AMP Deaminase Inhibitors. 5. Design, Synthesis, and SAR of a Highly Potent Inhibitor Series

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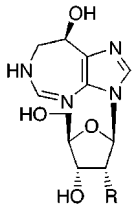
A highly potent AMP deaminase (AMPDA) inhibitor series was discovered by replacing the N3 substitutents of the two lead AMPDA inhibitor series with a conformationally restricted group. The most potent compound, 3-[2-(3-carboxy-4-bromo-5,6,7,8-tetrahydronaphthyl)ethyl]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (**24b**), represents a 10- to 250-fold enhancement in AMPDA inhibitory potency without loss in the enzyme specificity. The potency of the inhibitor **24b** (AMPDA $K_i = 0.002$ μM) is 10^5-fold lower than the K_m for the substrate AMP. It represents the most potent nonnucleotide AMPDA inhibitor known.

Introduction

Adenosine protects organs from ischemic injury. Adenosine levels increase during periods of ischemia or stress, and as a result cellular injury is minimized. The cellular protection is mediated through the activation of the P1 purine receptors.[1] It is anticipated that under conditions of net ATP breakdown, inhibition of AMPDA will further elevate adenosine levels, as the ATP breakdown product AMP is consumed through deamination to IMP.[2] A recent study by Holmes et al. which analyzed the association of partial AMPDA deficiency with improved prognosis in heart failure patients further supports AMPDA as a potential drug target.[3]

In our previous reports,[4−7] we described the design and characterization of the first potent and selective AMPDA inhibitors. Our strategy involved substitution of aliphatic and alkylaryl groups with carboxylic acids at the N3 position of the aglycon of the adenosine deaminase transition state inhibitor, coformycin **1a**[8] (AMPDA $K_i = 3.0$ μM). Herein, we report the design, rationale, and the detailed SAR study of this series of compounds, optimized through utilization of groups with significantly less conformational freedom.



1a, R = OH
1b, R = H

Design Rationale

This potent AMPDA inhibitor series evolved from the two structural leads, 3-[2-(3-carboxyphenyl)ethyl]coformycin aglycon **2** (AMPDA $K_i = 0.5$ μM) and 3-[(5-carboxy-5-benzyl)pentyl]coformycin aglycon **3** (AMPDA $K_i = 0.41$ μM) (Figure 1). We reported earlier that potency of the aliphatic carboxylic acid series was enhanced by α substituents. For example, a benzyl group improved potency 10-fold possibly because of increased hydrophobic interactions.[5]

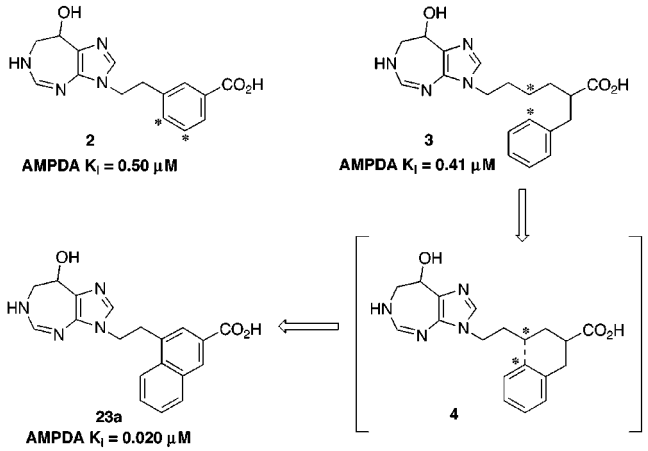


Figure 1. Inhibitor design.

In parallel with this observation, we also noticed this hydrophobic pocket in the phenethyl series by introducing substituents at the starred (*) positions of compound **2**.[6] To further optimize the binding affinity to this hydrophobic pocket, we examined the N3 substituents that encompass the features of the two surrogates but have significantly less conformational freedom. Connecting the starred (*) positions as depicted by structure **4**, we arrived at the naphthyl derivative **23a**, as an example in which to assess the effectiveness of this strategy.

Chemistry

The N3-substituted coformycin aglycon analogues (Table 1) were prepared from the heterocycle, 6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one **5**[9] using the general three-step procedure described previously (Scheme 1).[5]

The naphthyl electrophiles **9a**−**c** were prepared from the corresponding precursors **7a**−**c**[10] using a three-step procedure. The vinyl derivatives **8a**−**c** were prepared via the palladium-catalyzed vinylation of the bromide

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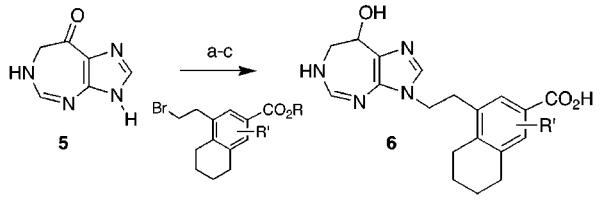
Table 1. Physical Data of AMPDA Inhibitors

cmpd	mp (°C)	formula[a]
23a	220−235[b]	$C_{19}H_{18}N_4O_3 \cdot 1.3H_2O \cdot 0.1AcOH$
23b	nd[c]	$C_{20}H_{16}N_4O_3F_3Na$[d]
23c	nd[c]	$C_{19}H_{16}N_4O_3\ BrNa$[d]
24a	220−235[b]	$C_{19}H_{22}N_4O_3 \cdot 0.5H_2O \cdot 0.3AcOH$
24b	200−220[b]	$C_{19}H_{21}N_4O_3Br \cdot 2.5H_2O \cdot 1.2AcOH$
24c	220−230[b]	$C_{19}H_{20}N_4O_3Cl_2 \cdot 1.4H_2O$
24d	220−230[b]	$C_{26}H_{28}N_4O_4 \cdot 0.3H_2O \cdot 0.33AcOH$
24e	220−230[b]	$C_{22}H_{28}N_4O_4 \cdot 3H_2O \cdot 0.6AcOH$
24f	>210[b]	$C_{20}H_{24}N_4O_4 \cdot 1.25H_2O \cdot 0.3AcOH$
24g	>230[b]	$C_{20}H_{24}N_4O_4 \cdot 0.5H_2O \cdot 1.0AcOH$
25a	237−239	$C_{20}H_{20}N_4O_3$
25b	202−203	$C_{22}H_{21}N_4O_3F_3$
25c	238−240[b]	$C_{21}H_{21}N_4O_3Br \cdot 1H_2O$
26a	160−165	C21H26N4O3
26b	147−150	$C_{26}H_{28}N_4O_3 \cdot 0.25H_2O$
26c	100−102	$C_{21}H_{25}N_4O_3Br \cdot 1.2H_2O \cdot 0.1Et_3N$
26d	132−135	$C_{21}H_{24}N_4O_3Cl_2 \cdot 0.5H_2O$
26e	159−162	$C_{28}H_{32}N_4O_4 \cdot 1.3H_2O$
26f	143−145	$C_{24}H_{32}N_4O_4 \cdot 0.25H_2O$
26g	170−172	$C_{22}H_{28}N_4O_4 \cdot 0.2H_2O$
26h	112−115	$C_{22}H_{28}N_4O_4 \cdot 0.8H_2O$
26i	108−110	$C_{26}H_{26}N_4O_3Cl_2 \cdot 0.6H_2O$

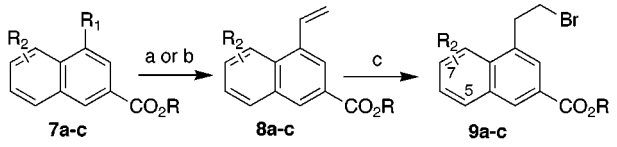
[a] Analyses for C, H, and N were within 0.4% of the theoretical values, unless otherwise stated. [b] Decomposed. [c] Not determined, very deliquescent compound. [d] Confirmed by LRMS.

Scheme 1[a]



[a] Reagents: (a) NaH, DMF, NaI; (b) $NaBH_4$, MeOH, CH_2Cl_2; (c) 1 N NaOH, dioxane or 10% Pd/C, H_2, MeOH (R = Bn).

Scheme 2[a]



7a, R_1 = Br, R_2 = H, R = Me
7b, R_1 = OH, R_2 = 5-CF_3, R = Et
7c, R_1 = OH, R_2 = 7-Br, R = Et

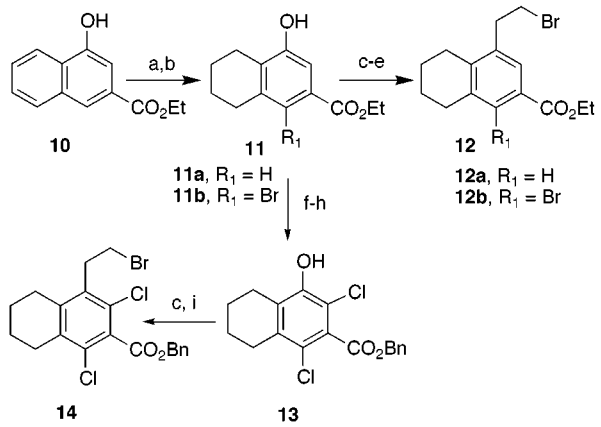
9a, R_2 = H, R = Me
9b, R_2 = 5-CF_3, R = Et
9c, R_2 = 7-Br, R = Et

[a] Reagents: (a) vinyltributyltin, $Pd(PPh_3)_4$, DMF (R_1 = Br); (b) i. $(CF_3SO_2)_2O$, Py, ii. vinyltributyltin, $(PPh_3)_2PdCl_2$, LiCl, DMF (R_1 = OH); (c) i. 9-BBN; 30% H_2O_2, 3 N NaOH, ii. CBr_4, PPh_3, CH_2Cl_2.

or the triflate. Hydroboration of **8a**−**c** with 9-BBN followed by oxidation gave the primary alcohols, which were converted to the electrophiles **9a**−**c** with CBr_4 in the presence of PPh_3 (Scheme 2).

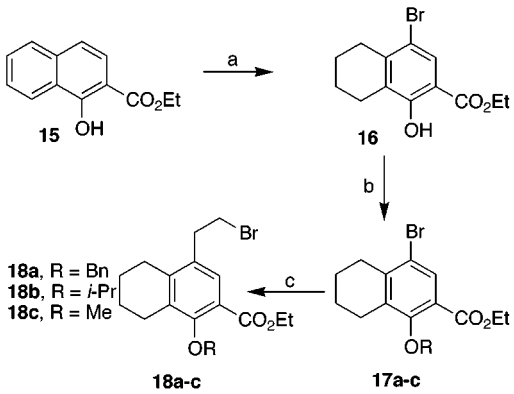
Tetrahydronaphthyl derivatives were prepared by two different routes (Schemes 3−5). The first route required partial hydrogenation of the naphthyl derivatives as shown in Schemes 3 and 4. Thus, intermediate **11a** was prepared from the naphthyl derivative **10**[11] by partial hydrogenation in the presence of $Pd(OH)_2/C$ in MeOH at 1 atm H_2 pressure. Vinylation of **11a** followed by hydroboration/oxidation and bromination gave the electrophile **12a**. Preparation of compound **12b** required electrophilic substitution of **11a** with bromine in acetic acid to deliver a single regioisomer **11b** (structure determined by nOe experiments) which then was subjected to the three-step procedure of palladium-catalyzed vinylation, hydroboration/oxidation, and bromination.

Scheme 3[a]



[a] Reagents: (a) $Pd(OH)_2/C$, H_2, MeOH; (b) Br_2, AcOH; (c) i. $(CF_3SO_2)_2O$, Py, ii. vinyltributyltin, $(PPh_3)_2PdCl_2$, LiCl, DMF; (d) 9-BBN, THF, 30% H_2O_2, 3 N NaOH; (e) CBr_4, PPh_3, CH_2Cl_2; (f) 1 N NaOH, dioxane; (g) Cs_2CO_3, BnBr, DMF; (h) $S0_2Cl_2$, CH_2Cl_2; (i) HBr, hexane, benzoyl peroxide.

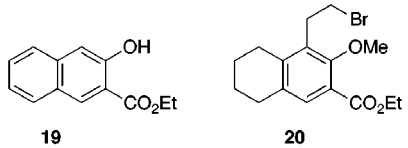
Scheme 4[a]



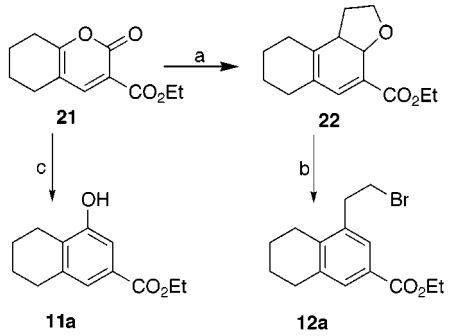
[a] Reagents: (a) i. $Pd(OH)_2/C$, H_2, MeOH, ii. Br_2, AcOH; (b) K_2CO_3, DMSO and BnBr or *i*-PrI or MeI; (c) i. vinyltributyltin, $Pd(PPh_3)_4$, DMF, ii. 9-BBN, THF, 30% H_2O_2, 3 N NaOH, iii. CBr_4, PPh_3, CH_2Cl_2.

The electrophile **14** was prepared from **11a** in the following six-step procedure. Saponification of **11a** followed by alkylation with benzyl bromide and chlorination with SO_2Cl_2 gave the dichloro analogue **13**. Palladium-catalyzed vinylation of **13**, followed by HBr addition to the olefin bond in the presence of benzoyl peroxide, gave the electrophile **14** (Scheme 3).[12] In this latter case, the usual two-step method (hydroboration/oxidation and bromination) to prepare the electrophile **14** failed and led only to decomposition byproducts.

Similarly, compound **16** was prepared from **15** by partial hydrogenation followed by electrophilic bromination (Scheme 4). Electrophiles **18a**−**c** were prepared by alkylation of the tetrahydronaphthol **16** followed by the three-step procedure of vinylation, hydroboration/oxidation, and bromination (Scheme 4). Finally, these methods were also used to prepare compound **20** from **19**.

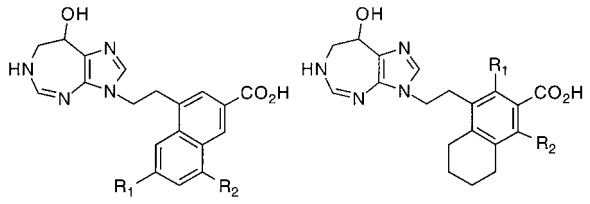


Scheme 5[a]



[a] Reagents: (a) dihydrofuran, toulene, sealed tube, 160 °C; (b) BBr_3, CH_2Cl_2; EtOH; (c) vinylene carbonate, toluene, sealed tube.

Table 2. SAR of the Naphthylethyl and 5,6,7,8-Tetrahydro-3-carboxy Naphthylethyl Series



23 24

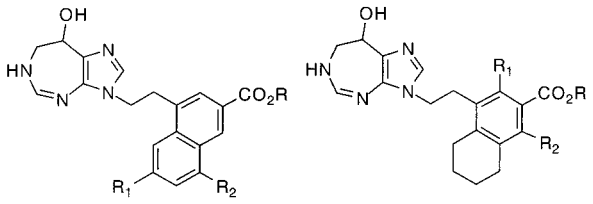
compd	R_1	R_2	AMPDA K_i (μM)	ADA K_i (μM)
23a	H	H	0.02	>1000
23b	H	CF_3	0.22	>7.5
23c	Br	H	0.96	>7.5
24a	H	H	0.015	>7.5
24b	H	Br	0.002	>7.5
24c	Cl	Cl	0.05	>7.5
24d	H	OBn	0.009	>7.5
24e	H	O*i*-Pr	0.09	>7.5
24f	H	OMe	0.03	>7.5
24g	OMe	H	0.04	>7.5

Alternatively, compounds **12a** and **11a** were prepared using the short sequence presented in Scheme 5. With some modifications (*t*-BuO^-K^+ in THF) of the procedure reported by Boger and co-workers,[13] the key intermediate **21** was prepared from cyclohexanone in one step in 82% yield. The rapid assembly of the tetrahydronaphthyl ring system, **12a**, with all the requisite substitutions on the aromatic ring was accomplished by a two-step procedure.[4] A Diels−Alder reaction of diene **21** with dihydrofuran in a sealed tube furnished the tricyclic intermediate **22** in good yield and high regioselectivity. Treatment of this intermediate with BBr_3 followed by addition of EtOH provided the electrophile **12a** in 54% yield. Last, intermediate **11a** was prepared in one step from **21** following the reported procedure.[13]

Results

The compounds reported in Table 1 were evaluated as inhibitors of recombinant human E-type AMPDA and calf intestinal adenosine deaminase (ADA).[4] Inhibitor potencies are reported in Tables 2 and 3. The inhibitor screening concentrations used in the AMPDA and ADA inhibition were 125 μM and 7.5 μM, respectively. In select examples, ADA inhibition was evaluated at higher concentrations in order to evaluate the full extent of the selectivity of the enzyme inhibition.

Table 3. SAR of the Naphthylethyl and 5,6,7,8-Tetrahydro-3-carboxynaphthylethyl Ester Series



25 26

compd	R_1	R_2	R	AMPDA K_i (μM)	ADA K_i (μM)
25a	H	H	Me	1.8	>7.5
25b	H	CF_3	Et	35	2.7
25c	Br	H	Et	14	4.4
26a	H	H	Et	1.3	3.4
26b	H	H	Bn	5.0	0.72
26c	H	Br	Et	1.0	0.53
26d	Cl	Cl	Et	0.5	>7.5
26e	H	OBn	Et	0.3	>7.5
26f	H	O*i*-Pr	Et	3.8	>7.5
26g	H	OMe	Et	2.3	3.7
26h	OMe	H	Et	2.4	>7.5
26i	Cl	Cl	Bn	0.3	>7.5

The targeted naphthyl derivative with a two-carbon tether at the 1-position and a carboxylate in the 3-position, **23a**, exhibited a 20-fold improvement in the inhibition potency (AMPDA K_i = 0.02 μM) relative to the two lead compounds **2** and **3**. The compound also retained the high selectivity for AMPDA (ADA K_i >1000 μM). In general, all of the final carboxylic acids in this series exhibited good selectivity over ADA (Table 2). Substitution of the B-ring of the naphthyl system of **23a** revealed that the binding affinity is very sensitive to small variations. For example, a trifluoromethyl substituent at C5 (**23b**) or a bromine at C7 (**23c**) of the naphthyl ring resulted in a 10−50-fold loss in affinity. In contrast, saturation of the B-ring of the naphthyl to the tetrahydronaphthyl system (i.e., **24a**, AMPDA K_i = 0.015 μM) retained the potency. On the basis of the above results and to avoid introducing chirality in the N3 substituent, the SAR developed for **24a** was focused on substitutions at C2 (R_1) and C4 (R_2) of the A-ring. A methoxy group at C2 or C4 (**24g** or **24f**) or dichloro at the C2- and C4 (**24c**) caused a 3−3.5-fold decrease in potency, compared to the parent compound **24a**. Increasing the size of the alkoxy substituent to isopropyloxy (**24e**) at C4 resulted in substantial loss of activity (6-fold). In contrast, the benzyloxy (**24d**) showed a 2-fold improvement in potency. Finally, introduction of a bromine at the C4 resulted in a 7.5-fold enhancement in potency and provided the most potent AMPDA inhibitor, compound **24b** (AMPDA K_i = 0.002 μM).

In accord with our earlier observations,[5−7] the corresponding esters showed much less inhibitory potency and selectivity (Table 3). The benzyloxy substituent (**26e**) and the benzyl ester (**26i**) are the most potent analogues among the esters, each with AMPDA K_i = 0.3 μM.

Discussion

Our previous structure−activity relationships established that coformycin aglycon analogues having an N3-phenethyl side chain with a carboxylic acid group at the

meta-position (e.g., **2**) are potent AMPDA inhibitors.[6] The previous study also showed that hydrophobic substituents at the C5- and C6-positions of the phenyl ring (*-positions in **2**) increased potency. This report highlights the design of a new inhibitor series with enhanced potency derived from conformational restriction of the N3 substituent and optimization of the hydrophobic interactions. Restricting conformational freedom, by connecting the *-carbons of **3** (Figure 1), led to a very potent series of AMPDA inhibitors (Table 2) that had the additional benefit of increasing the hydrophobic density at the *-carbons of **2** and eliminating the chiral center of **3**. Similar results where conformational restraint assisted to improve the binding affinity (5- to 10-fold) have been reported earlier.[14a−c] Subsequent analogues revealed the spacial limitations around the B-ring of the naphthyl (e.g., **23b** and **23c**).

Additionally, when the naphthyl ring was reduced to a tetrahydronaphthyl ring, no loss in binding affinity was observed. The electron-donating groups such as methoxy or propyloxy (e.g., **24e**, **24f,** and **24g**) on the A-ring decreased the potency 1.5- to 4.5-fold, similar to the result that was observed in the phenethyl series[6] with a methoxy group. However, a benzyloxy substitution resulted in a 2-fold increase in potency compared to the parent compound **24a**. This enhancement in activity with a benzyloxy substituent is reminiscent of observations made with other AMPDA inhibitors having benzyl substituents near the carboxylic acid group,[5,7] which suggests that there may be some favorable interactions between the π-electron density of the aromatic ring and the region near the phosphate binding site. Thus, it is apparent that a relatively large hydrophobic binding region exists close to the phosphate binding site of AMPDA. Introduction of a bromine at the C4 resulted in the most potent inhibitor, **24b**, AMPDA $K_i = 0.002$ μM. This represents a remarkably potent inhibitor considering that AMP has a K_m of ca. 1 mM and is thus approximately 10^5-fold lower in AMPDA affinity. This large improvement over AMP suggests that **24b** may bind in a manner that mimics the transition state of deamination. In contrast, the dichloro analogue, **24c**, was 2.5-fold less potent than the parent compound **24a**, analogous to that which was observed with the chloro substituent in the phenethyl series.[6]

Summary

We have demonstrated that attaching hydrophobic substituents to compound **2** or restraining the conformational freedom of the N3 substitution of compound **3** can boost the AMPDA inhibitory potency 160-fold. The most potent compound identified, **24b** (AMPDA $K_i =$ 0.002 μM), bears little structural resemblance to the substrate AMP and yet exhibits a remarkable improvement (>10^5-fold) in binding affinity relative to AMP. The tetrahydronaphthyl ring system with a 3-carboxylic acid has the necessary negative charge and hydrophobic composition to interact optimally with the ribose 5′-monophosphate binding region of the enzyme. Moreover, the N3 substitution may induce the correct orientation of the diazepine base in a fashion analogous to the transition state.[4] Some of these AMPDA inhibitors have demonstrated site- and event-specific adenosine regulation in a cellular model of net ATP depletion (e.g., **24a**).[4] Thus, they may represent potential drugs to treat ischemic tissue damage resulting from a stroke or a heart attack.

Experimental Section

General Methods. Glassware for moisture sensitive reactions was flame dried and cooled to room temperature in a desiccator, and all reactions were carried out under an atmosphere of nitrogen. Anhydrous solvents were purchased from Aldrich and stored over 4 Å molecular sieves. THF was freshly distilled from Na/benzophenone ketyl under nitrogen. Flash chromatography was performed on 230−400 mesh EM Science silica gel 60. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H spectra were obtained on a Varian Gemini-200 operating at 200 MHz and recorded in units δ with tetramethylsilane (δ 0.00) as a reference line internal standard. Microanalyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Low resolution mass spectra were obtained from Mass Consortium Corp., San Diego, CA.

Enzyme Assays. The AMPDA and ADA K_i determinations were performed as previously described.[4]

Methyl 1-Vinyl-3-naphthoate (8a). To a solution of methyl 1-bromo-3-naphthoate **7a** (2.0 g, 7.54 mmol) in 60 mL of dry DMF under nitrogen were added tetrakis(triphenylphosphine) palladium (0.44 g, 0.37 mmol) and vinyltributyltin (2.6 mL, 9.0 mmol). The mixture was degassed with N_2 for 5 min. The resulting mixture was heated at 80 °C for 3 h. NMR analysis indicated complete reaction. After cooling, it was partitioned between ether and brine. The organic phase was stirred over 10% aqueous NaF solution for 4 h. The ether layer was separated, washed with water and brine, and dried ($MgSO_4$). The solvent was removed, and the residue was purified by chromatography (5% EtOAc in hexane) to give 1.6 g (85%) of **8a** as an oil: ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 5.55 (d, 1H, J = 10.9 Hz), 5.9 (d, 1H, J = 17.3 Hz), 7.3−7.8 (m, 3H), 7.8−8.2 (m, 2H), 8.21 (s, 1H), 8.54 (s, 1H).

Methyl 1-(2-Bromoethyl)-3-naphthoate (9a). To a solution of 9-BBN dimer (3.6 g, 15.0 mmol) in 40 mL of THF was added a solution of **8a** (1.6 g, 7.5 mmol) in 10 mL of THF, and the resulting solution was stirred for 16 h. The solution was cooled to −30 °C, and 30% H_2O_2 (3.4 mL, 30.0 mmol) was added slowly, followed by 3 N NaOH (5.5 mmol, 16.5 mmol). The reaction was allowed to warm to 5 °C and stirred for 4 h at which time the heterogeneous solution was diluted with water (150 mL) and extracted with ether (3 × 80 mL). The combined ether layers were washed with water and brine and dried ($MgSO_4$). The solvent was removed, and the residue was purified by chromatography (30% EtOAc in hexane) to give 1.1 g (63%) of methyl 1-(2-hydroxyethyl)-3-naphthoate as an oil: ^{1}H NMR (DMSO-d_6) δ 3.26 (t, 2H, J = 7.0 Hz), 3.76 (q, 2H, J = 7.0 Hz), 3.89 (s, 3H), 4.8 (t, 1H, J = 5.6 Hz, exchangeable with D_2O), 7.5−7.8 (m, 2H), 7.88 (s, 1H), 8.0−8.3 (m, 2H), 8.5 (s, 1H).

To a solution of methyl 1-(2-hydroxyethyl)-3-naphthoate (1.1 g, 4.78 mmol) in 50 mL of dry CH_2Cl_2 under N_2 was added triphenylphosphine (1.88 g, 7.2 mmol), followed by carbon tetrabromide (2.37 g, 7.2 mmol) slowly at 0 °C. The resulting mixture was stirred for 30 min. The solvent was removed and the residue purified by chromatography (5% EtOAc in hexane) to give 1.1 g (80%) of **9a** as an oil: ^{1}H NMR (DMSO-d_6) δ 3.14 (t, 2H, J = 7.0 Hz), 3.68 (t, 2H, J = 7.0 Hz), 3.9 (s, 3H), 7.4−7.8 (m, 2H), 7.9 (s, 1H), 8.1−8.3 (m, 2H), 8.46 (s, 1H).

Ethyl 1-Vinyl-5-trifluoromethyl-3-naphthoate (8b). A solution of ethyl 1-hydroxy-5-trifluoromethyl-3-naphthoate **7b**[12] (8.7 g, 30.6 mmol) in 100 mL of pyridine was cooled to 0 °C and slowly treated with trifluoromethanesulfonic anhydride (6.0 mL, 35.7 mmol). After warming to room temperature, the mixture was stirred for 3 h and the solvent evaporated. The residue was diluted with 200 mL of water and extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated to afford 9.5 g of dark syrup.

The crude triflate was dissolved in 120 mL of DMF and combined with $(PPh_3)_2Pd(Cl)_2$ (3.23 g, 4.6 mmol), PPh_3 (3.23 g, 12.3 mmol), LiCl(10.38 g, 245.0 mmol), and vinyltributyl tin (10.8 mL, 37.0 mmol). The resultant mixture was heated at 90 °C for 5 h. Solvent was evaporated, and the residue was diluted with ether (300 mL), washed with water (2 × 50 mL) and aqueous NaF (2 × 50 mL), and dried ($MgSO_4$). The solvent was removed, and the residue was purified by chromatography (5% EtOAc in hexane) to give 7.2 g (85%) of **8b** as white solid: mp 67 °C; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 7.1 Hz), 4.48(q, 2H, J = 7.1 Hz), 5.61 (d, 1H, J = 11 Hz), 5.89 (d, 1H, J = 17.2 Hz), 7.4 (dd, 1H, J_1 = 11 Hz, J_2 = 7.2 Hz), 7.6 (t, 1H, J = 7.7 Hz), 7.95 (d, 1H, J = 7.2 Hz), 8.28 (s, 1H), 8.35 (d, 1H, J = 7.2 Hz), 8.9 (s, 1H). Similarly, compound **8c** was prepared from **7c**.

Ethyl 1-(2-Bromoethyl)-5-trifluoromethyl-3-naphthoate (9b). Compound **9b** was prepared from compound **8b** (75%) as an oil by using the procedures described for the preparation of compound **9a** from **8a**: ^{1}H NMR (DMSO-d_6) δ 1.39 (t, 3H, J = 7.0 Hz), 3.6−4.0 (m, 4H), 4.43 (q, 2H, J = 7.0 Hz), 7.87 (t, 1H, J = 8.1 Hz), 8.11 (s, 1H), 8.14 (d, 1H, J = 9.5 Hz), 8.54 (d, 1H, J = 8.4 Hz), 8.69 (s, 1H). Similarly, compound **9c** was made from **8c**.

Ethyl 1-Hydroxy-5,6,7,8-tetrahydro-3-naphthylcarboxylate (11a). A mixture of ethyl 1-hydroxy-3-naphthylcarboxylate **10**[12] (3.0 g, 13.8 mmol) and 20% $Pd(OH)_2$/C (1.0 g, wet) in 200 mL of methanol was stirred under a 1 atm of H_2 for 48 h. The catalyst was filtered through Celite, and the filtrate evaporated to give 3.0 g (98%) of **11a** as solid: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H, J = 7.2 Hz), 1.7−2.0 (m, 4H), 2.68 (t, 2H, J = 6.8 Hz), 2.78 (t, 2H, J = 6.8 Hz), 4.35 (q, 2H, J = 7.2 Hz), 5.48 (s, 1H, D_20 exchangeable), 7.35 (s, 1H), 7.36 (br s, 1H).

Ethyl 1-(2-Bromoethyl)-5,6,7,8-tetrahydro-3-naphthylcarboxylate (12a). Compounds **12a** and **12b** were prepared from compound **11a** and **11b,** respectively, by using the procedures described earlier.[4] This paper also describes an alternative method for the preparation of compound **12a** from **21**.

Benzyl 1-Hydroxy-2,4-dichloro-5,6,7,8-tetrahydro-3-naphthylcarboxylate (13). A solution of **11a** (12.38 g, 56.2 mmol) in 100 mL of dioxane and a solution of 1 N NaOH (112.5 mL, 112.5 mmol) was heated at 70 °C for 36 h. After cooling to room temperature, the solvents were removed under vacuum. The residue was dissolved in 100 mL of water, and the solution was adjusted to pH 3.5 with 3 N HCl, upon which the product precipitated out. The solid was recovered by filtration, washed with water and dried over P_2O_5 under vacuum to give 9.44 g (86%) of 5,6,7,8-tetrahydro-1-hydroxy-3-naphthoic acid.

To a mixture of 5,6,7,8-tetrahydro-1-hydroxy-3-naphthoic acid (9.44 g, 49.0 mmol) and Cs_2CO_3 (19.1 g, 58.8 mmol) in 150 mL of DMF was added benzyl bromide (5.8 mL, 49.0 mmol) dropwise, at −20 °C. The reaction mixture was slowly allowed to come to 0 °C. After it was stirred for 18 h, the solvent was removed under reduced pressure, and the residue was dissolved in 200 mL of ether. The ethereal solution was washed with 0.5 N HCl and water and dried ($MgSO_4$). The solvent was removed, and the residue was purified by chromatography (25% EtOAc in hexane) to give 12.6 g (96%) of benzyl 5,6,7,8-tetrahydro-1-hydroxy-3-naphthylcarboxylate: ^{1}H NMR (DMSO-d_6) δ 1.68 (m, 4H), 2.55 (m, 2H), 2.69 (m, 2H), 5.28 (s, 2H), 7.18 (s, 2H), 7.21 (s, 1H), 7.4 (m, 5H), 9.65 (s, 1H).

To a solution of benzyl 5,6,7,8-tetrahydro-1-hydroxy-3-naphthylcarboxylate (9.0 g, 31.5 mmol) in 100 mL of CH_2Cl_2 was added a solution of SO_2Cl_2 (79 mL, 79.0 mmol) at 0 °C. After it was stirred for 30 min, the mixture was neutralized with saturated $NaHCO_3$, diluted with cold water (100 mL), and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with water (2 × 20 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography (10% EtOAc in hexane) to give 8.3 g (74%) of **13**: ^{1}H NMR (DMSO-d_6) δ 1.71 (m, 4H), 2.63 (m, 4H), 5.39 (s, 2H), 7.4 (m, 5H), 9.7 (br peak, 1H).

Benzyl 1-(2-Bromoethyl)-2,4-dichloro-5,6,7,8-tetrahydro-3-naphthylcarboxylate (14). Into a mixture of **13** (8.3 g, 23.0 mmol) and benzoyl peroxide (0.24 g, 1.0 mmol) in 200 mL of hexane was bubbled HBr gas at 0 °C for 25 min. After the mixture was stirred for 2 h at room temperature, it was diluted with 200 mL of ether and washed with water (3 × 40 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by chromatography (2% EtOAc in hexane) to give 5.0 g (50%) of **14**: ^{1}H NMR (DMSO-d_6) δ 1.74 (m, 4H), 2.69 (m, 2H), 2.84 (m, 2H), 3.29 (t, 2H, J = 5.4 Hz), 3.60 (t, 2H, J = 5.4 Hz), 5.4 (s, 2H), 7.4 (m, 5H).

Ethyl 1-Hydroxy-4-bromo-5,6,7,8-tetrahydro-2-naphthylcarboxylate (16). Compound **16** was prepared in two steps from compound **15**. **Step 1** was performed using the procedure described for the preparation of compound **10** from **11a**.

Step 2. To a solution of ethyl 1-hydroxy-5,6,7,8-tetrahydro-2-naphthylcarboxylate (6.4 g, 29.0 mmol) in 50 mL of acetic acid was added a solution of bromine (1.5 mL, 29.0 mmol) in 50 mL of acetic acid over 2.0 h. After an additional 1 h, the solvent was evaporated, the residue was diluted with ice−water, and the compound was extracted with ether and dried ($MgSO_4$). The product was purified by chromatography (3% EtOAc in hexane) to give 3.5 g (40% after two steps) of **16**: ^{1}H NMR (DMSO-d_6) δ 1.36 (t, 3H, J = 7.1 Hz), 1.6−1.9 (m, 4H), 2.5−2.7 (m, 4H), 4.38 (q, 2H, J = 7.1 Hz), 7.7 (s, 1H).

Ethyl 1-Bromo-4-isopropyloxy-5,6,7,8-tetrahydronaphthyl-3-carboxylate (17b). To a solution of **16** (8.0 g, 26.7 mmol) in 120 mL of DMSO was added K_2CO_3 (11.0 g, 80.1 mmol) followed by 2-iodopropane (3.9 mL, 40.0 mmol). After 2.0 h at 60 °C, the mixture was diluted with water (200 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed to give 8.3 g of **17b** as oil and was used as is for the next step: ^{1}H NMR (DMSO-d_6) δ 1.19 (d, 6H, J = 6.1 Hz), 1.3 (t, 3H, J = 7.0 Hz), 1.5−1.8 (m, 2H), 2.6−2.8 (m, 2H), 4.0−4.4 (m, 3H), 7.69 (s, 1H). Similarly, compounds **17a** and **17c** were made from **16**.

Ethyl 1-(2-Bromoethyl)-4-isopropyloxy-5,6,7,8-tetrahydronaphthyl-3-carboxylate (18b). Compound **18b** was prepared from compound **17b** by using the procedures described for the preparation of compound **9a** from **7a** (69%) as an oil: ^{1}H NMR (DMSO-d_6) δ 1.18 (d, 6H, J = 6.1 Hz), 1.3 (t, 3H, J = 7.0 Hz), 1.5−1.8 (m, 2H), 2.6−2.8 (m, 2H), 3.1 (t, 1H, J = 7.4 Hz), 3.68 (t, 1H, J = 7.4 Hz), 4.1 (h, 1H, J = 6.8 Hz), 4.27 (q, 2H, J = 7.0 Hz), 7.37 (s, 1H). Similarly, compounds **18a** and **18c** were made from **17a** and **17c,** respectively.

Ethyl 1-(2-Bromoethyl)-2-methoxy-5,6,7,8-tetrahydronaphthyl-3-carboxylate (20). Compound **20** was prepared from compound **19** by using the procedures described for the preparation of compound **18b** from **15**: ^{1}H NMR (DMSO-d_6) δ 1.31 (t, 3H, J = 7.0 Hz), 1.6−1.8 (m, 2H), 2.6−2.8 (m, 2H), 3.1 (t, 1H, J = 7.2 Hz), 3.53 (t, 1H, J = 7.2 Hz), 3.7 (s, 1H), 4.27 (q, 2H, J = 7.0 Hz), 7.37 (s, 1H).

3-[2-(3-Carboxy-2,4-dichloro-5,6,7,8-tetrahydronaphthyl)ethyl]-3,6,7,8- tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (24c). A mixture of 3-[2-(3-carbobenzyloxy-2,4-dichloro-5,6,7,8-tetrahydronaphthyl)ethyl]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol **26i** (298 mg, 0.58 mmol) and 35 mg of 10% Pd/C in 20 mL of MeOH was stirred under H_2 at 1 atm (balloon) for 30 h and then filtered over Celite. The filtrate was evaporated, and the residue was taken into 1 mL of 0.1 N NaOH, mixed with 2.0 g of DOWEX-1 × 8−400 acetate ion-exchange resin for 45 min, and then filtered. The resin was washed with water (100 mL) followed by a mixture of 10:1 of 0.1 N AcOH and MeOH (500 mL). The AcOH/MeOH filtrate was lyophilized to provide 104 mg (46%) of **24c** as white powder: mp 220−230 °C (decomposes); ^{1}H NMR (DMSO-d_6) δ 1.68 (m, 4H), 2.65 (m, 4H), 3.12 (m, 2H), 3.18 (br s, 2H), 4.0 (m, 2H), 4.8 (br s, 1H), 7.0 (d, 1H, J = 4.0 Hz), 7.25 (s, 1H), 7.55 (m, 1H). Anal. ($C_{19}H_{20}N_4O_3Cl_2 \cdot 1.4H_2O$) C, H, N.

The following is the general three-step procedure for preparation of compound **24b** from 6,7-dihydroimidazo[4,5-*d*][1,3]-diazepin-8(3*H*)-one **5**.[9]

3-[2-(3-Carboxy-4-bromo-5,6,7,8-tetrahydronaphthyl)-ethyl]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (24b). Step 1. Alkylation. According to the procedure previously described,[5] compound 6,7-dihydroimidazo[4,5-*d*]-[1,3]diazepin-8(3*H*)-one **5**[9] was alkylated with ethyl 1-(2-bromoethyl)-4-bromo-5,6,7,8-tetrahydronaphthyl-3-carboxylate **12b** in the presence of NaH. Chromatography on SiO_2 with a CH_2Cl_2/MeOH gradient of 20:1, 18:1, and 15:1 provided 3-[2-(3-carboethoxy-4-bromo-5,6,7,8-tetrahydronaphthyl)ethyl]-6,7-dihydroimidazo-[4,5-*d*][1,3]diazepin-8(3*H*)-one: ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3H, J = 7.0 Hz), 1.74 (m, 4H), 2.74 (m, 4H), 3.0 (t, 2H, J = 7.4 Hz), 3.72 (d, 2H, J = 4.1 Hz), 4.17 (t, 2H, J = 7.4 Hz), 4.25 (q, 2H, J = 7.0 Hz), 7.19 (s, 1H), 7.43 (d, 1H, J = 4.6 Hz), 7.57 (s, 1H), 8.4 (m, 1H).

Step 2. Reduction. According to the procedure previously described,[4] 3-[2-(3-carboethoxy-5,6,7,8-tetrahydronaphthyl)-ethyl]-6,7-dihydroimidazo-[4,5-*d*][1,3]diazepin-8(3*H*)-one was reduced with $NaBH_4$. Chromatography on SiO_2 with a CH_2Cl_2/MeOH gradient of 15:1 and 10:1 with 0.3% Et_3N provided 3-[2-(3-carboethoxy-4-bromo-5,6,7,8-tetrahydronaphthyl)ethyl]-3,6,7,8-tetrahydroimidazo [4,5-*d*][1,3]diazepin-8-ol **26c**: mp 100−102 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3H, J = 7.0 Hz), 1.71 (m, 4H), 2.7 (m, 4H), 2.97 (t, 2H, J = 7.4 Hz), 3.1 (br s, 2H), 3.94.1 (m, 2H), 4.26 (q, 2H, J = 7.0 Hz), 4.78 (m, 1H), 4.9 (br s, 1H), 7.1 (d, 1H, J = 4.4 Hz), 7.2 (s, 1H), 7.7 (s, 1H), 7.8 (m, 1H). Anal. ($C_{21}H_{25}N_4O_3Br\cdot1.2H_2O\cdot0.1Et_3N$) C, H, N.

Step 3. Hydrolysis. According to the procedure previously described,[4] 3-[2-(3-carboethoxy-4-bromo-5,6,7,8-tetrahydronaphthyl)ethyl]-3,6,7,8-tetrahydroimidazo [4,5-*d*][1,3]diazepin-8-ol **26c** was hydrolyzed with 0.1 N NaOH in dioxane. The product was isolated with DOWEX-1 × 8−400 acetate ion-exchange resin to provide **24b** as a white powder: mp 200−220 °C (decomposes); ^{1}H NMR (DMSO-d_6) δ 1.69 (m, 4H), 2.65 (m, 4H), 2.85 (t, 2H, J = 7.4 Hz), 3.18 (br s, 2H), 4.0 (t, 2H, J = 7.4 Hz), 4.8 (br s, 1H), 4.95 (br s, 1H), 6.86 (s, 1H), 7.0 (d, 1H, J = 4.0 Hz), 7.27 (s, 1H), 7.5 (br s, 1H). Anal. ($C_{19}H_{21}N_4O_3Br\cdot3.0H_2O\cdot1.0CH_3CO_2H$) C, H, N.

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Supporting Information Available: Elemental analysis data for the compounds in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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