). A solution of **32** (6.1 g) and 20% palladium hydroxide on carbon (0.60 g) in ethanol (70 mL) was stirred overnight, filtered through Celite, and then concentrated under reduced pressure to afford the product as a viscous gum (3.9 g, 99%), which was used without purification.

N-[2-(*S*)-(3,4-Dichlorophenyl)-4-hydroxybutyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide (34). A solution of **33**[21] (5.51 g, 22.20 mmol) in DCM (175 mL) was combined with 10% aqueous sodium bicarbonate solution (100 mL). The mixture was cooled to 0 °C, and a solution of **21** (5.4 g, 22.20 mmol) in DCM (25 mL) was added dropwise over 30 min. After it was stirred overnight at room temperature, water was added to the reaction mixture and the organic phase was separated, dried ($MgSO_4$), and purified by chromatography (3% isopropyl alcohol in DCM) to afford the product as a white solid (9.3 g,

91%). ^{1}H NMR (DMSO-d_6): δ 8.67−8.58 (m), 8.07−8.02 (m), 7.72−7.65 (m), 7.64−7.43 (m), 7.37−7.34 (m), 7.02−7.01 (m), 6.98−6.87 (m), 6.77−6.74 (m), 6.31−6.28 (d, J = 9), 4.55−4.52 (m), 4.35−4.34 (m), 4.03−3.92 (m), 4.03−3.92 (m), 3.78−3.72 (m), 3.68 (s, 3H), 3.45−3.37 (m), 3.29−2.89 (m), 2.73 (s 3H), 2.59−2.49 (m), 1.91−1.78 (m), 1.58−1.46 (m). MS m/z = 457 (M^+).

N-[2-(*S*)-(3,4-Dichlorophenyl)-4-oxobutyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide (35). Compound **34** (5.69 g, 12.45 mmol) was oxidized using oxalyl chloride (2.17 mL) and DMSO (3.53 mL) and Et_3N (7.0 mL) in DCM (200 mL) using typical Swern conditions[22] to afford the aldehyde (5.0 g, 88%) after column chromatography (5% methanol and DCM). ^{1}H NMR (DMSO-d_6): δ 9.70−9.64 (ap m), 8.67−8.57 (ap m), 8.07−7.97 (m), 7.80 (s 1H), 7.72−7.55 (m), 7.52−7.48 (m), 7.40−7.33 (m), 7.12−7.02 (m), 6.87−6.83 (m), 6.37−6.34 (d, J = 9), 4.53−4.44 (m), 4.11−4.00 (m), 3.94−3.92 (m), 3.91−3.73 (m), 3.71 (s, 3H), 3.45−3.38 (m), 3.14 (s), 2.97−2.95 (d, J = 6), 2.63 (s, 3H), 2.60−2.49 (m). MS m/z 455 (M^+).

N-((*S*)-2-(3,4-Dichlorophenyl)-4-(4-(2-oxo-1-piperidinyl)-4-(N-methylaminocarbonyl))-1-piperidinyl)butyl)-N-methyl-3-cyano-2-methoxy-1-naphthamide (5). Compound **23** (0.52 g, 2.19 mmol) and compound **35** (1.0 g, 2.19 mmol) were dissolved in methanol (10 mL) and stirred for 15 min, and then, acetic acid (0.5 mL) was added. The reaction mixture was allowed to stir for 1 h. Next, $NaBH_3CN$ (0.21 g) was added and the reaction was allowed to stir overnight. The reaction was quenched with aqueous $NaHCO_3$ and extracted with DCM, washed with brine, dried ($MgSO_4$), and purified by chromatography (5% methanol in DCM) to give the title compound (740 mg, 50%) as a solid, which was converted to the citrate salt by combining with 1 equiv of citric acid in methanol and then concentrated and dried under reduced pressure. ^{1}H NMR (DMSO-d_6): δ 8.70−8.63 (m), 8.08−7.91 (m), 7.77−7.72 (m), 7.68 (s), 7.66−7.61 (m), 7.58−7.54 (m), 7.49−7.47 (m), 7.39−7.33 (m), 7.06−7.03 (m), 6.88−6.79 (m), 6.32−6.29 (d J = 9), 4.55−4.47 (m), 4.12−3.99 (m), 3.92−3.88 (m), 3.82−3.77 (m), 3.69 (s, 3H), 3.46−3.30 (m), 3.17−3.06 (m), 2.99−2.72 (m), 2.65−2.56 (m), 2.22−2.10 (m), 1.79−1.77 (m), 1.67−1.63 (m). MS m/z 678 (M^+). Anal. calcd for $C_{36}H_{41}N_5O_4Cl_2$, 1 citric acid, 1.34 water: C, 56.36; H, 5.82; N, 7.82. Found: C, 56.34; H, 5.73; N, 7.80. Data from ^{1}H NMR spectroscopy and HPLC indicated that the product existed as a mixture of atropisomers.

Supporting Information Available: Experimental details for the synthesis of **36a−k**, **37a−g**, **38b−f**, **39a−e**, and **40a−e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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