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Bioorganic & Medicinal Chemistry 12 (2004) 2653–2669
Bioorganic & Medicinal Chemistry

Naphtho[2,1-*b*][1,5] and [1,2-*f*][1,4]oxazocines as selective NK_1 antagonists

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Received 7 January 2004; revised 19 February 2004; accepted 8 March 2004

Available online 2 April 2004

Abstract—Previously we reported on the synthesis and properties of a series of highly potent piperidinyl 2-subsituted-3-cyano-1-naphthamide NK_1 antagonists that includes **3** and **4**. Here we report our efforts to alleviate a troublesome atropisomeric property of those derivatives by introduction of a tethering bridge that, in addition, could be used to lock the resulting cyclic derivatives in a purported NK_1 pharmacophore conformation. Using **3** as a starting point, the naphtho[2,1-*b*][1,5]oxazocine, **17**, was found to contain the optimal ring tether size (8) for retaining NK_1 activity, was more NK_1 versus NK_2 selective, and reduced the number of atropisomers from four to two. Cyclic derivatives **29** and **32**, which exist as essentially single atropisomers in the purported pharmacophore conformation, were prepared in the closely related naphtho[1,2-*f*][1,4]oxazocine series as part of an effort to use mono methyl substitution of the tethering bridge as a conformation stabilizing factor. Both **29** and **32** were found to be less active as NK_1 antagonists than the non-methylated parent **28** possibly due to methyl group destabilization of receptor interaction. We discuss the above findings in the context of a previously proposed NK_1 pharmacophore model and present a further refinement of that model.

1. Introduction

The term 'tachykinin' refers to a family of structurally related mammalian neuropeptides[1] sharing a common C-terminus of Phe-X-Gly-Leu-Met-NH_2. While it has long been held that human tachykinins were limited to only three [substance P (SP), neurokinin A (NKA), and neurokinin B (NKB)] it should be noted that there has been a recent report on the discovery of four additional human tachykinins [named endokinins (EK)A-D to reflect peripheral endocrine roles].[2] SP, NKA, and NKB are endogenous ligands at G protein-coupled receptors of the rhodopsin-like family named NK_1, NK_2, and NK_3, respectively. The three mammalian tachykinins are thought to be involved in numerous physiological functions and have been linked from animal studies to diseases and conditions such as asthma and COPD, inflammatory bowel disorders, inflammatory pain, cough, urinary disorders, and anxiety.[3–9] Early clinical studies with selective and mixed tachykinin antagonists were conducted in those medical areas where the individual or combined neuropeptide antagonists were anticipated to be useful. However the outcome of these clinical studies were often disappointing.[10–16] Recent evidence indicates that tachykinin antagonists are likely to find application in conditions that lack an overt inflammatory component such as emesis, depression/anxiety, and urinary incontinence.[17–21] Indeed, an NK_1 antagonist, Emend (aprepitant), is now available to prevent and control nausea and vomiting caused by chemotherapy treatment.[22]

Our interest in the tachykinin area began with a program aimed at selective NK_2 antagonists for use in

Keywords: Tachykinin; NK1; Atropisomers; Antagonist.
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doi:10.1016/j.bmc.2004.03.015

asthma,[23] progressed through a search for mixed NK_1/NK_2 antagonists, also primarily aimed at asthma,[24,25] and most recently to a search for an NK_1 selective antagonist aimed at depression.[26] This selectivity progression is notable in that it was accomplished largely by variation of the aryl amide moiety of a conserved core structure (Fig. 1). Within this structural family, key aspects that influence NK_1 and NK_2 affinity or selectivity have been described in prior reports. Briefly, the following observations were made; (1) the aryl amide orientation is important,[23] the s-*cis* isomer favors NK_2 and the s-*trans* isomer favors NK_1; (2) the nature of the substitution in the 'western region' is important for NK_2 binding, while changes are more broadly tolerated for NK_1 binding;[27] and (3) the balance of NK_1/NK_2 selectivity can be modulated by substitution at the naphthamide 2-position.[28]

From these observations, a detailed NK_1 pharmacophore model was proposed, and we identified the potent, orally active NK_1 antagonist **3**.[28] This compound existed as a mixture of four resolvable atropisomers (slowly interconverting conformational isomers). Unfortunately, this atropisomeric property leads to substantial complications in its further development as a drug. Subsequent efforts focused on modulating the rate of atropisomer interconversion and led to the identification of **4**,[26] which had a significantly slower interconversion rate. However, we sought to eliminate all atropisomeric properties.

This report describes our efforts to eliminate atropisomeric properties of compounds related to **2** and **3** by adding a rigidifying tether. Based on structure–activity relationships (SAR), modeling, and crystallographic studies, a detailed pharmacophore model was proposed for the NK_1 binding of **3**.[26] As shown in Figure 2, the pharmacophore model involves a *trans* arrangement of

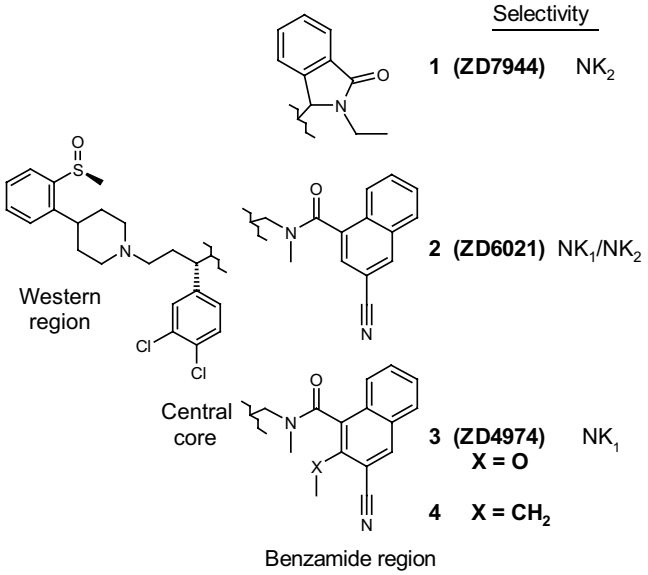


Figure 1. Changes in the benzamide region of the molecule allow a range of NK_1 and NK_2 selectivity.

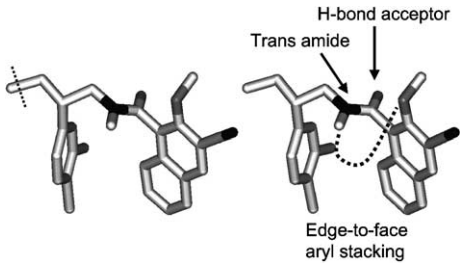


Figure 2. Pharmacophore model showing the dichloroaryl and naphthamide regions in **3**. Tethering linkage is shown as a dotted line. Relaxed-eye stereoview, hydrogens omitted for clarity.

the amide carbonyl, the positioning of the amide carbonyl as a hydrogen bond acceptor, and an aryl–aryl stacking interaction. Based on this model it seemed possible that cyclization between the amide methyl and naphthalene-2-moiety would enforce the desired conformation. This has led to the development of a series of new, potent, non-atropisomeric NK_1 antagonists and to the further refinement of our pharmacophore model.

2. Chemical synthesis

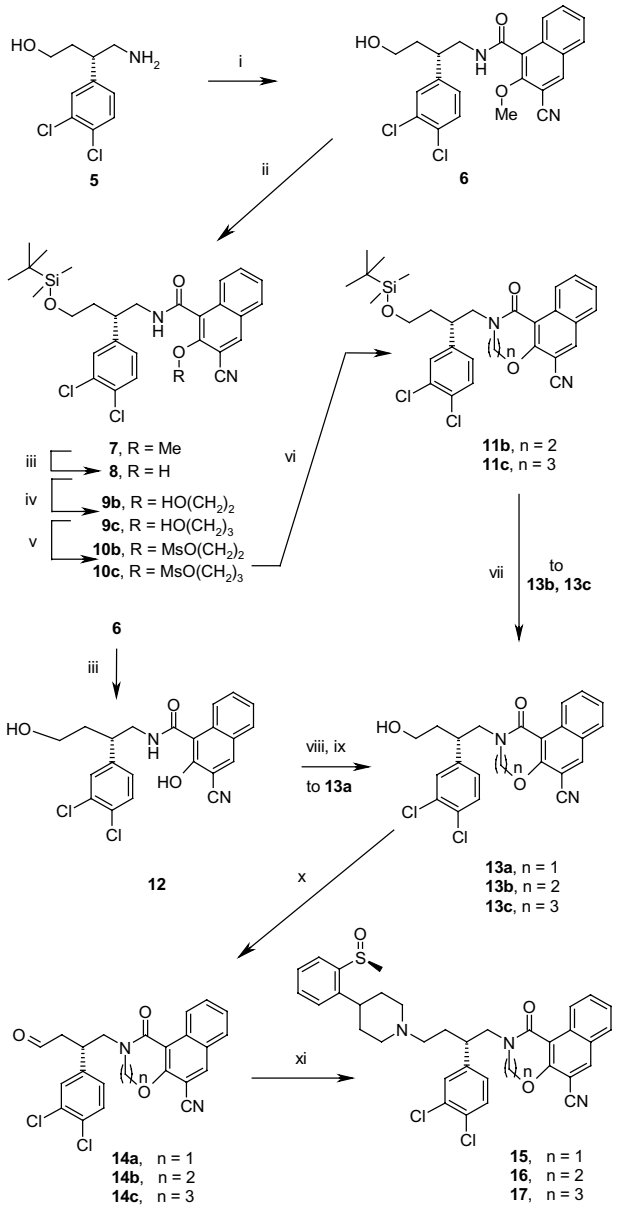
The cyclics used in the 'ring sizing' study were prepared as indicated in Scheme 1. The six-membered ring system was prepared by analogy to a literature method used in the synthesis of 2,3-dihydro-4H-1,3-benzoxazin-4-ones.[29] The seven- and eight-membered rings (**11b** and **11c**) were formed in good yields (71% and 54%, respectively) by the action of sodium hydride on the corresponding mesylates **10b** and **10c**.

The 1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]-oxazocines were prepared as indicated in Scheme 2. In this series, a BOP-Cl facilitated amide ring closure strategy proved to be most synthetically efficient. The ring closure yields in the preparation of **25a–e** varied from 36% to 62%.

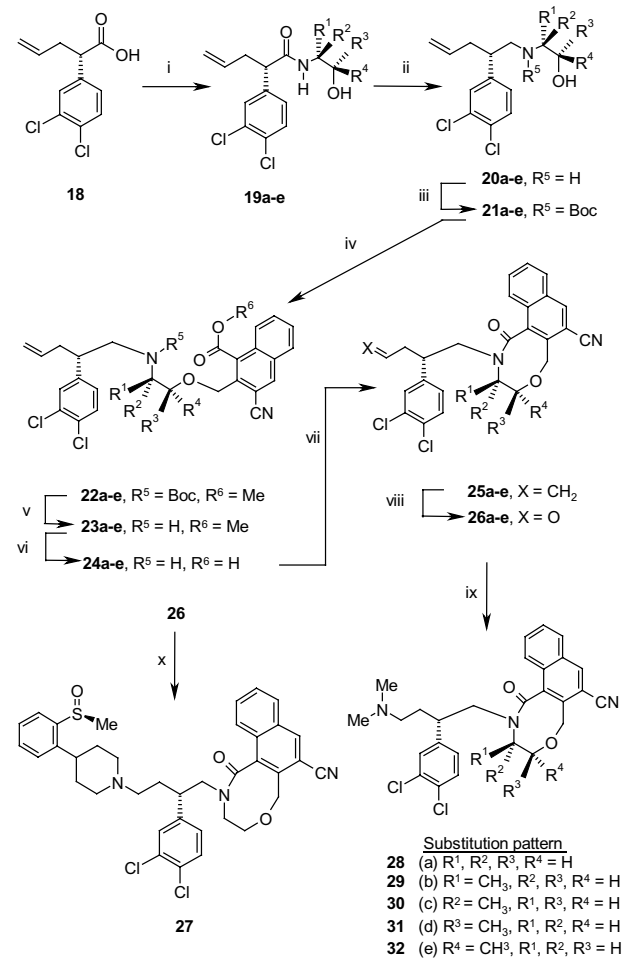
3. Results and discussion

3.1. Determination of appropriate ring size for the cyclizing tether

To eliminate atropisomeric properties we used **3** as a starting point and surveyed six-, seven-, and eight-membered rings to find the optimal length for a tethering group to bridge between the amide *N*-methyl and the naphthalene 2-position (Fig. 3). Based on prior work[26] our pharmacophore model involved the following features; (1) a nearly orthogonal arrangement of the amide and naphthalene ring, (2) an aryl–aryl stacking interaction between the dichloroaryl and naphthalene rings, and (3) a *trans* amide bond that positions the amide carbonyl to act as a hydrogen bonding acceptor. We anticipated that the seven and/or eight-membered ring tether could be acceptable.



Scheme 1. (i) 3-Cyano-2-methoxy-1-naphthoyl chloride, NaOH, CH_2Cl_2; (ii) *t*BuMe$_2$SiCl, DMAP, Et_3N, CH_2Cl_2; (iii) MgI_2, benzene; H_2O; (iv) $Cl(CH_2)_{2\text{-}3}OH$, DMF, K_2CO_3; (v) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (vi) NaH, THF; (vii) 5% HF/MeCN; (viii) trioxane, HOAc, H_2SO_4, CH_2Cl_2; (ix) 1 N NaOH, THF, MeOH, (x) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (xi) 4-[(*S*)-2-methylsulfinylphenyl]piperidine, $NaBH_4$, HOAc, MeOH.



Scheme 2. (i) iPr$_2$EtN, $H_2NCR^1R^2CR^3R^4OH$, DMAP, $Me_2NCH_2CH_2CH_2N{=}C{=}NEt{\cdot}HCl$; (ii) $LiAlH_4$, Et_2O; (iii) $O(CO_2t\text{-}Bu)_2$, Na_2CO_3, dioxane/H_2O; (iv) NaH, methyl 2-(bromomethyl)-3-cyano-1-naphthoate, **33**, DMF, THF; (v) TFA, CH_2Cl_2; (vi) pyridine hydrochloride, 180 °C; (vii) BOP-Cl, iPr$_2$EtN, MeCN, (viii) O_3, CH_2Cl_2, −78 °C, Me_2S; (ix) $Me_2NH{\cdot}HCl$, HOAc, $NaBH_3CN$, MeOH; (x) 4-[(*S*)-2-methylsulfinylphenyl]piperidine, HOAc, $NaBH_3CN$, MeOH.

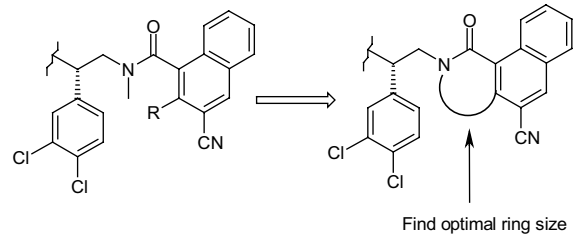
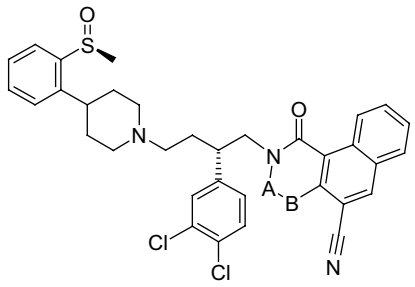


Figure 3. Schematic representation of tether addition.

The tethering rings did have a marked effect on the conformational properties. Whereas **3** existed as a mixture of four atropisomers (readily apparent by NMR and HPLC), the eight-membered ring **17** exists as mixtures of two atropisomers, while the seven- and six-membered rings, **16** and **15**, respectively, appeared (NMR and HPLC) to exist in only a single conformation.

To evaluate NK_1 antagonist activity, the cyclic ethers **15**–**17** were compared to the acyclic ether **3** in three biological assays.[26] The cyclized compounds had significantly greater binding affinity for the cloned human NK_1 receptor than for the NK_2 receptor (Table 1). This was anticipated since cyclization locks the amide in the *trans* configuration, and thus they cannot adopt the *cis*-amide configuration that appears necessary for activity at the NK_2 receptor.[23] Within the cyclics the NK_1 binding affinity was similar for the seven- and eight-membered rings, and significantly weaker for the six-membered ring.

Table 1. Effect of ring size on biological activity



Compound	A-B (ring size)	Binding	pK_i	RPA	GFT
		NK_1[a]	NK_2[b]	pK_b[c]	% inhib[d]
3	See Figure 1	9.50 ± 0.11	7.50 ± 0.03	22%[e]	93 ± 4
15	CH_2O (6)	8.68[f]	ND	6.32 ± 0.44	ND
16	CH_2CH_2O (7)	10.28[g]	6.42[g]	8.71 ± 0.10[h]	3 ± 1
17	$CH_2CH_2CH_2O$ (8)	9.96[g]	6.10[g]	34%[e]	2 ± 1
27	$CH_2CH_2OCH_2$ (8)	9.94[f]	ND	26%[e]	5 ± 2

ND = Not determined.

[a] hNK_1-MEL, ligand = ^{3}H-SP.

[b] hNK_2-MEL, ligand = ^{3}H-NKA.

[c] pK_b of **15** determined at 1 μM; **16** at 0.1 μM.

[d] Inhibition of ASMSP-induced foot tapping response in gerbil; determined 4 h after oral dosing of antagonist at 10 μmol/kg; initiated by CNS administration of ASMSP (100 pmol). Greater values indicate greater activity.

[e] Because these compounds displayed uncompetitive antagonism, potency is evaluated by monitoring the magnitude of the maximum tissue relaxation response (control response; ±5%); lower values indicate greater activity. Agonist: ASMSP, antagonist concentration: 10 nM.

[f] $n = 2$.

[g] $n = 1$.

[h] Compound causes a 56% suppression of the maximum tissue relaxation response (ASMSP 1 μM) therefore, by definition, it does not behave as a purely competitive antagonist. However, the affinity (pK_b) for this compound could be determined at a 0.1 μM antagonist concentration where suppression of the response was minimal.

In the in vitro rabbit pulmonary artery (RPA) assay, only the activity seen with the eight-membered ring compound **17** approached the potency of the acyclic **3.** As was noted in the earlier publication[26] the more potent NK_1 antagonists of this series induce a suppression of the maximal response to the selective NK_1 agonist Ac-[Arg(6), Sar(9), Met(O-2)(11)] Substance P(6-11) (ASMSP). This behavior was suggested to be associated with noncompetitive or partially competitive antagonism. A low concentration of **16** allowed a pK_b determination for that compound. With **3** and **17** a pK_b could not be determined, however the relative antagonist activity of the compounds could be estimated by recording the maximum tissue relaxation response to increasing agonist concentration following incubation of the tissue with antagonist at 10 nM. A smaller number (smaller percent of control, i.e. response in the absence of antagonist) is indicative of higher antagonist affinity. Thus **17** is seen as less active than **3** in the RPA screen.

An intracerebroventricular (icv) injection of ASMSP to gerbil induces a foot tapping response that can be attenuated by prior treatment with a CNS-penetrant NK_1 antagonist. This can provide a convenient way to assess CNS antagonist potency.[30] Despite the high affinity of **16**, and **17** (Table 1) these compounds were inactive in the GFT (gerbil foot tap) model (as is a similarly substituted close analog **27**, see text below). It was not clear if this is due to metabolism or distribution. In part to address this, we attempted to improve CNS distribution by reducing molecular weight. These efforts are also described below.

3.2. Elimination of atropisomeric properties by stereospecific substitution of the eight-membered ring system; structural and biological effects

By further optimizing the tethering ring, we hoped to stabilize the putative NK_1 active conformation in order to improve activity and completely eliminate atropisomeric properties. We speculated that it should be possible to stabilize and rigidify the conformation necessary for NK_1 receptor activity (relative to other possible eight-membered ring conformers) by stereospecific addition of a methyl group to one of the ring methylenes. Such an approach has been successfully demonstrated for a structurally unrelated series of cyclic NK_1 antagonists.[31] Additional study in the **17** series is hindered synthetically by the lack of an appropriate chiral pool of precursors. By moving the ether oxygen position in the eight-membered ring of **17**, the resulting ring system (i.e. **27**) was readily amenable to stereoselective methyl substitution at each of the positions in the ethyl portion of the ring. It was demonstrated that biological activity was maintained after reversal of the methylene and ether oxygen in the ring; NK_1 antagonist affinity and atropisomeric properties are very similar for **17** and

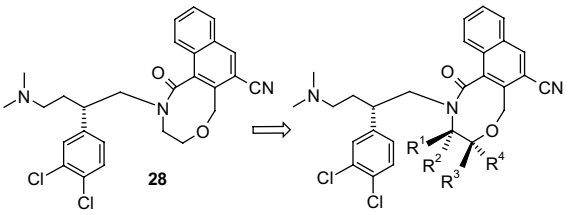


Figure 4. Left: compound **28** lacks the piperidine substitution found in **27** and acyclic analogs **3** and **4**. Right: methyl substitution at each of the sites in the aminoethanol region (R^1–R^4) was explored.

27 [both exist as a mixture of two atropisomers of ratio 6:4 (NMR, HPLC)]. Since compounds **17** and **27** had similar biological activity, either could have served as a starting point for further elaboration, however; we chose to focus on the ring system from **27** because synthesis of such analogs was more direct.

In a separate report, we describe that removal of the piperidine region from acyclic compounds related to **3** leads to markedly reduced NK_2 affinity, and retention of NK_1 affinity.[27] This was also observed for the current cyclic series where replacement of the aryl piperidine in **27** with a simple dimethyl amine group led to compound **28** (Fig. 4) with equivalent NK_1 binding affinity (both $pK_i = 9.9$). Compound **28** was thus used as the template in our effort to stabilize the active NK_1 conformation by ring methylation.

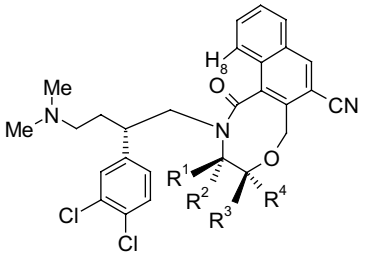
Individual substitution at each of the sites in the aminoethanol region (Fig. 4) was explored as a means to stabilize the bioactive ring conformation. Such substitution altered both the NK_1 affinity and atropisomeric properties (Table 2). The unsubstituted analog **28** displays the best NK_1 binding affinity and potency in the gerbil foot tap (GFT) in vivo assay. However, solutions of this compound exist as a mixture of two atropisomers in a ratio of approximately 7:3 (HPLC). NMR analysis of this mixture showed two signals for the naphthyl H^8 proton in approximately the same 7:3 ratio (Table 2, Fig. 5). The NMR signal corresponding to the minor component (7.3 ppm) was in the normal region expected. However, the H^8 NMR signal corresponding to the major component had a chemical shift of 6.6 ppm, which was atypically upfield shifted. Similarly upfield shifted H^8 signals had been previously noted in the **3** atropisomer mixture and with the NK_1 preferring isomer of **4**.[27]

One possible explanation for the unusually upfield-shifted signal is that the conformation of the major component adopts an edge-to-face aryl–aryl folded geometry that places the H^8 proton into the shielding cone of the dichloroaryl ring. Such a folded geometry has been hypothesized for structurally distinct NK_1 antagonists[32–37] and has been identified by molecular modeling as being a critical part of the NK_1 pharmacophore in the acyclic series.[26]

Positioning of the ring methyl substituent in **28** substantially altered the conformational equilibrium among the atropisomers. For example, **29** (Table 2) exists predominantly in a conformation that affords the NMR upfield shifted naphthalene H^8, while inversion of the stereochemistry (affording **30**) appears to reverse the conformational bias.

Among the series of regioisomers, compound **32** had the best combination of in vivo potency and conformational properties (only a single conformational form was detected by HPLC and NMR). It is evident that there is no direct correlation between the atropisomer distribution and antagonist potency. For example, **29** and **32** appear to exist in the (putatively desired) folded conformation as suggested from NMR (δ $H^8 = 6.3$ and 6.7 ppm, respectively); however, they differ significantly when tested in the GFT model. Addition of the methyl substitution at any of the four positions moderately reduces antagonist activity relative to **28**. Therefore, we speculate that while methyl substitution can serve to stabilize

Table 2. Activity and atropisomers distribution of mono-methyl substituted **28** analogs



Compound	Methyl position	RPA pK_b	GFT[a] % inhibition	H^8 Shifted:unshifted[b]
28	None	9.10 ± 0.03	38 ± 11	68:32
29	R^1	8.63 ± 0.13	3 ± 1	>98:2
30	R^2	8.64 ± 0.09	8 ± 3	10:90
31	R^3	8.29 ± 0.15	23 ± 13	31:68
32	R^4	8.34 ± 0.02	63 ± 23	>98:2

[a] % Inhibition, 30 μM/kg, 4 h post dose, [ASMSP] = 100 pmol.
[b] NMR integration % atropisomer with H^8 shifted upfield: % atropisomers with H^8 unshifted.

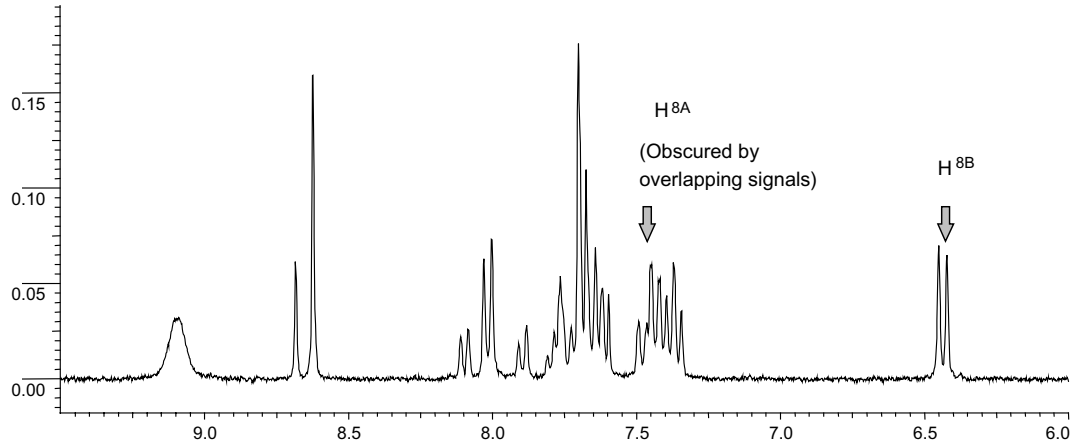


Figure 5. NMR spectrum of the equilibrium mixture of **28** indicating position of H^8 in the two atropisomeric forms.

the bioactive conformation of the ring system it also adds destabilizing interactions with the receptor. As a consequence, we regard **32** as an improved compound for structural reasons, but sub-optimal as an NK_1 antagonist.

3.3. Pharmacophore model

Conformational features of the eight-membered ring system were investigated by molecular modeling to better understand the factors responsible for the observed atropisomeric properties. For compound **28** two discrete low energy conformers were identified, which were consistent with the population distribution and spectral properties that were experimentally observed.

Shown in Figure 6 are the two predicted low energy conformers for the core region of **32**. In conformation 'A', the phenyl and naphthyl groups are oriented with an edge-to-face stacking interaction. Such a conformation would place the naphthalene H^8 into the shielding zone of the phenyl ring. This is consistent with the previously presented NMR spectral data that show an upfield shift of about 1 ppm for the H^8 proton. In conformation 'B', the orientation of the eight-membered ring positions the naphthalene away from the face of the phenyl ring such that a stacking interaction is no longer possible. This is further consistent with NMR spectroscopy of the less active component, which shows the naphthalene H^8 in the expected, nonshifted region. Modeling of **32** predicted that conformation A would be favored by 3 kcal/mol. The remaining compounds (**28**–**31**) showed essentially the same preferred conformations, but with different associated energies. Taken together, these modeling data, which are consistent with experimental results, suggest a detailed model for the NK_1 pharmacophore; the key elements of which are the aryl–aryl folded geometry and the positioning of the amide carbonyl as a hydrogen bond acceptor.

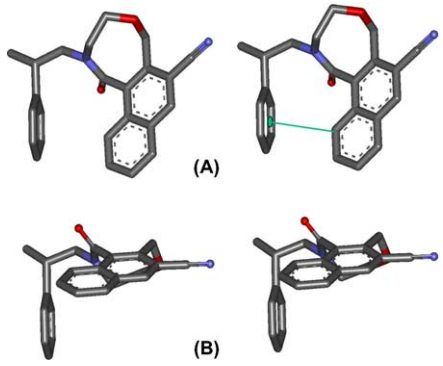


Figure 6. Stereoview representation (relaxed eye) of two low energy conformers of the right side fragment of **28**.

This refined pharmacophore model, developed from the cyclized derivates discussed here, corroborates our earlier model developed through the analysis of the NK_1-preferential isomer of **4**.[26] In that earlier work, the chemically diverse NK_1 receptor antagonists TAK-637[32] and MK-869[38] overlaid well with the pharmacophore model.[26]

4. Conclusions

Through prior efforts we had developed a series of 2-substituted naphthamides as potent and selective NK_1 antagonists; however these compounds contained two bonds with restricted rotation. Therefore, compounds in that series existed as a mixture of four slowly interconverting conformational isomers (atropisomers). In this report we demonstrated that by introducing a tethering bridge, the resulting eight-membered cyclic ethers had a conformational bias that reduced the number of atropisomers to two, while retaining high affinity, selective NK_1 binding. Equilibration between the two atropisomers could be further controlled by methyl substitution of positions on the eight-membered ring. In this cyclic series, the preferred methyl ring substitution is that found in **32**. This compound exists essentially as a single atropisomer.

Molecular modeling of the eight-membered ring system indicated two low energy conformers. In one proposed conformer, the naphthyl ring participates in an aryl–aryl

edge to face stacking interaction. This is consistent with experimental results that indicate an atypically upfield-shifted position for the naphthalene H^8 proton in the NK_1 active atropisomer. Additionally such aryl–aryl stacking interactions have been proposed as key elements in structurally unrelated NK_1 antagonists. Based on these observations, we have proposed an NK_1 pharmacophore model that involves an aryl–aryl stacking interaction and the amide carbonyl as a hydrogen bond acceptor.

5. Experimental

5.1. Biological studies

The cloning, heterologous expression and scale-up growth of MEL cells transfected with either the NK_1 or NK_2 receptor were conducted as previously described for the human NK_2 receptor.[39,40] Functional pharmacology studies, RPA and GFT, were carried out as previously described.[25,26]

5.2. Molecular modeling

Molecular mechanics computations were performed in vacuo, using the AESOP[41] force field with full geometry optimization of all conformations examined and results were visualized using the in-house molecular graphics program ENIGMA.

5.3. Chemistry

^{1}H NMR spectra were obtained at 300 MHz using a Bruker DPX 300 spectrometer in $CDCl_3$ and were referenced to TMS unless otherwise noted. Unit mass spectral data were obtained on a Micromass platform LCZ equipped with APCI. Accurate mass measurements were obtained on a Micromass GCT TOF 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 by MicroAnalysis, Wilmington, DE. All materials obtained commercially were 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 atropisomers; and in these cases ^{1}H NMR integrations are not reported.

5.4. 3-Cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-hydroxybutyl]-2-methoxy-1-naphthamide (6)

To a stirred solution of 3-cyano-2-methoxy-1-naphthoic acid[28] (0.506 g, 2.22 mmol) and dichloromethane (28 mL) was added oxalyl chloride (0.24 mL, 2.78 mmol) and two drops of dimethylformamide. After 2 h at room temperature toluene (10 mL) was added, the solvent removed in vacuo and the residue set under vacuum pump pressure for 2 h. The crude 3-cyano-2-methoxy-1-naphthalenecarbonyl chloride in dichloromethane (10 mL) was added to a rapidly stirred, cooled (0 °C) mixture of (*S*)-2-(3,4-dichlorophenyl)-4-hydroxybutylamine[42] (**5**) (0.518 g, 2.22 mmol) in dichloromethane (20 mL) and 10% NaOH (2.67 mL). The stirred reaction was allowed to warm in the ice bath to room temperature overnight, partitioned between additional dichloromethane and water, the organic phase separated, washed with water, dried (Na_2SO_4) and the solvent removed in vacuo. The crude material was purified by gradient chromatography (0.5%, 2.0%, 5.0% MeOH/dichloromethane) to give **6** (0.95 g, 97%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.82 (d, 1H), 7.65–7.32 (m, 5H), 7.14 (dd, 1H), 6.18 (t, 1H), 3.98 (s, 3H), 3.8–3.68 (m, 3H), 3.54 (m, 1H) 3.18 (m, 1H), 2.05 (m, 1H), 1.77 (m, 1H), MS APCI, $m/z = 443$ (M+H).

5.5. *N*-[(2*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)butyl]-3-cyano-2-methoxy-1-naphthamide (7)

To a stirred solution of 3-cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-hydroxybutyl]-2-methoxy-1-naphthamide **(6)** (5.51 g, 12.46 mmol) and dichloromethane (100 mL) was successively added *tert*-butyldimethylsilylchloride (2.82 g, 18.69 mmol), 4-dimethylaminopyridine (0.076 g, 0.623 mmol), and triethylamine (2.78 mL, 19.94 mmol) and the reaction mixture stirred at room temperature overnight. The mixture was partitioned between additional dichloromethane and water, the organic layer was collected, washed with water and dried (Na_2SO_4). The crude product was purified by gradient chromatography (eluting with 70%, 50% hexane/Et_2O) to yield the title compound (6.48 g, 94%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.2 (s, 1H), 7.82 (d, 1H), 7.62–7.36 (m, 5H), 7.16 (dd, 1H), 6.14 (t, 1H), 4.01 (s, 3H), 3.88–3.78 (m, 2H), 3.64 (m, 1H), 3.47 (m, 1H), 3.20 (m, 1H), 2.03 (m, 1H), 1.84 (m, 1H), 0.86 (s, 9H), 0.016 (s, 6H). MS APCI, $m/z = 557$ (M+H).

5.6. *N*-[(2*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)butyl]-3-cyano-2-hydroxy-1-naphthamide (8)

A three-neck flask containing a magnetic stirrer and magnesium chips (0.68 g, 27.96 mmol) was flame dried and allowed to cool to room temperature under nitrogen. After the addition of diethyl ether (30 mL), benzene (15 mL), and iodine (3.55 g, 13.98 mmol), the reaction mixture was heated at reflux for 2 h. After cooling to room temperature the solution was transferred by cannula to a flask containing **7** (6.48 g, 11.65 mmol) in 108 mL benzene. Heating under reflux was continued for 1 h, the mixture allowed to cool to room temperature then 1 N HCl and dichloromethane were introduced and the mixture stirred for 15 min. The collected organic phase was washed twice with water, dried (Na_2SO_4) filtered and concentrated. The crude product was purified by gradient chromatography (eluting with 2%, 5%,

10% MeOH/dichloromethane) to give the title compound (5.57 g, 88%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.91 (br s, 1H), 8.15 (s, 1H), 7.77 (m, 1H), 7.45–7.13 (m, 6H), 6.28 (m, 1H), 3.96 (m, 1H), 3.62–3.25 (m, 4H), 1.99 (m, 1H), 1.84 (m, 1H), 0.70 (s, 9H), 0.011 (s, 6H). MS APCI, $m/z = 543$ (M+H).

5.7. *N*-[(2*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)butyl]-3-cyano-2-(2-hydroxyethoxy)-1-naphthamide (9b)

A stirred mixture of **8** (1.50 g, 2.76 mmol), DMF (15.0 mL), K_2CO_3 (0.574 g, 4.15 mmol) and 2-bromoethanol (0.22 mL, 3.1 mmol) was heated in a 100 °C oil bath for 4 h. After cooling to room temperature dichloromethane, water, and saturated NH_4 Cl were added and the mixture stirred for 30 min. After further dilution with water the organic layer was collected, washed twice with water, dried (Na_2SO_4), filtered, and the solvent removed in vacuo. Purification by column chromatography (5%, 10%, 50% diethyl ether/dichloromethane) gave the title compound (0.49 g, 30% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.83 (dd, 1H, $J = 7$ Hz, $J = 2$ Hz), 7.51–7.55 (m, 2H), 7.43 (d, 1H, $J = 8$ Hz), 7.39–7.44 (m, 1H), 7.37 (d, 1H, $J = 2$ Hz), 7.15 (dd, 1H, $J = 8$ Hz, $J = 2$ Hz), 6.26 (t, 1H, $J = 6$ Hz), 3.43–3.46 (m, 2H), 3.73–3.91 (m, 5H), 3.61–3.68 (m, 1H), 3.41–3.49 (m, 1H), 3.13–3.23 (m, 1H), 1.97–2.08 (m, 1H), 1.76–1.86 (m, 1H), 0.83 (s, 9H), −0.02 (s, 3H), −0.04 (s, 3H). MS APCI, $m/z = 587$ (M+H).

5.8. *N*-[(2*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)butyl]-3-cyano-2-(3-hydroxypropoxy)-1-naphthamide (9c)

The procedure described for **9b** substituting 3-bromo-1-propanol (0.28 mL, 3.1 mmol) for 2-bromoethanol, gave the title compound (0.59 g, 36%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.80–7.84 (m, 1H), 7.49–7.57 (m, 2H), 7.43 (d, 1H, $J = 8.3$ Hz), 7.36–7.40 (m, 2H), 7.15 (dd, 1H, $J = 8.3$ Hz, $J = 2.3$ Hz), 6.17 (t, 1H, $J = 5.7$ Hz), 4.25–4.37 (m, 2H), 3.47–3.95 (m, 4H), 3.60–3.67 (m, 1H), 3.40–3.47 (m, 1H), 3.11–3.21 (m, 1H), 2.58 (t, 1H, $J = 6$ Hz), 1.95–2.06 (m, 3H), 1.74–1.85 (m, 1H), 0.83 (s, 9H), −0.03 (s, 3H), −0.04 (s, 3H). MS APCI, $m/z = 601$ (M+H).

5.9. 2-{[1-({[(2*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)butyl]amino}carbonyl)-3-cyano-2-naphthyl]oxy}ethyl methanesulfonate (10b)

A stirred cooled (0 °C) solution of **9b** (0.487 g, 0.831 mmol), triethylamine (0.177 mL, 1.27 mmol), and dichloromethane (10 mL) was treated dropwise with methanesulfonyl chloride (0.072 mL, 0.931 mmol) and the mixture kept in the ice bath and allowed to slowly warm to room temperature overnight. The mixture was portioned between additional dichloromethane and water, the organic layer was collected, washed consecutively with two portions of 0.5 N HCl and two portions of saturated sodium bicarbonate, dried (Na_2SO_4), filtered, and the solvent removed in vacuo. Flash chromatography (70% diethyl ether/hexane) returned the title compound **10b** (0.454 g, 82%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.88–7.85 (m, 1H), 7.65–7.55 (m, 2H), 7.53–7.40 (m, 3H), 7.21–7.17 (dd, 1H), 6.21 (t, 1H), 4.58–4.55 (m, 2H), 4.50–4.47 (m, 2H), 3.94–3.81 (m, 2H), 3.69–3.64 (m, 1H), 3.53–3.47 (m, 1H), 3.21–3.19 (m, 1H), 3.16 (s, 3H), 2.04–2.00 (m, 1H), 1.88–1.83 (m, 1H), 0.85 (s, 9H), 0.01 (s, 6H). MS APCI, $m/z = 665$ (M+H).

5.10. 2-{[1-({[(2*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)butyl]amino}carbonyl)-3-cyano-2-naphthyl]oxy}propyl methanesulfonate (10c)

Compound **9c** (0.592 g, 0.986 mmol) and triethylamine (0.21 mL, 1.50 mmol) was reacted with methanesulfonyl chloride (0.086 mL, 1.10 mmol) as described above to yield, after gradient chromatography (60%, 80% diethyl ether/hexane), **10c** (0.647g, 97%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.83–7.80 (m, 1H), 7.59–7.52 (m, 2H), 7.43–7.41 (m, 2H), 7.36 (m, 1H), 7.16–7.13 (dd, 1H), 6.10 (t, 3H), 4.50 (t, 2H), 4.30 (t, 2H), 3.90–3.80 (m, 2H), 3.65–3.59 (m, 1H), 3.46–3.42 (m, 1H), 3.14 (m, 1H), 3.07 (s, 3H), 2.27–2.19 (m, 2H), 2.01–1.96 (m, 1H), 1.83–1.79 (m, 1H), 0.83 (s, 9H), −0.057 (s, 6H). MS APCI, $m/z = 679$ (M+H).

5.11. 2-[(2*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)butyl]-1-oxo-1,2,3,4-tetrahydronaphtho[1,2-*f*][1,4]oxazepine-6-carbonitrile (11b)

To a stirred solution of **10b** (0.24 g, 0.36 mmol) and tetrahydrofuran (THF) (12.0 mL) was added 95% NaH (0.010 g, 0.38 mmol) and the mixture refluxed for 40 min. After quenching with NH_4Cl, the mixture was partitioned between dichloromethane and water, the organic phase was collected, washed twice with water, dried (Na_2SO_4), filtered, and concentrated. Purification by gradient chromatography (80%, 60%, 20% hexane/Et_2O) gave the title compound (0.23 g, 71%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.91–7.82 (m, 2H), 7.64 (t, 1H), 7.54 (t, 1H), 7.39 (m, 2H), 7.16 (dd, 1H), 4.43 (m, 2H), 3.96 (m, 2H), 3.64 (m, 1H), 3.46–3.27 (m, 4H), 2.04 (m, 1H), 1.87 (m, 1H), 0.89 (s, 9H), 0.011 (s, 6H). MS APCI, $m/z = 569$ (M+H).

5.12. 2-[(2*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)butyl]-1-oxo-2,3,4,5-tetrahydro-1H-naphtho[2,1-*b*][1,5]oxazocine-7-carbonitrile (11c)

Reaction of **10c** (0.890 g, 1.31 mmol) in THF (36.0 mL) with 90% NaH (0.035 g, 1.39 mmol) as described above for **10b** gave, after gradient chromatography (80%, 60% hexane/Et_2O), **11c** (0.411 g, 54%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19–8.12 (m, 1H), 7.70 (m, 1H), 7.54–7.34 (m, 4H), 7.24 (m, 1H), 6.64 (m, 1H), 4.88–4.59 (m, 2H), 4.19 (m, 1H), 3.62 (m, 1H), 3.49–3.07

(m, 5H), 2.20–1.83 (m, 4H), 0.88 (s, 9H), 0.11 (s, 6H). MS APCI, $m/z = 583$ (M+H).

5.13. 3-Cyano-*N*-[(2*S*)-2-(3,4-dichlorophenyl)-4-hydroxybutyl]-2-hydroxy-1-naphthamide (12)

Using the procedure described in the preparation of **8**, **6** (0.95 g, 2.15 mmol) was converted to the title compound; light yellow solid (0.82 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.89 (s, 1H), 8.15 (s, 1H), 7.82–7.76 (m, 1H), 7.55–7.26 (m, 5H), 7.16 (dd, 1H), 6.42 (t, 1H), 4.05–3.97 (m, 1H), 3.76–3.48 (m, 3H), 3.31–3.25 (m, 1H), 2.09–1.83 (m, 2H), 1.70–1.58 (m, 1H). MS APCI, $m/z = 429$ (M+H).

5.14. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-hydroxybutyl]-1-oxo-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine-5-carbonitrile (13a)

This compound was prepared by modification of a synthetic method reported by Finkelstein and Chiang.[29] A stirred solution of **12** (0.82 g, 1.9 mmol) in acetic acid (19.2 mL) was treated successively with chloroform (24 mL) and trioxane (0.112 g, 1.24 mmol). The reaction was cooled to 5 °C and concentrated sulfuric acid (1.0 mL) was added dropwise during which time the mixture became light red in color. The mixture was stirred at room temperature overnight and then partitioned between dichloromethane and a large volume of water. The organic phase was collected, washed twice with water, dried (Na_2SO_4), and the solvent removed in vacuo. Gradient column chromatography (0.5%, 2%, 5% methanol/dichloromethane) returned a white foam (0.77 g), which was shown (^{1}H NMR and MS) to consist of a mixture of the alcohol acetates of **12** and **13a**.

A stirred solution of the above acetate mixture and THF (18 mL) was treated with water (7 mL) and 1 N-NaOH (3.2 mL). Methanol (~3 mL) was added give a clear solution. After 2.75 h at room temperature the mixture was partitioned between dichloromethane and water, the organic collected and combined with an additional washing of the aqueous layer with dichloromethane. The organics were dried (Na_2SO_4) and the solvent removed in vacuo. Gradient column chromatography (2%, 3% 5% methanol/dichloromethane) gave the title material as a white solid (0.28 g, 33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (d, 1H), 8.22 (s, 1H), 8.0–7.73 (m, 2H), 7.57–7.52 (m, 1H), 7.45–7.26 (m, 2H), 7.14 (dd, 1H), 5.07 (d, 1H), 4.92 (d, 1H), 4.11 (dd, 1H), 3.73–3.66 (m, 1H), 3.62–3.50 (m, 2H), 3.35–3.27 (m, 1H), 2.08–2.03 (m, 1H), 1.92–1.85 (m, 1H), 1.72 (t, 1H). MS APCI, $m/z = 441$ (M+H).

5.15. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-hydroxybutyl]-1-oxo-1,2,3,4-tetrahydronaphtho[1,2-*f*][1,4]oxazepine-6-carbonitrile (13b)

A solution of **11b** (0.23 g, 0.397 mmol) in CH_3CN (5 mL) was added to stirred 5% HF/CH_3CN (4 mL 50% HF/36 mL CH_3CN) and the mixture stirred at room temperature for 40 min. The reaction was quenched by the addition of dichloromethane, water, and solid $NaHCO_3$ until pH = 6–7 was obtained. The organic phase was collected, washed twice with water, dried (Na_2SO_4), filtered, and concentrated to yield **13b** (0.175 g, 97%) as a white solid. ^{1}H NMR (300 MHZ, $CDCl_3$) δ 8.25 (s, 1H), 7.97 (d, 1H), 7.84 (d, 1H), 7.65 (t, 1H), 7.54 (t, 1H), 7.41 (m, 2H), 7.17 (dd, 1H), 4.39 (m, 2H), 4.07 (m, 1H), 3.89–3.69 (m, 2H), 3.55 (m, 1H), 3.37–3.29 (m, 3H), 2.11–1.91 (m, 2H), 1.74 (t, 1H). MS APCI $m/z = 455$ (M+H).

5.16. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-hydroxybutyl]-1-oxo-2,3,4,5-tetrahydro-1*H*-naphtho[2,1-*b*][1,5]oxazocine-7-carbonitrile (13c)

Compound **11c** (0.411 g, 0.706 mmol) was reacted as above with 5% HF/CH_3CN (7 mL 50% HF/63 mL CH_3CN) to yield **13c** (0.316 g, 95%) as a white solid. No purification was required. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21–8.10 (m, 1H), 8.01–7.34 (m, 5H), 7.25 (m, 1H), 6.65 (m, 1H), 4.83–4.58 (m, 2H), 4.20–4.13 (m, 1H), 3.69 (m, 1H), 3.50–2.72 (m, 5H), 2.17–1.80 (m, 4H), 1.45 (m, 1H). MS APCI, $m/z = 469$ (M+H).

5.17. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-oxobutyl]-1-oxo-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine-5-carbonitrile (14a)

To a stirred −78 °C solution of oxalyl chloride (0.082 mL, 0.94 mmol) and dichloromethane (8 mL) was added a solution of dimethyl sulfoxide (0.134 mL, 1.56 mmol) in dichloromethane (4 mL). After stirring for 5 min a solution of **13a** (0.276 g, 0.627 mmol) in dichloromethane (8 mL) was added. After stirring for 15 min, triethylamine (0.53 mL, 3.76 mmol) was added. The mixture was stirred an addition 15 min in the bath, the bath removed and stirring continued at ambient temperature for an additional 2 h. The reaction mixture was partitioned between dichloromethane and a large volume of water, the organic phase collected, washed with additional water, the organic phase dried (Na_2SO_4), and concentrated. Gradient chromatography (1%, 20%, 50% Et_2O/dichloromethane) yielded 0.228 g, (83%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 9.13 (d, 1H), 8.35 (s, 1H), 8.02–7.74 (m, 2H), 7.58–7.53 (m, 1H), 7.43–7.35 (m, 2H), 7.15 (dd, 1H), 5.11–5.02 (m, 2H), 3.98–3.91 (m, 1H), 3.74–3.66 (m, 2H), 3.06–2.82 (m, 2H). MS APCI, $m/z = 439$ (M+H).

5.18. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-oxobutyl]-1-oxo-1,2,3,4-tetrahydronaphtho[1,2-*f*][1,4]oxazepine-6-carbonitrile (14b)

Using the standard Swern oxidizing conditions described in the preparation of **14a**, **13b** (0.175 g, 0.385 mmol) was converted to 0.148 g (84%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.26 (s, 1H), 7.93–7.83 (m, 2H),

7.64 (t, 1H), 7.54 (t, 1H), 7.43 (m, 2H), 7.18 (dd, 1H), 4.42 (m, 2H), 3.95 (m, 2H), 3.75 (m, 1H), 3.40 (m, 2H), 3.10–2.90 (m, 2H). MS APCI, $m/z = 453$ (M+H).

5.19. 2[(2*S*)-2-(3,4-Dichlorophenyl)-4-oxobutyl]-1-oxo-2,3,4,5-tetrahydro-1*H*-naphtho[2,1-*b*][1,5]oxazocine-7-carbonitrile (14c)

Using the standard Swern oxidizing conditions described in the preparation of **14a**, **13c** (0.271 g, 0.580 mmol) was converted to 0.261 g (96%) of **14c** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 9.79 (m, 1H), 8.28–8.25 (m, 1H), 7.98–7.37 (m, 5H), 7.25 (m, 1H), 6.68 (m, 1H), 4.82–4.57 (m, 2H), 4.22–4.15 (m, 1H), 3.92–3.36 (m, 3H), 3.17–2.88 (m, 3H), 2.19–1.97 (m, 2H). MS APCI, $m/z = 467$ (M+H).

5.20. 2-((2*S*)-2-(3,4-Dichlorophenyl)-4-{4-[2-(methylsulfinyl)phenyl]piperidin-1-yl}butyl)-1-oxo-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine-5-carbonitrile (15)

To a stirred solution of 4-[(S)-2-methylsulfinylphenyl]-piperidine[43] (0.108 g, 0.427 mmol) and MeOH (10 mL) was added acetic acid (0.03 mL, 0.470 mmol) and a solution of **14b** (0.187 g, 0.427 mmol) in MeOH (18 mL). The mixture was stirred for 30 min then a solution of sodium cyanoborohydride (0.030 g, 0.47 mmol) in MeOH (2 mL) was added and stirring was continued overnight. The mixture was quenched with saturated $NaHCO_3$ and partitioned between dichloromethane and water. The organic phase was collected, consecutively washed with saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and the solvent removed in vacuo. The crude product was purified by gradient chromatography (2%, 3%, 5% MeOH/dichloromethane) to yield the title compound (0.260 g, 94%) as a white solid that was converted to the citrate salt. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (d, 1H), 8.29 (s, 1H), 7.99–7.96 (m, 1H), 7.85–7.74 (m, 2H), 7.58–7.55 (m, 1H), 7.46–7.26 (m, 5H), 7.13 (dd, 1H), 5.09 (d, 1H), 4.91 (d, 1H), 4.12–4.05 (m, 1H), 3.58–3.51 (m, 1H), 3.23–3.17 (m, 1H), 3.01–2.90 (m, 2H), 2.73–2.70 (m, 1H), 2.67 (s, 3H), 2.31–2.21 (m, 2H), 2.09–1.59 (m, 8H). MS APCI, $m/z = 646$ (M+H). Anal. Calcd for $C_{35}H_{33}Cl_2N_3O_3S{\cdot}1.0C_6H_8O_7{\cdot}1.2H_2O$: C, 57.23; H, 5.08; N 4.88. Found: C, 57.10; H, 5.12; N, 4.67.

5.21. 2-((2*S*)-2-(3,4-Dichlorophenyl)-4-4-[(*S*)-2-(methylsulfinyl)phenyl]piperidin-1-ylbutyl)-1-oxo-1,2,3,4-tetrahydronaphtho[1,2-*f*][1,4] oxazepine-6-carbonitrile (16)

4-[(*S*)-2-methylsulfinyl-phenyl]-piperidine (0.078 g, 0.326 mmol) was reacted with **14b** (0.148 g, 0.326 mmol) in the presence of sodium cyanoborohydride under the standard reductive amination conditions described in the preparation of **15** to yield **16** (0.271 g, 72%) as a white solid that was converted to the citrate salt. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.0 (m, 2H), 7.84 (d, 1H), 7.66 (t, 1H), 7.56 (t, 1H), 7.48–7.35 (m, 5H), 7.17 (dd, 1H), 4.43–4.30 (m, 2H), 4.4 (m, 1H), 3.84 (m, 1H), 3.30 (m, 2H), 3.18 (m, 1H), 3.04–2.91 (m, 2H), 2.72 (m, 1H), 2.68 (s, 3H), 2.27 (m, 2H), 2.07–1.61 (m, 8H). MS APCI, $m/z = 660$ (M+H). Anal. Calcd for $C_{36}H_{35}Cl_2N_3O_3S{\cdot}1.0C_6H_8O_7{\cdot}2.0H_2O$: C, 56.75; H, 5.33; N, 4.72. Found: C, 56.50; H, 5.26; N, 4.43.

5.22. 2-((2*S*)-2-(3,4-Dichlorophenyl)-4-4-[2-(methylsulfinyl)phenyl]piperidin-1-ylbutyl)-1-oxo-2,3,4,5-tetrahydro-1*H*-naphtho[2,1-*b*][1,5]oxazocine-7-carbonitrile (17)

4-[(*S*)-2-methylsulfinyl-phenyl]-piperidine (0.134 g, 0.560 mmol) was reacted with **14c** (0.261 g, 0.560 mmol) in the presence of sodium cyanoborohydride under the standard reductive amination conditions described in the preparation of **15** to yield **17** (0.271 g, 72%) as a white solid, which was converted to the citrate salt. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20–8.14 (m, 1H), 7.98 (m, 1H), 7.81–7.70 (m, 1H), 7.53–7.33 (m, 7H), 7.25 (m, 1H), 6.72 (m, 1H), 4.83–4.58 (m, 2H), 4.17 (m, 1H), 3.60–3.32 (m, 2H), 3.14–2.91 (m, 3H), 2.79 (m, 1H), 2.68 (s, 3H), 2.33–2.26 (m, 2H), 2.19–1.63 (m, 11H). MS APCI, $m/z = 674$ (M+H). Anal. Calcd for $C_{37}H_{37}Cl_2N_3O_3S{\cdot}1.0C_6H_8O_7{\cdot}1.8H_2O$: C, 57.43; H, 5.44; N, 4.67. Found: C, 57.43; H, 5.36; N, 4.49.

5.23. (2*S*)-2-(3,4-Dichlorophenyl)-*N*-(2-hydroxyethyl)pent-4-enamide (19a)

A solution of (2*S*)-2-(3,4-dichlorophenyl)pent-4-enoic acid[44] (**18**, 2.0 g, 8.2 mmol), diisopropylethyl amine (1.56 mL, 9.0 mmol), ethanolamine (0.59 mL, 9.8 mmol), and 4-dimethylaminopyridine (1.0 g, 8.2 mmol) in dichloromethane (32 mL) was cooled to 5 °C and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.65 g, 8.6 mmol) was added. The cooling bath was removed and reaction stirred for 50 min, then heated briefly to reflux. After cooling, additional ethanolamine (0.3 mL, 5.0 mmol) was added and stirring continued for 10 min. The mixture was concentrated, diluted with ethyl acetate; washed with 1 N HCl, then saturated aqueous sodium carbonate, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (30–80% ethyl acetate/hexanes) to afford the title compound (1.0 g, 39%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) 7.40 (m, 2H), 7.18 (m, 1H), 5.93 (br s, 1H), 5.68 (m, 1H), 5.05 (m, 2H), 3.64 (m, 2H), 3.40 (m, 3H), 2.84 (m, 1H), 2.48 (m, 1H). MS APCI, $m/z = 288$ (M+H).

19b–e were prepared analogously to **19a**, using the appropriate methyl substituted ethanolamine.

5.24. (2*S*)-2-(3,4-Dichlorophenyl)-*N*-[(1*R*)-2-hydroxy-1-methylethyl]pent-4-enamide (19b)

Solid (88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 1H), 7.40 (d, 1H), 7.18 (m, 1H), 5.69 (m, 2H), 5.06 (m, 2H), 4.04 (m, 1H), 3.65 (m, 1H), 3.53 (m, 1H), 3.30 (t, 1H), 2.83 (m, 1H), 2.46 (m, 2H), 1.10 (d, 3H). MS APCI, $m/z = 302$ (M+H).

5.25. (2*S*)-2-(3,4-Dichlorophenyl)-*N*-[(1*S*)-2-hydroxy-1-methylethyl]pent-4-enamide (19c)

Solid (81%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, 1H), 7.40 (d, 1H), 7.19 (m, 1H), 5.68 (m, 2H), 5.05 (m, 2H), 4.04 (m, 1H), 3.59 (m, 1H), 3.47 (m, 1H), 3.31 (t, 1H), 2.82 (m, 1H), 2.47 (m, 1H), 2.31 (t, 1H), 1.16 (d, 3H). MS APCI, $m/z = 302$ (M+H).

5.26. (2*S*)-2-(3,4-Dichlorophenyl)-*N*-[(2*S*)-2-hydroxypropyl]pent-4-enamide (19d)

Oil (82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.18 (dd, 1H), 6.19 (br s, 1H), 5.68 (m, 1H), 5.06 (m, 1H), 3.87 (m, 1H), 3.01 (m, 1H), 2.83 (m, 1H), 2.47 (m, 1H), 1.12 (d, 3H). MS APCI, $m/z = 302$ (M+H). MS APCI, $m/z = 302$ (M+H).

5.27. (2*S*)-2-(3,4-Dichlorophenyl)-*N*-[(2*R*)-2-hydroxypropyl]pent-4-enamide (19e)

Oil (98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.21–7.15 (m, 1H), 5.90 (br, 1H), 5.76–5.60 (m, 1H), 5.12–4.97 (m, 2H), 3.92–3.80 (m, 1H), 3.44–3.31 (m, 2H), 3.17–3.06 (m, 1H), 2.91–2.78 (m, 1H), 2.54–2.41 (m, 1H), 2.12 (br, 1H), 1.15 (d, 3H, $J = 6.1$ Hz). MS APCI, $m/z = 302$ (M+H).

5.28. 2-{[(2*S*)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]-amino}ethanol (20a)

To a solution of **19a** (1.5 g, 5.2 mmol) in diethyl ether (105 mL) was added 13 mL of a 1 M solution of lithium aluminum hydride in THF. The mixture was heated under reflux for 3 h. After cooling, 10 mL of saturated aqueous sodium sulfate was cautiously added and the suspension stirred for 0.5 h. Solid sodium sulfate (10 g) was added and the suspension stirred for 0.5 h, filtered through Celite, rinsed with ethyl acetate, concentrated under reduced pressure, and purified by passing through a plug of silica gel with 3–7% methanol/dichloromethane to afford the title compound (1.25 g, 88%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, 1H), 7.26 (d, 1H), 7.03 (dd, 1H), 5.64 (m, 1H), 4.98 (m, 2H), 3.55 (t, 2H), 2.71–2.94 (m, 5H), 2.26–2.51 (m, 2H). MS APCI, $m/z = 274$ (M+H).

20b–**e** were prepared analogously to **20a**:

5.29. (2*R*)-2-{[(2*S*)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]amino}propan-1-ol (20b)

Oil (quant.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, 1H), 7.28 (d, 1H), 7.03 (m, 1H), 5.64 (m, 1H), 4.98 (m, 2H), 3.49 (m, 1H), 3.14 (m, 1H), 2.79 (m, 4H), 2.36 (m, 2H), 0.97 (d, 3H). MS APCI, $m/z = 288$ (M+H).

5.30. (2*S*)-2-{[(2S)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]amino}propan-1-ol (20c)

Oil (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, 1H), 7.27 (d, 1H), 7.03 (m, 1H), 5.64 (m, 1H), 4.99 (m, 2H), 3.50 (m, 1H), 3.18 (m, 1H), 2.97 (m, 1H), 2.73 (m, 3H), 2.44 (m, 1H), 2.31 (m, 1H), 0.99 (d, 3H). MS APCI, $m/z = 288$ (M+H).

5.31. (2*S*)-1-{[(2*S*)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]amino}propan-2-ol (20d)

Oil (91%). ^{1}H NMR ((300 MHz, $CDCl_3$) δ 7.29 (d, 1H), 7.27 (d, 1H), 7.03 (dd, 1H), 5.63 (m, 1H), 4.99 (m, 1H), 2.92–2.61 (m, 4H), 2.34 (m, 3H), 1.10 (d, 3H). MS APCI, $m/z = 288$ (M+H).

5.32. (2*R*)-1-[(2*S*)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]aminopropan-2-ol (20e)

Colorless oil (85%). The free-base reduction product was used in the next reaction without additional purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52 (d, 1H, $J = 8.3$ Hz), 7.46 (s, 1H), 7.21 (dd, 1H, $J = 1.7$, 8.3 Hz), 5.62 (m, 1H), 4.91 (m, 2H), 4.29 (br, 1H), 3.58 (m, 1H), 3.29 (s, 1H), 2.84 (m, 1H), 2.71 (m, 2H), 2.43 (m, 1H), 2.37 (d, 2H, $J = 5.7$ Hz), 2.26 (m, 1H), 0.98 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.72, 136.91, 131.04, 130.54, 130.30, 128.78, 128.64, 116.72, 65.42, 57.49, 54.74, 44.81, 37.89, 21.82. MS APCI, $m/z = 288$ (M+H). An analytical sample was prepared by treating a dichloromethane solution of the title compound with a slight excess of ethereal HCl at room temperature. The hydrochloride salt of the title compound was isolated as a white solid. Anal. Calcd for $C_{14}H_{19}Cl_2NO$ 1.0 HCl: C 51.79, H 6.21, N 4.31. Found: C 51.41, H 5.86, N 4.18.

5.33. *tert*-Butyl [(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl](2-hydroxyethyl)carbamate (21a)

To a solution of compound **20a** (1.25 g, 4.6 mmol) in dioxane (10 mL), water (10 mL), and sodium carbonate (0.51 g, 4.8 mmol) was cooled to 0 °C and di-*tert*-butyldicarbonate (1.04 g, 4.8 mmol) was slowly added as a solution in dioxane (5 mL). After 1 h the mixture was diluted with ethyl acetate, washed with water, and brine, dried ($MgSO_4$); filtered and concentrated under reduced pressure. The resulting residue was passed through a plug of silica to afford 1.4 g (81%) of the title compound as an oil.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 1H), 7.26 (d, 1H), 7.00 (m, 1H), 5.62 (m, 1H), 5.00 (m, 2H), 3.71–2.94 (m, 7H), 2.34 (m, 2H), 1.41 (s, 9H).

21b–**e** were prepared analogously to **21a**:

5.34. *tert*-Butyl [(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl][(1*R*)-2-hydroxy-1-methylethyl]carbamate (21b)

Oil (99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 1H), 7.28 (d, 1H), 7.02 (m, 1H), 5.60 (m, 1H), 4.98 (m, 2H), 3.45 (m, 5H), 2.98 (s, 1H), 2.35 (m, 2H), 1.40 (s, 9H), 1.11 (d, 3H). MS APCI, $m/z = 288$ (M−Boc+H).

5.35. *tert*-Butyl [(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl][(1 *S*)-2-hydroxy-1-methylethyl]carbamate (21c)

Oil (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 1H), 7.27 (d, 1H), 7.01 (m, 1H), 5.62 (m, 1H), 4.98 (m, 2H),

3.52 (m, 5H), 3.14 (m, 1H), 2.97 (s, 1H), 2.36 (m, 2H), 1.43 (s, 9H), 1.03 (s, 3H). MS APCI, $m/z = 410$ (M+Na).

5.36. *tert*-Butyl [(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl][(2*S*)-2-hydroxypropyl]carbamate (21d)

Oil (59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 1H), 7.26 (d, 1H), 7.00 (m, 1H), 5.61 (m, 1H), 4.97 (m, 1H), 3.38 (m, 1H), 2.37 (m, 1H), 1.39 (s, 9H), 1.10 (d, 3H). MS APCI, $m/z = 288$ (M−Boc+H).

5.37. *tert*-Butyl [(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl][(2*R*)-2-hydroxypropyl]carbamate (21e)

ethyl acetate), (82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, 1H, $J = 8.3$ Hz), 7.25 (s, 1H), 7.00 (m, 1H), 5.69–5.55 (m, 1H), 5.04–4.93 (m, 2H), 3.86 (m, 1H), 3.53 (br, 1H), 3.32 (m, 1H), 3.03 (m, 3H), 2.35 (m, 2H), 1.41 (s, 9H), 1.08 (d, 3H, $J = 6.6$ Hz). MS APCI, $m/z = 388$ (M+H).

5.38. Methyl 2-[(2-{(*tert*-butoxycarbonyl) [(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]amino}ethoxy)methyl]-3-cyano-1-naphthoate (22a)

A mixture of **21a** (1.4 g, 3.7 mmol)), **33** (1.36 g, 4.5 mmol), and sodium hydride (0.18 g of 60% dispersion in mineral oil, 4.5 mmol) in dimethylformamide (6 mL) and tetrahydrofuran (6 mL) was stirred overnight. Additional sodium hydride (30 mg of 60% dispersion in mineral oil, 0.75 mmol) was added and the reaction heated at 50 °C for 0.25 h, then at 60 °C for 0.25 h. The mixture was cooled, diluted with ethyl acetate, washed with water (twice), and brine, dried ($MgSO_4$), filtered, concentrated under reduced pressure to afford **22a**, which was used without further characterization or purification.

22b–**e** were prepared analogously to **22a**:

5.39. Methyl 2-{[((2*R*)-2-(*tert*-butoxycarbonyl)[(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]aminopropyl)oxy]-methyl}-3-cyano-1-naphthoate (22b)

Used without further characterization or purification.

5.40. Methyl 2-{[((2*S*)-2-{(*tert*-butoxycarbonyl)[(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]amino}propyl)oxy]-methyl}-3-cyano-1-naphthoate (22c)

Used without further characterization or purification.

5.41. Methyl 2-[((1*S*)-2-{(*tert*-butoxycarbonyl)[(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]amino}-1-methyl-ethoxy)methyl]-3-cyano-1-naphthoate (22d)

Oil (65%). ^{1}H NMR (300 MHz, $CDCl_3$, 52 °C) δ 8.32 (s, 1H), 7.90 (m, 2H), 7.68 (m, 2H), 7.25 (m, 2H), 6.95 (dd, 1H), 5.52 (m, 1H), 4.85 (m, 3H), 4.70 (m, 1H), 4.03 (m, 3H), 3.82 (m, 1H), 3.65 (m, 2H), 3.48 (m, 1H), 3.09 (m, 2H), 2.93 (m, 1H), 2.30 (m, 2H), 1.32 (s, 9H), 1.16 (m, 3H). MS APCI, $m/z = 511$ (M−Boc+H).

5.42. Methyl 2-[((1*R*)-2-{(*tert*-butoxycarbonyl)[(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]amino}-1-methyl-ethoxy)methyl]-3-cyano-1-naphthoate (22e)

Purification by flash chromatography (4:1 hexanes–ethyl acetate) afforded the title compound as a colorless oil (77%). ^{1}H NMR (300 MHz, $CDCl_3$, conformational isomers evident) δ 8.32 (1H), 7.90 (2H), 7.67 (2H), 7.26 (2H), 6.96 (1H), 5.54 (1H), 4.98–4.81 (3H), 4.71 (1H), 4.04 (3H), 3.91–3.54 (2H), 3.35–2.85 (3H), 2.81–2.60 (1H), 2.29 (2H), 1.45–1.28 (9H), 1.11 (3H). MS APCI, $m/z = 511$ (M−Boc+H).

5.43. Methyl 3-cyano-2-[(2-{[(2*S*)-2-(3,4-dichlorophenyl)-pent-4-en-1-yl]amino}ethoxy)methyl]-1-naphthoate (23a)

A solution of crude **22a** and trifluoroacetic acid (10 mL) was stirred in dichloromethane (10 mL), heated under reflux for 20 min, concentrated, diluted with dichloromethane, concentrated again, then purified by flash chromatography (1–5% methanol/dichloromethane) to afford **23a** (1.5 g, 81%) as a foam solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.95 (d, 1H), 7.76 (m, 3H), 7.31 (d, 1H), 7.24 (d, 1H), 7.05 (dd, 1H), 5.55 (m, 1H), 4.98 (m, 2H), 4.76 (d, 2H), 4.03 (s, 3H), 3.83 (t, 2H), 3.42–3.12 (m, 5H), 2.38 (m, 2H). MS APCI, $m/z = 497$ (M+H).

23b–**e** were prepared analogously to **23a**:

5.44. Methyl 3-cyano-2-{[((2*R*)-2-{[(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]amino}propyl)oxy]methyl}-1-naphthoate (23b)

(11% from **21b**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.97 (d, 1H), 7.76 (m, 3H), 7.30 (d, 1H), 7.15 (d, 1H), 7.00 (m, 1H), 5.54 (m, 1H), 4.99 (m, 2H), 4.75 (s, 2H), 4.04 (s, 3H), 3.71 (m, 2H), 3.56 (s, 1H), 3.29 (m, 2H), 3.11 (m, 1H), 2.38 (m, 2H), 1.34 (d, 3H). MS APCI, $m/z = 511$.

5.45. Methyl 3-cyano-2-{[((2*S*)-2-[(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]aminopropyl)oxy]methyl}-1-naphthoate (23c)

Oil (74% from **21c**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s), 8.36 (s), 7.97 (d), 7.77 (m), 7.27 (d), 7.07 (m), 6.63 (s), 5.55 (m), 4.99 (m), 4.76 (m), 4.05 (s), 3.71 (m), 3.52 (s), 3.40 (s), 3.06 (m), 2.36 (m), 1.35 (d). MS APCI, $m/z = 511$ (M+H).

5.46. Methyl 3-cyano-2-[((1*S*)-2-{[(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]amino}-1-methylethoxy)methyl]-1-naphthoate (23d)

Solid (72%). (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.87 (dd, 2H), 7.67 (m, 2H), 7.24 (m, 2H), 6.98 (d, 1H), 5.60 (m, 1H), 4.90 (m, 2H), 4.69 (d, 1H), 4.00 (s, 3H), 3.72 (m, 1H), 3.46 (s, 3H), 2.79 (m, 2H), 2.62 (m, 2H), 2.40 (m, 1H), 2.45 (m, 1H), 1.19 (d, 3H). MS APCI, $m/z = 511$ (M+H).

5.47. Methyl 3-cyano-2-[((1*R*)-2-{[(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]amino}-1-methylethoxy)methyl]-1-naphthoate (23e)

Compound **22e** (15.80 g, 25.84 mmol) was dissolved in 9:1 (v/v) dichloromethane–trifluoroacetic acid at 0 °C under N_2. After 30 min the solution was allowed to warm to ambient temperature and stirred an additional 2 h. The solvent was evaporated and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was separated, dried (Na_2 SO_4), filtered and evaporated to afford 12.78 g (97%) of the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.94 (d, 1H, $J = 7.9$ Hz), 7.82 (d, 1H, $J = 7.9$ Hz), 7.70 (m, 2H), 7.25 (m, 1H), 7.16 (d, 1H, $J = 8.3$ Hz), 6.99 (dd, 1H, $J = 2.2, 8.3$ Hz), 5.56 (m, 1H), 5.00–4.80 (m, 4H), 4.62 (d, 1H, $J = 10.9$ Hz), 4.03 (s, 3H), 3.89 (br, 1H), 3.14–2.86 (m, 4H), 2.81–2.71 (m, 1H), 2.48–2.23 (m, 2H), 1.27 (d, 3H, $J = 6.1$ Hz). MS APCI, $m/z = 511$ (M+H).

5.48. 3-Cyano-2-[(2-{[(2*S*)-2-(3,4-dichlorophenyl)pent-4-en-1-yl]amino}ethoxy)methyl]-1-naphthoic acid hydrochloride (24a)

A mixture of **23a** (1.5 g, 3.0 mmol) and pyridine hydrochloride (3.5 g, 30 mmol) was heated with stirring in a pre-heated 180 °C oil bath for 15 min. The cooled residue was partitioned between ethyl acetate and water, washed with 0.5 N HCl and brine, dried ($MgSO_4$), filtered, concentrated under reduced pressure, and diluted with diethyl ether to afford a precipitate, which was collected to afford **24a** (1.1 g, 70%) as a tan solid.^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (br s, 1H), 8.17 (s, 1H), 7.98 (d, 1H), 7.82 (d, 1H), 7.73 (t, 1H), 7.62 (t, 1H), 7.40 (d, 1H), 7.27 (d, 1H), 7.11 (dd, 1H), 5.61 (m, 1H), 5.05 (m, 2H), 4.97 (s, 2H), 4.03 (m, 2H), 3.40 (m, 2H), 3.20 (m, 3H), 2.48 (m, 2H). MS APCI, $m/z = 483$ (M+H).

24b–**e** were prepared analogously to **24a**:

5.49. 3-Cyano-2-{[((2*R*)-2-{[(2*S*)-2-(3,4-dichlorophenyl)-pent-4-en-1-yl]amino}propyl)oxy]methyl}-1-naphthoic acid hydrochloride (24b)

Solid (68%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.30 (s, 1H), 8.01 (d, 1H), 7.93 (d, 1H), 7.71 (m, 2H), 7.56 (s), 7.27 (d, 1H), 7.10 (d, 1H), 7.04 (m, 1H), 5.60 (m, 1H), 4.99 (m, 4H), 3.87 (m, 2H), 3.50 (m, 1H), 3.23 (m, 2H), 2.43 (m, 2H), 2.09 (m, 1H), 1.40 (d, 3H). MS APCI, $m/z = 497$ (M+H).

5.50. 3-Cyano-2-{[((2*S*)-2-[(2*S*)-2-(3,4-dichlorophenyl)-pent-4-en-1-yl]aminopropyl)oxy]methyl}-1-naphthoic acid hydrochloride (24c)

Solid (49%). ^{1}H NMR (300 MHz, DMSO) δ 8.76 (s, 1H), 8.16 (d, 1H), 7.96 (d, 1H), 7.81 (m, 2H), 7.53 (m, 2H), 7.26 (m, 1H), 5.53 (m, 1H), 4.86 (m, 4H), 3.66 (d, 2H), 3.29 (m), 2.47 (m), 2.28 (m, 1H), 1.21 (d, 3H). MS APCI, $m/z = 497$ (M+H).

5.51. 3-Cyano-2-[((1*S*)-2-{[(2*S*)-2-(3,4-dichlorophenyl)-pent-4-en-1-yl]amino}-1-methylethoxy)methyl]-1-naphthoic acid hydrochloride (24d)

Solid (62%). (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.78 (d, 1H), 7.71–7.52 (m, 3H), 7.37 (s, 1H), 7.24 (d, 1H), 7.06 (dd, 1H), 5.30 (d, 2H), 4.99 (m, 4H), 4.65 (d, 1H), 4.30 (m, 1H), 3.46 (m, 1H), 3.35 (m, 1H), 3.13 (d, 1H), 2.86 (t, 1H), 2.56 (m, 1H), 2.35 (m, 1H), 1.34 (d, 3H). MS APCI, $m/z = 497$ (M+H).

5.52. 3-Cyano-2-[((1*R*)-2-{[(2*S*)-2-(3,4-dichlorophenyl)-pent-4-en-1-yl]amino}-1-methylethoxy)methyl]-1-naphthoic acid hydrochloride (24e)

Tan solid (88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.75 (br, 1H), 8.23 (s, 1H), 7.90 (m, 2H), 7.66 (m, 2H), 7.23 (m, 1H), 7.12 (m, 1H), 7.00 (m, 1H), 6.68 (br, 2H), 5.54 (m, 1H), 5.02 (m, 3H), 4.71 (m, 1H), 4.25 (m, 1H), 3.34–2.82 (m, 5H), 2.57–2.32 (m, 2H), 1.38 (d, 3H, $J = 6.1$ Hz). MS APCI, $m/z = 497$ (M+H).

5.53. 2-[(2*S*)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (25a)

A solution of **24a** (0.78 g, 1.7 mmol), *N*,*N*-diisopropylethylamine (0.54 mL, 3.1 mmol) and bis-(2-oxo-3-oxazolidinyl)-phosphinic chloride (0.40 g, 1.57 mmol) in acetonitrile (40 mL) was stirred for 1 h. Additional diisopropylethylamine (0.14 mL, 0.80 mmol) and bis-(2-oxo-3-oxazolidinyl)-phosphinic chloride (0.10 g, 0.39 mmol) were added and the mixture stirred for 0.5 h, concentrated, diluted with ethyl acetate; washed with 0.5 N HCl, and brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (20–30% ethyl acetate/hexanes) to afford 0.41 g (53%) of the title compound as a foam solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s), 8.23 (s), 8.04 (d), 7.91 (d), 7.80 (m), 7.66 (t), 7.50 (m), 7.37 (m), 7.28 (m), 7.13 (dd), 6.69 (d), 5.67 (m), 5.11–4.74 (m), 4.62 (m), 4.02–3.68 (m), 3.49–2.98 (m), 2.64–2.43 (m). MS APCI, $m/z = 465$ (M+H).

25b–**e** were prepared analogously to **25a**:

5.54. (3*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]-3-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]-oxazocine-7-carbonitrile (25b)

Solid (36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.79 (d, 1H), 7.54 (m, 2H), 7.41 (m, 3H), 6.53 (d, 1H), 5.69 (m, 1H), 5.39 (m, 1H), 5.07 (m, 2H), 4.86 (m, 1H), 4.61 (m, 1H), 3.99 (m, 1H), 3.76 (m, 1H), 3.47 (m, 1H), 3.07 (m, 2H), 2.49 (m, 2H), 1.21 (d, 3H). MS APCI, $m/z = 479$ (M+H).

5.55. (3*S*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]-3-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]-oxazocine-7-carbonitrile (25c)

(49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s), 7.97 (d), 7.88 (d), 7.76 (t), 7.63 (t), 7.52 (m), 7.40 (m), 7.14 (m), 6.56 (d), 5.73 (m), 5.36 (d), 5.06 (m), 4.85 (d), 4.15 (m), 3.84 (m), 3.53 (m), 2.93 (m), 2.69 (m), 2.52 (m), 0.93 (d), 0.61 (d), 0.42 (d). MS APCI, $m/z = 479$ (M+H).

5.56. (4*S*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2H-naphtho[1,2-*f*][1,4]-oxazocine-7-carbonitrile (25d)

Solid (57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.09 (d, 1H), 7.92 (d, 1H), 7.77 (t, 1H), 7.65 (t, 1H), 7.38 (m, 2H), 7.14 (dd, 1H), 5.72 (m, 1H), 5.30 (s, 1H), 5.11 (m, 1H), 5.04 (m, 2H), 4.57 (m, 2H), 3.89 (m, 1H), 3.45 (m, 1H), 3.07 (m, 2H), 2.51 (m, 2H), 1.01 (d, 3H). MS APCI, $m/z = 479$ (M+H).

5.57. (4*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)pent-4-en-1-yl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]-oxazocine-7-carbonitrile (25e)

Purification by flash chromatography (100:1, dichloromethane–methanol) afforded the title compound as a colorless oil (58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.82 (d, 1H, $J = 7.4$ Hz), 7.60–7.47 (m, 3H), 7.37 (m, 1H), 7.26 (m, 1H), 6.71 (d, 1H, $J = 8.3$ Hz), 5.66 (m, 1H), 5.19–4.86 (m, 4H), 4.57 (d, 1H, $J = 13.5$ Hz), 3.96 (m, 1H), 3.22–3.00 (m, 4H), 2.50 (t, 2H, $J = 7.0$ Hz), 1.17 (d, 3H, $J = 6.6$ Hz). MS APCI, $m/z =$ 479 (M+H); Anal. Calcd for $C_{27}H_{24}Cl_2N_2O_2 \cdot 1.0H_2O$: C, 65.20; H, 5.27; N, 5.63. Found: C, 65.23; H, 4.88; N, 5.61.

5.58. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-oxobutyl]-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (26a)

A stream of ozone was passed through a solution of **25a** (0.40 g, 0.89 mmol) in methanol (10 mL) and dichloromethane (20 mL) at −78 °C for 5 min when the blue solution color persisted. Stirring was continued for 10 min then nitrogen was bubbled through for 5 min. The reaction was warmed to −30 °C and dimethyl sulfide (0.32 mL, 4.4 mmol) was added. The mixture was warmed to room temperature, stirred 1.5 h, concentrated, and purified by chromatography using 50–60% ethyl acetate/hexanes to afford the product (0.30 g, 75%) as a foam solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (d), 8.31 (s), 8.23 (s), 8.03 (d), 7.92 (d), 7.80 (m), 7.67 (t), 7.59–7.37 (m), 7.28 (m), 7.19 (dd), 6.66 (d), 5.08–4.74 (m), 4.61 (m), 4.05–3.01 (m), 2.96 (d), 2.76 (m). MS APCI, $m/z = 467$ (M+H).

26b–e were prepared analogously to **26a**:

5.59. 2-(2*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-oxobutyl]-3-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (26b)

Solid (71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.16 (s, 1H), 7.79 (d, 1H), 7.53 (m, 3H), 7.40 (m, 2H), 6.49 (d, 1H), 5.11 (q, 2H), 4.55 (m, 1H), 3.98 (m, 1H), 3.76 (t, 1H), 3.60 (m, 1H), 3.47 (m, 1H), 3.20 (m, 1H), 2.97 (m, 2H), 1.31 (d, 3H). MS APCI, $m/z = 481$ (M+H).

5.60. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-oxobutyl]-3,3-dimethyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]-oxazocine-7-carbonitrile (26c)

Solid (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s), 8.24 (s), 7.96 (d), 7.90 (d), 7.78 (t), 7.65 (t), 7.48 (d), 7.41 (d), 7.19 (m), 6.51 (d), 5.34 (d), 5.22 (d), 4.87 (d), 4.43 (d), 4.15 (m), 3.92 (m), 3.63 (t), 3.44 (m), 3.32 (d), 3.06 (m), 0.71 (d), 0.45 (d). MS APCI, $m/z = 481$ (M+H).

5.61. (3*R*,4*S*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-oxobutyl]-3,4-dimethyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (26d)

Solid (67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 9.00 (d, 1H), 8.32 (s, 1H), 8.09 (t, 1H), 7.92 (d, 1H), 7.77 (m, 1H), 7.67 (m, 1H), 7.41 (m, 2H), 5.12 (d, 1H), 4.56 (m, 2H), 3.90 (m, 1H), 3.45 (d, 2H), 3.09 (m, 3H), 1.05 (m, 3H). MS APCI, $m/z = 481$ (M+H).

5.62. (3*R*,4*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-oxobutyl]-3,4- dimethyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (26e)

Colorless oil (47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.26 (s, 1H), 7.83 (d, 1H, $J = 8.3$ Hz), 7.61–7.46 (m, 3H), 7.42 (d, 1H, $J = 2.2$ Hz), 7.28 (m, 1H), 6.68 (d, 1H, $J = 8.3$ Hz), 5.16 (d, 1H, $J = 14.0$ Hz), 4.90 (m, 1H), 4.55 (d, 1H, $J = 14.0$ Hz), 3.96 (m, 1H), 3.75–3.57 (m, 1H), 3.18 (m, 3H), 2.95 (d, 2H, $J = 7.0$ Hz), 1.21 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.15, 168.54, 140.92, 136.81, 133.28, 132.74, 132.34, 132.01, 131.57, 131.26, 130.82, 130.69, 130.36, 128.32, 128.26, 127.93, 125.78, 117.3, 110.02, 73.78, 66.79, 53.07, 47.92, 47.8, 36.28, 20.02. MS APCI, $m/z = 481$ (M+H).

5.63. 2-((2*S*)-2-(3,4-Dichlorophenyl)-4-4-[2-(methylsulfinyl)phenyl]piperidin-1-ylbutyl)-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (27)

A solution of **26a** (50 mg, 0.11 mmol), 4-[(*S*)-2-methylsulfinylphenyl]-piperidine[43] (30 mg, 0.13 mmol), and acetic acid (0.012 mL) was stirred in methanol (2 mL) for 0.5 h. Sodium cyanoborohydride (12 mg, 0.19 mmol) was added as a solution in methanol (1 mL) in three portions over 10 min., stirred 2 h, then concentrated under reduced pressure. The residue was diluted with ethyl acetate, washed with water and brine, dried

($MgSO_4$), filtered, concentrated, and purified by flash chromatography to afford the product (50 mg, 69%) as a solid, which was converted to the citrate salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (s), 8.62 (s), 8.09 (d), 8.01 (d), 7.94–7.36 (m), 6.47 (d), 4.87 (m), 4.72 (t), 4.00 (t), 3.90–3.64 (m), 3.51–1.75 (m). MS APCI, m/z = 674 (M+H). HRMS (CI) m/z calculated for $C_{37}H_{37}Cl_2N_3O_3S$ (M+H) 674.2011, found: 674.2009.

5.64. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(dimethylamino)-butyl]-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]-oxazocine-7-carbonitrile (28)

A solution of **26a** (0.10 g, 0.021 mmol), triethylamine (0.034 mL, 0.038 mmol), and dimethylamine hydrochloride (23 mg, 0.28 mmol) was dissolved in 2 mL of methanol. Acetic acid was added dropwise until the pH was between 4 and 5. After stirring for 1.5 h a solution of sodium cyanoborohydride (23 mg, 0.37 mmol) in methanol (1 mL) was added in three portions over 10 min and the reaction was allowed to stir for 3 h. The mixture was concentrated; diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$); filtered, concentrated, and purified by flash chromatography (6–10% methanol/dichloromethane). An ethyl acetate solution of the product containing trace amount of triethylamine was washed with water and brine; dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the title compound (80 mg, 75%) as an oil. This material was converted to the citrate salt by combining with an equimolar amount of citric acid in methanol, then drying. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (s), 8.62 (s), 8.09 (d), 8.01 (d), 7.90 (d), 7.82–7.59 (m), 7.40 (m), 6.44 (d), 4.87 (m), 4.71 (t), 4.32 (dd), 3.99 (t), 3.89–3.64 (m), 3.42–2.94 (m), 2.83–2.55 (m), 2.10. MS APCI, m/z = 496 (M+H). HRMS (CI) m/z calculated for $C_{27}H_{27}Cl_2N_3O_2$ (M+H) 496.1559, found: 496.1553.

29, **30**, **31**, and **32** were prepared analogously to **28**. They were purified by reverse phase HPLC on a Phenomenex LUNA C-18(2), 250×21.2 mm (10μ) column eluting with acetonitrile–water gradient containing 0.1% TFA (40–70% acetonitrile over 20 min) and several were isolated as the trifluoroacetate salt by concentration of the appropriate fractions.

5.65. (3*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(dimethylamino)butyl]-3-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile trifluoroacetate (29)

Gum (quant.) ^{1}H NMR (300 MHz, DMSO) δ 9.46 (s, 1H), 8.54 (s, 1H), 7.98 (d, 1H), 7.73 (m, 2H), 7.61 (t, 1H), 7.51 (d, 1H), 7.33 (t, 1H), 6.31 (d, 1H), 5.07 (q, 2H), 4.48 (t, 1H), 3.92 (m, 1H), 3.73 (t, 1H), 3.57 (m, 1H), 3.10 (m, 3H), 2.75 (t, 7H), 2.09 (m, 2H), 1.16 (d, 3H). MS APCI, m/z = 510 (M+H). Anal. Calcd for $C_{28}H_{29}Cl_2N_3O_2 \cdot 1.5\,C_2HF_3O_2$: C, 54.64; H, 4.51; N, 6.17. Found: C, 54.86; H, 4.25; N, 6.21.

5.66. (3*S*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(dimethylamino)butyl]-3-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile trifluoroacetate (30)

Oil (95%). ^{1}H NMR (300 MHz, DMSO) δ 9.46 (s), 8.67 (s), 8.62 (s), 8.08 (d), 8.03 (d), 7.90 (d), 7.82 (t), 7.71 (t), 7.64 (d), 7.43 (m), 6.37 (d), 5.30 (d), 5.01 (d), 4.84 (d), 4.35 (d), 3.68 (m), 3.20 (m), 2.80 (t), 2.15 (m), 0.45 (d), 0.23 (d). MS APCI, m/z = 510 (M+H). HRMS (CI) m/z calculated for $C_{28}H_{29}Cl_2N_3O_2$ (M+H) 510.1710, found 510.1733.

5.67. (4*S*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(dimethylamino)butyl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (31). Oil (21%)

^{1}H NMR (300 MHz, DMSO) δ 8.33 (s, 1H), 8.03 (d, 1H), 7.93 (d, 1H), 7.77 (t, 1H), 7.67 (t, 1H), 7.43 (m, 2H), 7.21 (dd, 1H), 5.15 (d, 1H), 4.53 (m, 2H), 3.87 (m, 1H), 3.46 (m, 1H), 3.08 (m, 2H), 2.84 (m, 3H), 2.31 (m, 2H), 2.13 (br s, 6H), 1.02 (d, 3h). MS APCI, m/z = 510 (M+H).

5.68. (4*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(dimethylamino)butyl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (32)

Compound **26e** (160 mg, 0.333 mmol) was dissolved in THF (1 mL) and dimethylamine (2 M solution in THF, 416 μL, 0.832 mmol) was added. The mixture was diluted with methanol (3 mL) and stirred for 10 min. Sodium cyanoborohydride (50 mg, 0.796 mmol) was added and the reaction was stirred for 2 h at ambient temperature. The reaction mixture evaporated and the residue purified by preparative HPLC [Phenomenex LUNA C-18(2), 250×21.2 mm (10μ) column eluting with acetonitrile–water gradient containing 0.1% TFA (40–70% acetonitrile over 20 min.)]. Fractions containing product were pooled and partially concentrated to remove the acetonitrile. The residual aqueous solution was made basic by addition of 10% aqueous sodium carbonate, and the solution extracted with ethyl acetate (3x). The organic extracts were dried (Na_2SO_4), filtered, and evaporated to afford 73 mg (0.143 mmol, 43% yield) of the title compound as a white foamy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.81 (m, 1H), 7.59–7.45 (m, 3H), 7.39 (m, 1H), 7.29–7.24 (m, 1H), 6.74 (d, 1H, J = 8.2 Hz), 5.15 (d, 1H, J = 14.2 Hz), 4.91 (t, 1H, J = 14.2 Hz), 4.56 (d, 1H, J = 14.2 Hz), 3.96 (m, 1H), 3.21–3.03 (m, 4H), 2.19 (m, 8H), 1.96–1.75 (m, 2H), 1.17 (d, 3H, J = 6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.69, 142.35, 137.05, 133.97, 132.87, 132.58, 132.36, 131.67, 131.37, 131.27, 131.16, 131.00, 130.62, 129.20, 128.57, 128.37, 126.26, 117.72, 110.39, 74.03, 67.15, 57.36, 53.47, 49.17, 45.76, 40.99, 32.13, 20.45. MS APCI, m/z = 510 (M+H). Anal. Calcd for $C_{27}H_{27}Cl_2N_3O_2 \cdot 1.0H_2O$: C, 63.64; H, 5.91; N, 7.95. Found: C, 63.96; H, 5.58; N, 8.03.

5.69. Methyl 2-(bromomethyl)-3-cyano-1-naphthoate (33)

A solution of methyl-3-cyano-2-methyl-1-naphthoate[26] (4.8 g, 21.3 mmol), *N*-bromosuccinimide (15.2 g, 85.4 mmol), and 2,2′-azobis(2-methylisobutyronitrile) (0.35 g, 2.1 mmol) in carbon tetrachloride (85 mL) was heated under reflux for 3 h. The cooled mixture was diluted with dichloromethane and water and the excess *N*-bromosuccinimide quenched by adding sodium thiosulfate pentahydrate (15.2 g, 61.2 mmol) and stirring for 0.5 h. The layers were separated and the organic washed with water and brine, dried ($MgSO_4$), filtered; and concentrated under reduced pressure. The crude material was then passed through a plug of silica gel using 40–60% dichloromethane/hexanes as eluant to afford the title compound as a white solid (5.2 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.90 (m, 2H), 7.69 (m, 2H), 4.82 (s, 2H), 4.13 (s, 3H). MS APCI, $m/z = 304$ (M^+).

Acknowledgements

We gratefully acknowledge Herbert G. Barthlow and Linda C. Litwin for the RPA and GFT analysis, and James E. Hall for detailed NMR analysis.

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