Synthesis and Structure−Activity Studies on *N*-[5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]methanesulfonamide, an Imidazole-Containing α_{1A}-Adrenoceptor Agonist[1]

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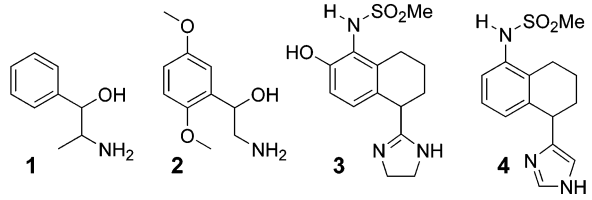
Structure−activity studies were performed on the α_{1A}-adrenoceptor (AR) selective agonist *N*-[5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]methanesulfonamide (**4**). Compounds were evaluated for binding activity at the α_{1A}, α_{1b}, α_{1d}, α_{2a}, and α_{2B} subtypes. Functional activity in tissues containing the α_{1A} (rabbit urethra), α_{1B} (rat spleen), α_{1D} (rat aorta), and α_{2A} (rat prostatic vas deferens) was also evaluated. A dog in vivo model simultaneously measuring intraurethral pressure (IUP) and mean arterial pressure (MAP) was used to assess the uroselectivity of the compounds. Many of the compounds that were highly selective in vitro for the α_{1A}-AR subtype were also more uroselective in vivo for increasing IUP over MAP than the nonselective α_1-agonists phenylpropanolamine (PPA) (**1**) and ST-1059 (**2**, the active metabolite of midodrine), supporting the hypothesis that greater α_{1A} selectivity would reduce cardiovascular side effects. However, the data also support a prominent role of the α_{1A}-AR subtype in the control of MAP.

Introduction

Stress urinary incontinence (SUI) is due to the inability of the urethra to restrict the leakage of urine during stresses such as coughing or sneezing. In the human, postsynaptic urethral tone is largely mediated by activation of α-adrenoceptors (α-ARs).[2] The nonselective α_1-adrenergic agonists **1**[3] and midodrine[4] have been found to be efficacious in clinical studies for the treatment of SUI. Unfortunately, these agents suffer from side effects that include increases in blood pressure (BP).[2−5]

Three subtypes of the α_1-AR have been identified (α_{1A}, α_{1B}, and α_{1D}),[6] and there is strong evidence that the α_{1A}-AR is the primary subtype in the human urethra and the receptor most likely to be responsible for constriction of the urethra.[7] Evidence has pointed toward a prominent role of the α_{1B}-AR in the control of BP. In vitro radioligand binding selectivity of antagonists selective for the α_{1A} over the α_{1B} subtype has been shown to correspond to selectivity in vivo for blockade of agonist-induced increases of intraurethral pressure (IUP) versus arterial pressure.[8,9] Treatment with tamsulosin, an α_1-antagonist with affinity for the α_{1B}-AR lower than that of the α_{1A} and α_{1D} subtypes, is associated with fewer vascular events, compared to classical nonselective α_1-AR antagonists.[10] In addition, a mouse knockout study provided evidence for a prominent role of the α_{1B} subtype in the control of blood pressure.[11] The role of the α_{1D}-AR has not been fully elucidated, but this subtype has been demonstrated to play a part in the pressor responses to sympathetic stimulation.[12−14] Therefore, we were interested in finding α_{1A} selective agonists with the hope that these agents would constrict the urethra with fewer hypertensive side effects than seen with the nonselective α_1 agonists.

Chart 1. Selective and Nonselective α_1-Agonists



In searching for novel structures based on the selective α_{1A}-agonist A-61603 (**3**),[15] we discovered imidazole **4**.[16] An in vivo dog model demonstrated that **4** was more selective than **1**−**3** (see Chart 1) for increasing IUP over mean arterial pressure (MAP). SAR studies were performed on **4** in which modifications were made to the sulfonamide, the aromatic ring, the tetralin, and the imidazole. The results of these studies are presented.

Chemistry

The syntheses of the compounds are shown in Schemes 1−3. Starting with a nitroketone of structure **A** (see Scheme 1), the imidazole ring was introduced via a Grignard reagent generated in situ from 4-iodo-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazole **5**[17] or 4-iodo-1-trityl-1*H*-imidazole **6**.[18] The intermediate alcohol (not shown)

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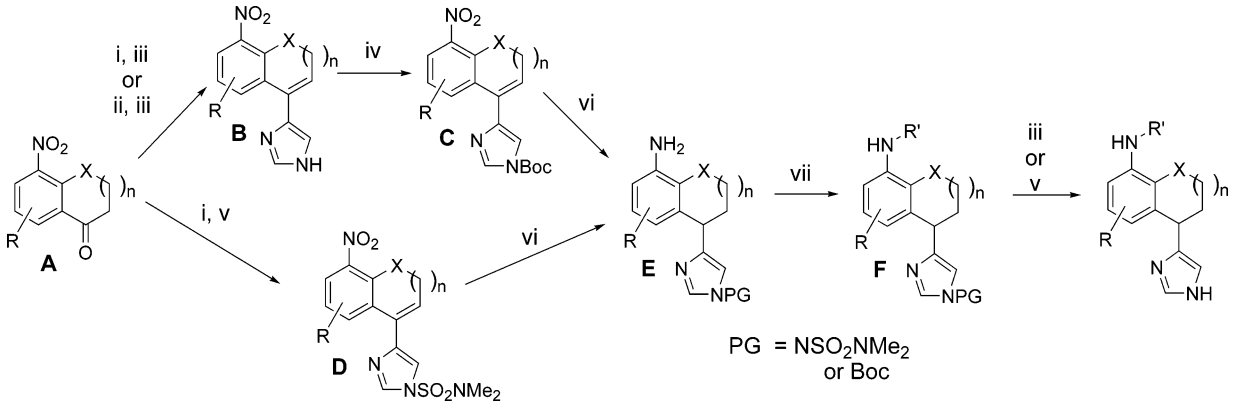
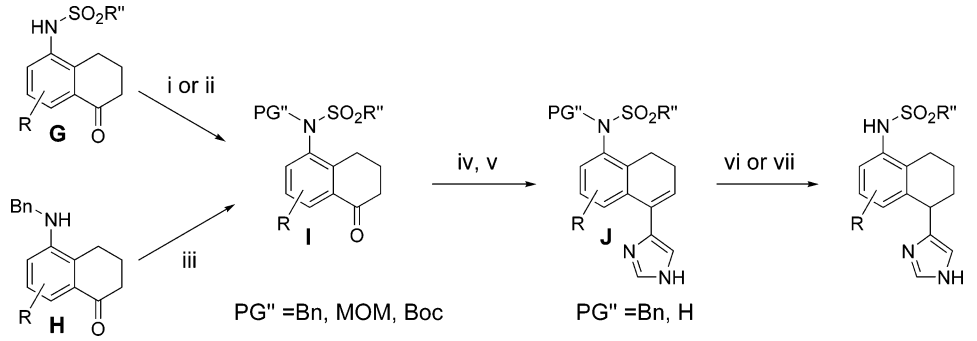
Scheme 1[a]



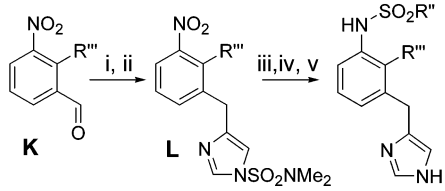
[a] Conditions: (i) EtMgBr, **5**, CH_2Cl_2; (ii) EtMgBr, **6**, CH_2Cl_2; (iii) aqueous HCl, Δ; (iv) Boc_2O, CH_3CN, Δ; (v) TFA; (vi) H_2, Pd/C, EtOAc; (vii) R′Cl or R'_2O, pyridine, CH_2Cl_2. Method A: conditions i, iii. Method B: conditions ii, iii. Method C: conditions i, v. Method D: condition iv. Method E: condition vi. Method F: condition vii. Method G: condition v. Method H: condition iii.

Scheme 2[a]



[a] Conditions: (i) NaH, DMF; MOMCl; (ii) NaH, DMF; Boc_2O; (iii) R″SO_2Cl, pyridine, CH_2Cl_2; (iv) EtMgBr, **5**, CH_2Cl_2; (v) aqueous HCl, Δ; (vi) H_2, Pd/C (0.1 wt equiv), MeOH; (vii) H_2, Pd/C (1 wt equiv), MeOH. Method B: conditions iv, v. Method I: condition vii; Method J: condition vi.

Scheme 3[a]



[a] Reagents and conditions: (i) EtMgBr, **5**, CH_2Cl_2; (ii) Et_3SiH, TFA, Δ; (iii) H_2, Pd/C, EtOAc; (iv) R″SO_2Cl, pyridine, CH_2Cl_2; (v) aqueous HCl, Δ.

was dehydrated under acidic conditions with or without deprotection of the imidazole to provide alkenes **B** or **D**. Imidazole **B** was protected with a Boc group to provide derivative **C**. Hydrogenation of **C** or **D** provided the saturated aniline intermediate of structure **E**. Formation of the sulfonamide, carbamate, or amide followed by deprotection provided the desired products. Enantiomeric separation for several examples was accomplished by chiral chromatography of the Boc-protected intermediates of structure **F**.

In certain cases, protected sulfonamidotetralones of structure **I** were suitable intermediates for elaboration to the final compounds (see Scheme 2). Intermediate **I** was available via N-protection of sulfonamides **G** or by sulfonation of benzylanilines **H**. Treatment of the protected ketosulfonamides with the Grignard reagent derived from **5** followed by acidic deprotection provided the unsaturated imidazoles **J**. In the cases where the protecting group (PG″) was MOM or Boc, the NH sulfonamide was obtained after the dehydration step. Reduction of the double bond with concomitant removal of the Bn group when PG″ = Bn provided the desired products.

In cases where the benzylic position was unsubstituted (Scheme 3), nitroaldehydes of structure **K** were treated with the Grignard reagent derived from **5**. The resulting intermediate alcohol was reduced by treatment with triethylsilane in the presence of TFA to provide intermediate **L**, which was sulfonated and deprotected as described in Scheme 1.

Syntheses of individual compounds such as the imidazole modifications in Table 5 can be found in the Experimental Section.

Biological Evaluation

Compounds were evaluated in radioligand binding assays. The α_1 binding assays (α_{1A}, α_{1b}, and α_{1d}) were performed (see Tables 1−5) essentially as described by Knepper et al.[19] The α_{2a} and α_{2B} binding assays (see Table 6) were performed as described.[20,21] The binding selectivities of the compounds for the α_{1A} subtype versus the other subtypes are shown.

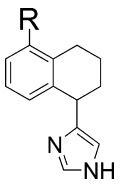
The functional agonism of the test compounds to constrict tissue containing the α_{1A} (rabbit urethra), α_{1B} (rat spleen), and α_{1D} (rat aorta) ARs was evaluated.[22a] Efficacy of less than 15% relative to phenylephrine (PE) was considered inactive. The α_{1D} functional data for the test compounds were excluded from Tables 2−5 because all of the compounds except for two were inactive in rat

Table 1. In Vitro Profile of **1**−**3**

	α_1 binding,[a] pK_i					functional, pD_2 (% efficacy)[b]				
				selectivity					selectivity	
compd	α_{1A}	α_{1b}	α_{1d}	α_{1b}/α_{1A}	α_{1d}/α_{1A}	rabbit urethra α_{1A}	rat spleen α_{1B}	rat aorta α_{1D}	α_{1B}/α_{1A}	α_{1D}/α_{1A}
1	5.01 ± 0.20	5.02 ± 0.18	5.07 ± 0.19	1	1	3.63 ± 0.10 (68)	3.55 ± 0.14 (34)	4.12 ± 0.11 (91)	1	0.2
2	5.70 ± 0.10	5.16 ± 0.05	5.78 ± 0.06	3	0.8	5.15 ± 0.07 (133)	4.07 ± 0.07 (68)	5.73 ± 0.14 (68)	12	1
3	7.92 ± 0.10	5.53 ± 0.18	5.83 ± 0.05	200	100	8.03 ± 0.13 (88)	6.50 ± 0.10 (91)	5.59 ± 0.07 (100)	30	200

[a] α_{1A}, rat submaxillary gland; α_{1b}, hamster clone; α_{1d}, rat clone. Number of determinations, ≥3. The pK_i (−log K_i) ± standard error of the mean (SEM) are reported. [b] α_1-Agonist dose−response curves were determined against rabbit urethra (α_{1A}), rat spleen (α_{1B}), and rat aorta (α_{1D}). The pD_2 (−log EC_{50}) ± SEM of the dose that contracted the tissue 50% (EC_{50}) and percent (%) efficacy (in parentheses) relative to phenylephrine (PE) are reported. Number of determinations, ≥4.

Table 2. Sulfonamide Modifications of **4**



		α_1 binding,[a] pK_i					functional, pD_2 (% efficacy)[a]	
					selectivity			
compd	R	α_{1A}	α_{1b}	α_{1d}	α_{1b}/α_{1A}	α_{1d}/α_{1A}	rabbit urethra α_{1A}	rat spleen α_{1B}
4	N(H)SO_2Me	6.71 ± 0.05	5.33 ± 0.12	5.80 ± 0.03	20	8	6.35 ± 0.06 (83)	inactive
7	(*R*)-(+)-N(H)SO_2Me	7.04 ± 0.06	5.70 ± 0.02	5.72 ± 0.03	20	20	6.45 ± 0.06 (84)	inactive
8	(*S*)-(−)-N(H)SO_2Me	5.94 ± 0.05	4.98 ± 0.02	5.77 ± 0.02	9	1	4.67 ± 0.08 (57)	inactive
9	N(Me)SO_2Me	6.69 ± 0.01[b]	<5[b]	6.15 ± 0.08[b]	>50	3	6.16 ± 0.09 (79)	5.65 ± 0.09 (21)
10	(+)-N(H)SO_2Et	7.33 ± 0.06[b]	5.88 ± 0.01[b]	5.97 ± 0.04[b]	30	20	6.77 ± 0.11 (71)	inactive
11	(+)-N(H)$SO_2CH_2CF_3$	6.91 ± 0.01[b]	<5[b]	<5[b]	>80	>80	5.73 ± 0.12 (52)	inactive
12	N(H)SO_2n-Pr	5.77 ± 0.06[b]	<5[c]	<5[c]	>6	>6	NT	NT
13	N(H)SO_2i-Pr	5.94 ± 0.04[b]	<5[b]	5.69 ± 0.03[b]	>9	2	5.17 ± 0.08[b](74)	inactive
14	N(H)SO_2c-Pr	6.27 ± 0.05[b]	<5	5.57 ± 0.07	>19	5	5.25 ± 0.1 (51)	NT
15	N(H)SO_2(2-nap)	6.16 ± 0.20[b,d]	6.67[c]	7.00[c]	1	0.4	inactive	NT
16	N(H)SO_2NMe_2	6.01 ± 0.01[b,d]	<5[c]	5.80[c]	20	3	NT	NT
17	N(H)COMe	6.28 ± 0.01[b]	<5[b]	<5[b]	20	19	5.89 ± 0.05 (70)	4.84 ± 0.07 (35)
18	N(H)$COCF_3$	6.78 ± 0.04[b]	<5[b]	5.48 ± 0.04[b]	60	20	6.28 ± 0.16(118)	5.47 ± 0.15 (19)
19	N(H)COOMe	6.83 ± 0.08[b,d]	5.00[c]	5.52[c]	100	30	NT	NT
20	OH	6.94 ± 0.02[b,d]	6.84[c]	7.51[c]	3	1	NT	NT
21[e]	NH_2	6.86 ± 0.02[b,d]	6.28[c]	6.72[c]	4	2	6.56 ± 0.14 (84)	6.01 ± 0.01[b] (35)

[a] See Table 1 footnotes. NT = not tested. [b] Number of determinations is 2. [c] Number of determinations is 1. [d] Bovine clone. [e] Compound **21** is a chroman derivative.

aorta.[23] Relaxation of field-stimulated rat prostatic vas deferens was used to measure the α_{2A} functional activity and referenced against clonidine.[22a]

In vivo assessment of uroselectivity was performed in a dog model similar to one used to evaluate α_1 antagonists. Briefly, MAP and IUP were measured[24] simultaneously in isoflurane anesthetized female beagles using a chronically implanted telemetry transducer/transmitter and a urethral catheter, respectively. Increasing doses of the target agents were administered via iv injection, and the maximal effect[25] of each dose was determined. The doses corresponding to a 5 mmHg increase in IUP (IUP $ED_{\Delta 5}$)[26] and a 20 mmHg increase in MAP (MAP $ED_{\Delta 20}$)[27] were calculated. For the purposes of comparing compounds, the ratios of the MAP $ED_{\Delta 20}$ over the IUP $ED_{\Delta 5}$ (MAP/IUP ratio) for selected test compounds are shown in Table 7.

In Vitro Studies

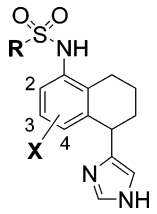
In vitro data for the α_1-AR agonists **1**−**3** are displayed in Table 1. Compounds **1** and **2** demonstrated no selectivity for the α_{1A} subtype in binding studies, and only **2** showed any functional (α_{1A} over α_{1B}) selectivity. Compound **3** was highly selective for the α_{1A}-AR in binding and functional studies.

Compound **4** bound to the α_{1A} subtype with a pK_i of 6.71 and was 20- and 8-fold selective for the α_{1A} over α_{1b} and α_{1d} subtypes, respectively (see Table 2). In comparison to the compounds displayed in Table 1, **4** was between **3** and **2** in binding potency and selectivity for the α_{1A} subtype. Compound **4** had similar binding potency for the α_{1A} and the α_2 subtypes (see Table 6). Many of the compounds in this series bound with high affinity to the α_2 subtypes, and this will be addressed later in this paper.

In functional studies, **4** contracted the rabbit urethra (α_{1A}) with a pD_2 = 6.35 and an efficacy of 83% relative to PE. In contrast to the agents depicted in Table 1, **4** was inactive at both rat spleen (α_{1B}) and rat aorta (α_{1D}). Separation of the enantiomers revealed that the (*R*)-(+)-enantiomer **7** possessed the activity and had an in vitro profile similar to that of the racemate.

Small modifications to the sulfonamide of **4** were allowed. Methylation of the sulfonamide NH produced **9**, a compound with a binding potency similar to that of **4** but over twice as selective for the α_{1A} over the α_{1B} subtype. The (+)-ethylsulfonamide, **10**, was more potent and selective for the α_{1A} subtype than **4** in the binding assay and functional studies. The improved potency of **10** led us to incorporate the ethyl sulfonamide into many

Table 3. Substitutions on the Aromatic Portion of **4**



			α_1 binding,[a] pK_i			selectivity		functional, pD_2 (% efficacy)[a]	
compd	X	R	α_{1A}	α_{1b}	α_{1d}	α_{1b}/α_{1A}	α_{1d}/α_{1A}	rabbit urethra α_{1A}	rat spleen α_{1B}
22	2-OH	Me	7.44 ± 0.06	5.60 ± 0.01	5.90 ± 0.09	70	30	7.77 ± 0.04[c] (104)	6.64 ± 0.13 (94)
23	2-OCH_3	Me	6.30 ± 0.03[b]	5.77 ± 0.12[b]	6.32 ± 0.04[b]	3	1	inactive[c]	inactive
24	3-F	Et	7.08 ± 0.10	<5	5.44 ± 0.22	>121	44	NT	NT
25	3-Cl	Et	7.34 ± 0.06	<5	6.44 ± 0.06	>217	8	NT	NT
26	3-c-hexyl	Et	6.57 ± 0.00[b]	6.05 ± 0.03	6.35 ± 0.02	3	2	NT	NT
27	4-OH	Me	6.15 ± 0.11[b]	<5[b]	<5[b]	>14	>14	4.61 ± 0.12 (34)	inactive
28	4-MeO	Me	5.77 ± 0.05	<5	<5	>6	>6	4.81 ± 0.10 (57)	4.74 ± 0.21 (26)
29	4-Me	Me	6.41 ± 0.12[b]	<5[b]	5.57 ± 0.03[b]	>26	7	4.40 ± 0.10 (35)	inactive
30	4-F	Me	6.51 ± 0.07[b]	<5[b]	5.52 ± 0.07[b]	>32	10	5.31 ± 0.11 (64)	inactive
31	4-Cl	Me	6.35 ± 0.06[b]	<5[b]	5.54 ± 0.04[b]	>20	6	4.35 ± 0.14 (41)	inactive

[a] See Table 1 footnotes. NT = not tested. [b] Number of determinations is 2. [c] Agonist dose−response curves determined against rat epididymal vas deferens.[22b]

of the modifications of compound **4**. The (+)-trifluoroethyl analogue **11** had a similar binding affinity compared to **4** for the α_{1A} subtype but was less potent in functional studies.

Further increases in the size of the aliphatic group on the sulfonamide (compounds **12**−**14**) resulted in decreased potency in binding and functional studies. Aromatic sulfonamides were generated using parallel synthesis techniques. In summary, aromatic substitutions on the sulfonamide provided compounds that either had no affinity for the α_{1A} subtype or bound (i.e., **15**) but did not have any functional activity in rabbit urethra.

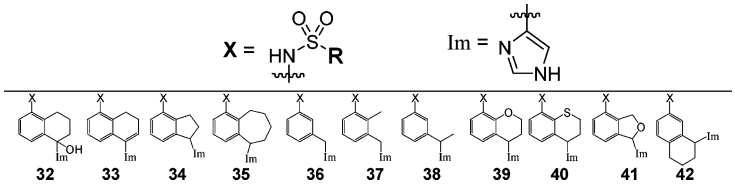
Replacement of the sulfonamide with other groups was examined. Compared with **4**, the sulfonyl urea, **16**, and the acetamide, **17**, provided slightly reduced potency for the α_{1A} subtype in binding studies. The trifluoroacetamide **18** was equipotent with **4** for the α_{1A} subtype in binding and functional studies. The carbamate **19** showed good potency and selectivity in binding studies. The phenol and aniline, **20**[28] and **21**, bound effectively with the α_{1A} subtype but were less selective against the α_{1B} and α_{1D} subtypes.

Substitutions were made on the aromatic portion of the tetralin of **4** (Table 3). The 2-hydroxy analogue, **22**, is structurally similar to **3** and has a similar pharmacological profile as a full agonist at the α_{1B} and α_{1D}[23] subtypes. The 2-methoxy derivative **23** had reduced activity and selectivity in binding studies and was inactive in functional studies. Substitution at the 3 position with F or Cl provided compounds both potent and highly selective for the α_{1A} subtype vs α_{1B}. Compound **26**, with a bulky cyclohexyl group at the 3 position, maintained good affinity for the α_{1A} subtype, but the selectivity was diminished. Substitution at the 4 position resulted in compounds (**27**−**31**) with reduced potency in binding and functional studies.

Modifications were made to the aliphatic portion of the tetralin ring of **4** (Table 4). Incorporation of a hydroxyl group α to the imidazole (**32**) or oxidation of the ring to the dihydronaphthalene (**33**) resulted in a loss of activity. Reduction of the ring size from tetralin to indane, **34**, resulted in a compound that was approximately 8-fold more potent and more selective for the α_{1A} subtype in binding and functional studies.[29] Increasing the size of the tetralin to the benzocycloheptane **35** resulted in a significant loss of in vitro potency. The chroman **39** and thiochroman **40** displayed a 2- and 5-fold reduction in potency, respectively, compared to **4**. The isobenzofuran **41** was over 40-fold less potent in binding to the α_{1A} subtype than the indane **34**. This reduction in potency may be a result of hydrogen bonding between the imidazole and the oxygen of **41**. A similar hydrogen-bonding effect may be the cause for the reduced potency for compound **28**. The regioisomeric derivative **42** essentially lost all activity for the α_{1A} subtype but was fairly potent at the α_2 subtypes (see Table 6). Removal of the aliphatic portion of the tetralin provided **36** (ABT-866), an agent on which we have previously published.[22a,30] Compound **36** was found to possess antagonistic activity for the α_{1B} and α_{1D} subtypes. Compound **37** had a α_{1A} binding potency similar to that of **36** but with improved selectivity. A methyl group at the benzylic position as in **38** was found to be deleterious to α_{1A} potency.

Several modifications were made to the imidazole and the benzylic portion of the molecule (see Table 5). None of the modifications examined were favorable. Methyl substitution of the imidazole (**43**−**45**) reduced activity. Although **43** displayed binding potency (α_{1A} pK_i = 6.56) similar to that of **4**, **43** was very weak in constricting the rabbit urethra (pD_2 = 5.26). Primary and secondary amines (**46**, **47**, **51**, and **54**) had moderate affinity for the α_{1A} subtype (α_{1A} pK_i = 6.10, 5.86, 6.15, and 6.30, respectively) but were found to be inactive in functional studies. The 2-imidazoline, **48**, was slightly weaker in binding potency at the α_{1A} subtype but had an overall in vitro profile similar to that of **4** (α_{1A} pK_i = 6.34, rabbit urethra (α_{1A}) pD_2 = 6.19, inactive in rat spleen (α_{1B})). The clonidine analogue **50** was very weak in binding (pK_i = 5.35) to the α_{1A} subtype and inactive in rabbit urethra. Removal (compound **49**) or replacement of the

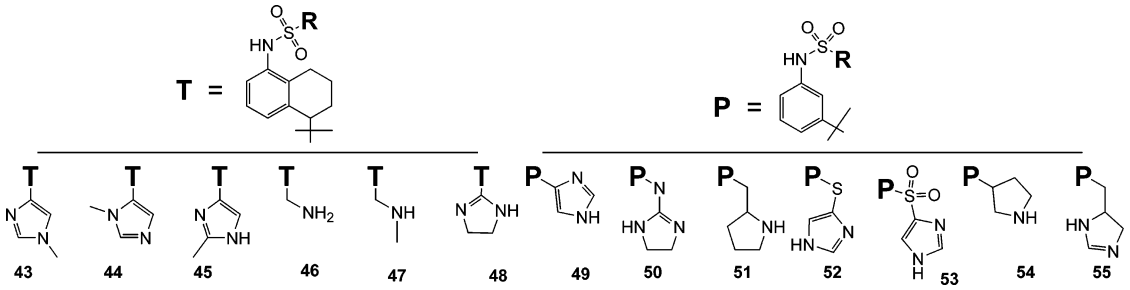
Table 4. Carbocyclic Modifications to **4**



		binding[a] (pK_i)			selectivity		α_1 functional, pD_2 (% efficacy)[a]	
compd	R	α_{1A}	α_{1b}	α_{1d}	α_{1b}/α_{1A}	α_{1d}/α_{1A}	rabbit urethra α_{1A}	rat spleen α_{1B}
32	Et	<5[b]	<5[b]	<5[b]	1	1	NT	NT
33	Me	6.08 ± 0.04[b]	<5[b]	5.67 ± 0.05[b]	>10	3	4.54 ± 0.21 (23)	inactive
34	Et	7.65 ± 0.06	5.70 ± 0.07	6.01 ± 0.1	90	40	7.18 ± 0.15[b](87)	inactive[b]
35	Me	5.87 ± 0.02[b]	5.00[b]	5.60 ± 0.03[b]	>7	2	4.72 ± 0.14[b](17)	NT
36	Et	6.87 ± 0.05	6.05 ± 0.07	6.56 ± 0.06	7	2	6.22 ± 0.05 (80)	inactive
37	Et	6.89 ± 0.13	5.09 ± 0.09	6.00 ± 0.1	60	8	5.6 ± 0.09 (69)	inactive
38	Me	6.08 ± 0.02	<5	6.16 ± 0.04	10	1	5.38 ± 0.04 (92)	inactive
39	Me	6.32 ± 0.04	<5	5.94 ± 0.07	20	2	6.00 ± 0.26 (88)	5.09 ± 0.09 (17)
40	Et	6.00[c]	<5[c]	<5[c]	10	10	NT	NT
41	Et	6.03 ± 0.00[b]	<5[c]	<5[c]	10	10	NT	NT
42	Et	5.69 ± 0.02[b,d]	5.87[c]	6.47[c]	1	0.2	NT	NT

[a] See Table 1 footnotes. NT = not tested. [b] Number of determinations is 2. [c] Number of determinations is 1. [d] Bovine clone.

Table 5. Modifications to Imidazole



			binding[a] (pK_i)			selectivity		α_1 functional, pD_2 (% efficacy)[a]	
compd	T/P	R	α_{1A}	α_{1b}	α_{1d}	α_{1b}/α_{1A}	α_{1d}/α_{1A}	rabbit urethra α_{1A}	rat spleen α_{1B}
43	T	Me	6.56 ± 0.03	5.69 ± 0.05	5.98 ± 0.08	7	4	5.26 ± 0.15 (40)	inactive
44	T	Me	<5	<5	<5			NT	NT
45	T	Et	6.10[c]	<5[c]	<5[c]	>10	>10	NT	NT
46	T	Et	6.10 ± 0.02[b]	<5[b]	<5[b]	>10	>10	inactive	inactive
47	T	Et	5.86 ± 0.04[b]	<5[b]	<5[b]	>7	>7	NT	NT
48	T	Me	6.34 ± 0.21	5.13 ± 0.14	5.37 ± 0.3	20	9	6.19 ± 0.07 (87)	inactive
49	P	Et	<5[b]	<5[b]	<5[b]			NT	NT
50	P	Et	5.53 ± 0.02[b]	<5[b]	6.45 ± 0.13[b]	>3	<0.04	NT	NT
51	P	Et	6.15 ± 0.01[b]	<5[b]	6.30 ± 0.*02*[b]	>10	1	4.44 ± 0.09 (17)	inactive
52	P	Et	<5[b]	<5[b]	<5[b]			NT	NT
53	P	Et	<5[b]	<5[b]	<5[b]			NT	NT
54	P	Et	6.30 ± 0.08[b]	<5[b]	6.00 ± 0.00	>20	2	inactive	NT
55	P	Et	<5[b]	5.00	5.19 ± 0.19			NT	NT

[a] See Table 1 footnotes. NT = not tested. [b] Number of determinations is 2. [c] Number of determinations is 1.

methylene with a sulfur or sulfoxide group (compounds **52** and **53**) led to inactive compounds. Partial reduction of the imidazole (compound **55**) also resulted in complete loss of activity.

In Vivo Studies

Many of the compounds were evaluated in vivo, and the results are shown in Table 7. The in vitro nonselective α_1 agonist **1** was found to have a MAP/IUP ratio of 0.4 in vivo. Compounds **2** and **3**, both selective for the α_{1A} over the α_{1B} subtype in functional studies, had improved in vivo profiles relative to **1**.

Compound **4**, an α_{1A}-agonist devoid of activity at functional α_{1B} and α_{1D} subtypes, was approximately 100-fold less potent in vivo but more uroselective than **3** with an MAP/IUP ratio of 4.8. The active enantiomer **7** had an in vivo profile similar to that of the racemate.

Small modifications to the sulfonamide of **4** were allowed in vivo. Although the N-methylated sulfonamide **9** had in vitro functional potency and selectivity similar to those of **4**, its in vivo potency was reduced by over 3-fold and the in vivo selectivity was reduced. As expected from their relative α_{1A} functional potencies in rabbit urethra, the (+)-ethylsulfonamide **10** was 2-fold more potent than **7** in vivo for constricting the urethra, and the (+)-trifluoroethyl analogue **11** was less potent. No improvement with in vivo uroselectivity over **7** was found with these analogues.

Table 6. α_2 Binding and Functional Data[a]

	α_2 binding[b] (pK_i)					
			selectivity		α_{2A} functional, pD_2 (% efficacy)[c]	
compd	α_{2a}	α_{2B}	α_{2a}/α_{1A}	α_{2B}/α_{1A}	rat prostatic vas α_{2A}	selectivity α_{2A}/α_{1A}
1	6.56 ± 0.13	6.58 ± 0.04	0.03	0.03	5.17 ± 0.09 (85)	0.03
2	5.84 ± 0.16	5.73 ± 0.07	0.7	0.9	8.23 ± 0.05 (20)	0.001
3	7.48 ± 0.11	6.61 ± 0.21	3	20	NT	
4	6.98 ± 0.08	6.17 ± 0.08	0.5	3	7.45 ± 0.44 (62)	0.08
7	NT	NT			8.05 ± 0.18 (29)	0.03
9	7.07 ± 0.06[c]	6.04[d]	0.4	4	7.08 ± 0.13 (100)	0.12
10	6.88 ± 0.06[c]	5.77 ± 0.15[c]	3	40	5.95 ± 0.14 (66)	7
11	6.02 ± 0.02[c]	<5[c]	8	>80	6.59 ± 0.1 (100)	0.14
17	6.26 ± 0.05[c]	5.52[d]	1	6	6.64 ± 0.24 (100)	0.2
18	6.51 ± 0.09[c]	6.18[d]	2	4	7.14 ± 0.11 (100)	0.1
20	8.06[d]	8.42[d]	0.2	0.1	NT	
21	7.14[d]	7.31[d]	0.6	0.4	NT	
22	7.35 ± 0.05	7.32 ± 0.06	1	1	NT	
34	7.01 ± 0.06	6.73 ± 0.16	4	8	6.68 ± 0.51[c] (26)	3
36	6.77 ± 0.11	6.01 ± 0.02	1	7	5.45 ± 0.19 (34)	6
42	7.64[d]	7.65[d]	0.02	0.02	NT	

[a] Complete α_2 table available in Supporting Information. [b] α_{2a}, human clone; α_{2B}, rat neonatal lung. Number of determinations, ≥3. The pK_i ($-\log K_i$) ± standard error of the mean (SEM) are reported. NT = not tested. [c] α_{2A} dose−response curves were determined by the inhibition of the field-stimulated contraction of rat prostatic vas deferens. The pD_2 ($-\log EC_{50}$) ± SEM, which resulted in 50% (EC_{50}) of the total relaxation, and percent (%) efficacy (in parentheses) relative to clonidine are reported. Number of determinations, ≥4. NT = not tested. [c] Number of determinations is 2. [d] Number of determinations is 1.

Table 7. In Vivo Assessment of Agonist Uroselectivity

compd	IUP $ED_{\Delta 5}$ [a]	MAP $ED_{\Delta 20}$ [a]	MAP/IUP ratio[b]
1	1100 ± 400	330 ± 80	0.40 ± 0.10
2	205 ± 32	250 ± 20	1.3 ± 0.2
3	0.16 ± 0.02	0.27 ± 0.05	1.7 ± 0.4
4	25.5 ± 5.3	102.3 ± 23.9	4.8 ± 1.2
7	20.4 ± 4.6	48.7 ± 5.9	4.4 ± 1.9
8	inactive	inactive	
9	91.9 ± 16.2	225.3 ± 34.6	2.5 ± 0.1
10	10.5 ± 1.6	34.0 ± 9.4	3.3 ± 0.7
11	156 ± 18	450 ± 103	3.0 ± 0.8
17	68.4 ± 10.5	220 ± 52	3.1 ± 0.4
18[c]	188 ± 46	216 ± 59	1.1 ± 0.0
21[c]	33.0 ± 6.6	35.1 ± 1.7	1.1 ± 0.2
22	0.18 ± 0.03	0.16 ± 0.03	1.0 ± 0.1
25[c]	19.1 ± 1.6	47.7 ± 0.2	2.5 ± 0.2
28[c]	653 ± 148	1850 ± 1140	2.6 ± 1.2
30	844 ± 298	632 ± 96	1.0 ± 0.2
34	4.4 ± 0.6	5.6 ± 1.0	1.3 ± 0.3
36	12 ± 1	80 ± 10	6.5 ± 0.5
37[d]	41.1 ± 6.2	202 ± 67	5.6 ± 2.7
38	91.6 ± 19.1	234 ± 43	3.4 ± 1.2
39	67.1 ± 15.5	163.9 ± 57.7	2.3 ± 0.3
43	inactive	inactive	
48[c]	11.9 ± 4.7	9.2 ± 3.8	1.1 ± 0.7

[a] Data expressed as nmol/kg ± SEM. Number of determinations, ≥4. [b] Data expressed as the mean ± SEM of the calculated MAP/IUP ratios for each determination. [c] Number of determinations is 2. [d] Number of determinations is 3.

Replacement of the sulfonamide with an acetate group (compounds **17** and **18**) led to lower in vivo potency and selectivity relative to **4**. Removal of the sulfonamide, as in **21**, provided an agent with in vivo potency similar to that of **4** but with reduced uroselectivity. Substitutions to the aromatic ring of **4** had no advantage in vivo (**22**, **25**, **28**, and **30**). The highly potent 2-hydroxy analogue **22** was very similar to **3** in its overall pharmacological profile.

Modifications to the tetralin ring of **4** were also examined in vivo. The chroman **39** had in vitro potency similar to that of **4** but was less potent in vivo. Indane **34** was 6-fold more potent than **4** at increasing IUP but had a similar potency for increasing MAP. Compound **36** was found to possess antagonistic activity for the α_{1B} and α_{1D} subtypes and had an improved MAP/IUP ratio relative to **4** of 6.5.[30] In vivo analysis revealed that **37** lost 3-fold potency for increasing IUP compared to **36** but had similar uroselectivity.

Although incorporation of a methyl group at the benzylic position of **36** reduced in vitro and in vivo potency, compound **38** had a MAP/IUP ratio similar to that of compound **4**.

The N-methylated imidazole **43** was inactive in vivo. The imidazoline **48**, similar to **4** in its in vitro profile, was nonselective in vivo.

Discussion

Our original hypothesis was that compounds selective for the α_{1A} subtype would have reduced cardiovascular effects over nonselective α_1 agonists. Indeed, a number of compounds such as **4**, **10**, **36**, and **37** have improved MAP/IUP ratios compared with **1** and **2**. Surprisingly, these highly selective α_{1A} agents still possessed significant ability for increasing MAP. In addition, many of the highly in vitro selective agents such as **34** and **48** were nonselective in vivo. Recent evidence indicates that the α_{1A} subtype is important in the vasoconstriction of human[31] and other species.[32] Although the α_{1B} and α_{1D} subtypes may play a role in the control of MAP,[11−14] the compounds of this series are generally inactive in functional studies for these subtypes. The α_{2A}[21b,33] and α_{2B}[34] subtypes have also been implicated in the control of BP. The α_{2B}-AR subtype in particular has been shown to be responsible for the transient hypertensive effects of iv administered α_2 agonists. The compounds in this series do have affinity for the α_{2A} and α_{2B} subtypes and many have functional activity in the rat prostatic vas deferens (α_{2A}) and this α_2 activity could play a role in their MAP effects.

Correlation plots were generated in order to compare the α_1 and α_2 in vitro activity of the compounds in this series with in vivo increases in IUP and MAP (see Tables 8 and 9).[35] A moderate correlation existed for the binding affinity for the α_{1A} subtype vs MAP $ED_{\Delta 20}$ ($r^2 = 0.46$) and vs IUP $ED_{\Delta 5}$ ($r^2 = 0.62$). Similar correlations were seen for α_{2a} binding vs MAP $ED_{\Delta 20}$ ($r^2 = 0.63$) and

Table 8. Correlation of α-AR Binding Affinity (pK_i) with MAP (p $ED_{\Delta 20}$) and IUP (p $ED_{\Delta 5}$)

	MAP (p $ED_{\Delta 20}$)			IUP (p $ED_{\Delta 5}$)		
	r^2	slope	*n*	r^2	slope	*n*
α_{1A}	0.46	0.47	21	0.62	0.55	21
α_{1b}	0.05	0.09	12	0.11	0.13	12
α_{1d}	0.01	0.04	18	0.08	0.12	17
α_{2a}	0.63	0.35	19	0.56	0.34	19
α_{2B}	0.38	0.35	18	0.21	0.26	18

Table 9. Correlation of Functional Agonism (pD_2) with MAP (p $ED_{\Delta 20}$) and IUP (p $ED_{\Delta 5}$)

	MAP (p $ED_{\Delta 20}$)			IUP (p $ED_{\Delta 5}$)		
	r^2	slope	*n*	r^2	slope	*n*
rabbit urethra (α_{1a})	0.70	0.81	20	0.82	0.87	20
rat vas deferens (α_{2A})	0.02	0.14	16	0.05	0.21	16
rat vas deferens (α_{2A}), 100% efficacy	0.57	0.72	6	0.26	0.52	6

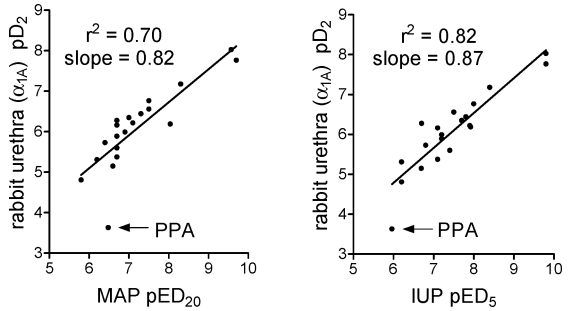


Figure 1. MAP and IUP vs functional α_{1A} (rabbit urethra).

vs IUP $ED_{\Delta 5}$ (r^2 = 0.56). However, the potency for relaxation of the rat prostatic vas deferens (α_{2A}) had no correlation vs MAP (r^2 = 0.002) or IUP (r^2 = 0.03). There was also no correlation seen between α_{1b} or α_{1d} binding and MAP or IUP.

The best correlations were observed for functional α_{1A} activity (constriction of rabbit urethra) vs MAP (r^2 = 0.70) and IUP (r^2 = 0.82). As can be seen from Figure 1, compound **1** appears to be an outlier, being more potent in vivo than in vitro relative to the other compounds. Recalculation of the plots in the absence of **1** improves both of these correlations (r^2 for rabbit urethra vs MAP and vs IUP = 0.85 and 0.85, respectively). These correlations provide evidence that both the MAP and IUP effects of the compounds in this series are due to stimulation of the α_{1A}-AR.

The lack of correlation between the rat prostatic vas deferens vs MAP and IUP in the dog may be due to the species differences. In addition, no correlation (r^2 = 0.002) was observed between the α_{2A} binding (human clone) and the rat prostatic vas deferens (graph not shown). The α_{2A} subtype found in humans, dogs, and rabbits is a species orthologue of the α_{2A} subtype found in rat, known as the α_{2D}-AR.[36] Differences in affinities of antagonists for these two receptors have been reported.[37] Therefore, the α_{2A} binding data (human clone) may be more predictive of the α_{2A} activity in dogs than the rat prostaic vas deferens. Interestingly, reevaluation of the rat prostatic vas deferens using only compounds that were fully efficacious (100%) revealed an improved correlation with the α_{2A} binding data (r^2 = 0.53, slope = 0.77) as well as with the MAP (r^2 = 0.57) and IUP (r^2 = 0.26).

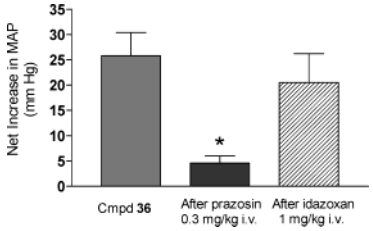


Figure 2. Pressor effects of **36** in the presence of prazosin and idazoxan.

To more directly ascertain the potential influence of α_2 activity of this series on MAP, the pressor effects of an iv administered 100 nmol/kg dose of **36** were measured in a conscious dog model in the presence of 0.3 mg/kg of the α_1 antagonist prazosin or 1 mg/kg of the α_2 antagonist idazoxan (see Figure 2). Prazosin significantly attenuated the vasoconstrictive effects of **36** whereas idazoxan did not, thus providing further evidence for the prominent role of the α_{1A} subtype in the control of MAP.

In summary, the SAR of a series of imidazoles based on the α_{1A} selective agonist **4** was described. Small modifications to the sulfonamide portion of the molecule were allowed, and the ethyl sulfonamide **10** was found to be more potent in vivo. Modifications to the aromatic portion of the molecule were allowed, and some increases in potency were noted. Removal of the carbocylic ring allowed for the discovery of compound **36**, an α_{1A} selective agonist with antagonism at the α_{1B} and α_{1D} subtypes.

In vivo analysis demonstrated that many of the compounds were more uroselective than the nonselective α_1-agonists **1** and **2**, supporting the hypothesis that greater α_{1A} selectivity would reduce cardiovascular side effects. Surprisingly, some of the highly in vitro selective α_{1A}-agonists such as **34** and **48** were nonselective in vivo. Although we cannot completely rule out the influence of other factors that may contribute to cardiovascular (CV) effects such as peripheral postsynaptic α_2-ARs, this data set supports an important role of the α_{1A}-AR in the control of α_1-agonist mediated increases in MAP. Our results suggest that absolute uroselectivity may not be achievable with agents that act solely via the α_{1A} mechanism. However, a partial α_{1A}-agonist has recently been reported to have efficacy in the treatment of SUI with minimal CV effects.[38]

Experimental Section

Chemistry. Proton NMR spectra were obtained on a General Electric QE 300 or QZ 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories. Column chromatography was carried out on silica gel 60 (230−400 mesh). Optical rotations were measured with a Perkin-Elmer 541 polarimeter. Thin-layer chromatography (TLC) was performed using 250 mm silica gel 60 glass-backed plates with F_{254} as indicator. NMR, MS, and rotational data on intermediates are available in the Supporting Information.

Method A. 4-(5-Nitro-3,4-dihydronaphthalen-1-yl)-1*H*-imidazole (4B). In part 1, a solution of **5** (3.0 g, 10 mmol) in anhydrous CH_2Cl_2 (40 mL) under N_2 was treated with EtMgBr (3.0 M in Et_2O, 3.3 mL) over 5 min, stirred for 30 min, cooled

to 0 °C, treated with 5-nitro-1-tetralone[39] (2.6 g, 11.8 mmol), stirred at ambient temperature overnight, and concentrated.

In part 2, this intermediate alcohol was treated with 30 mL of 2 M HCl, heated to reflux for 7 h, cooled, neutralized to pH 8 with solid Na_2CO_3, and extracted with CH_2Cl_2 (4 × 150 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$), filtered, and concentrated to provide **4B** that was carried to the next step without purification.

Method B. 4-(8-Methoxy-5-nitro-3,4-dihydronaphthalen-1-yl)-1*H*-imidazole (28B). A solution of **6** (2.2 g, 5.1 mmol) in anhydrous CH_2Cl_2 (20 mL) under N_2 was treated with EtMgBr (3 M in Et_2O, 1.7 mL, 5.1 mmol) over 2 min, stirred for 30 min, treated with **28A** (0.94 g, 4.2 mmol) in anhydrous CH_2Cl_2 (5 mL), stirred for 2 h, treated with NH_4Cl solution, and extracted with CH_2Cl_2 (2×). The combined CH_2Cl_2 layers were dried ($MgSO_4$), filtered, concentrated, and treated with EtOAc and hexane, at which time the product was allowed to crystallize for 15 min. The crystals were collected by filtration, washed with 5:1 hexanes/EtOAc, dried under vacuum, treated with TFA (25 mL), heated to reflux for 30 min, concentrated, treated with $NaHCO_3$ solution, and extracted with CH_2Cl_2 (2×). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and concentrated to provide **28B**.

Method C. 4-(8-Nitro-2*H*-thiochromen-4-yl)imidazole-1-sulfonic Acid Dimethylamide (40D). 8-Nitrothiochroman-4-one[40] (**40A**) (0.48 g, 2.3 mmol) was reacted with **5** (0.79 g, 2.6 mmol) as described in method A, part 1. The intermediate alcohol was dehydrated by stirring in refluxing TFA (10 mL) for 2 h. The mixture was cooled, concentrated, and neutralized with aqueous $NaHCO_3$ to provide **40D** as a brown solid, 0.31 g (37%), which was isolated by filtration.

Method D. *tert*-Butyl 4-(5-Nitro-3,4-dihydro-1-naphthalenyl)-1*H*-imidazole-1-carboxylate (4C). A mixture of compound **4B** (6.9 g, 29 mmol) and Boc_2O (12.5 g, 57 mmol) was refluxed in CH_3CN (100 mL) for 15 min, cooled, concentrated, and chromatographed (3:2 hexane/EtOAc) to provide 6.7 g (89%) of **4C**.

Method E. *tert*-Butyl 4-(5-Amino-1,2,3,4-tetrahydro-1-naphthalenyl)-1*H*-imidazole-1-carboxylate (4E). A mixture of **4C** (3.45 g, 10.1 mmol) and 10% Pd/C (0.42 g) in EtOAc (30 mL) was stirred under H_2 (1 atm) for 16 h and filtered. The filtrate was concentrated and chromatographed (2:1, 3:2, and then 1:1 hexane/EtOAc) to provide 2.83 g (89%) of intermediate **4E**.

Method F. *tert*-Butyl 4-{5-[(Methylsulfonyl)amino]-1,2,3,4-tetrahydro-1-naphthalenyl}-1*H*-imidazole-1-carboxylate (4F). A solution of **4E** (0.15 g, 0.48 mmol) in CH_2Cl_2 (3 mL) was treated with pyridine (0.12 mL, 1.4 mmol) and then MsCl (0.060 mL, 0.72 mmol), stirred at ambient temperature overnight, concentrated, and chromatographed (1% MeOH in NH_3-saturated CH_2Cl_2) to provide 0.18 g (94%) of **4F**.

Method G. (+)-*N*-[5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]ethanesulfonamide, Maleate (10). A solution of (+)-**10F** (0.26 g, 0.64 mmol) in CH_2Cl_2 (4 mL) was treated with TFA (5 mL), heated on a steam bath for 1 min, and concentrated. Purification of the residue on silica gel using 5% and then 10% MeOH in NH_3-saturated CH_2Cl_2 provided the free base of **10** (0.19 g), which was converted to the maleic acid salt: mp 129−130 °C; $[\alpha]^{23}_D$ (free base) +55.2 (*c* 1.1, 1:1 MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.28 (t, 3H), 1.67−1.85 (m, 2H), 1.87−2.06 (m, 2H), 2.83 (t, 2H), 3.13 (q, 2H), 4.30 (t, 1H), 6.05 (s, 2H), 6.80 (d, 1H), 7.12 (t, 1H), 7.16−7.23 (m, 2H); MS (DCI/NH_3) *m*/*z* 306 $(M + H)^+$. Anal. ($C_{15}H_{19}N_3O_2S{\cdot}C_4H_4O_4$) C, H, N.

Method H. *N*-[3-Cyclohexyl-5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]ethanesulfonamide (26). Compound **26F** (670 mg, 1.36 mmol) and 1 N HCl (5 mL) in THF (10 mL) were refluxed for 2 h. The mixture was cooled to ambient temperature, and the THF was removed under reduced pressure. The mixture was neutralized with solid $NaHCO_3$ and the resulting solid was filtered, dried under reduced pressure, and purified on a silica gel column (12:1 CH_2Cl_2/MeOH) to provide **26** (365 mg) (70%): mp 207−209 °C; ^{1}H NMR (DMSO-d_6) δ 1.26 (m, 8 H), 1.70 (m, 7 H), 1.93 (m, 2 H), 2.33 (m, 1 H), 2.72 (m, 2 H), 3.10 (q, J = 7 Hz, 2 H), 4.03 (m, 1 H), 6.5 (s, 1 H), 6.75 (s, 1 H), 6.95 (s, 1 H), 7.53 (s, 1 H), 8.80 (s, 1 H); MS (APCI+) *m*/*z* 388 $(M + H)^+$; MS (APCI−) *m*/*z* 386 $(M - H)^-$, 422 $(M + Cl)^-$. Anal. ($C_{21}H_{29}N_3O_2S{\cdot}0.375H_2O$) C, H, N.

Method I. *N*-[(5R)-5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]methanesulfonamide (4). Intermediate **4J** (1.1 g, 2.9 mmol) was hydrogenated using 10% Pd/C (1.1 g) in MeOH (30 mL) overnight under H_2 (1 atm). After the atmosphere was exchanged with N_2, the mixture was diluted with MeOH (300 mL), filtered to remove the Pd/C, concentrated, and chromatographed (5%, 10%, and then 20% MeOH in NH_3-saturated CH_2Cl_2) to provide 0.36 g (43%) of **4**, which was converted to the HCl salt: mp 113−114 °C; ^{1}H NMR (DMSO-d_6) δ 1.75 (m, 2 H), 1.98 (m, 2 H), 2.82 (t, J = 6.25 Hz, 2 H), 3.03 (s, 3 H), 4.34 (t, J = 6.43 Hz, 1 H), 6.82 (d, J = 7.72 Hz, 1 H), 7.13 (t, J = 7.72 Hz, 1 H), 7.23 (d, J = 7.35 Hz, 1 H), 7.25 (s, 1 H), 9.03 (s, 1 H), 9.07 (s, 1 H), 14.34 (s, 1 H). Anal. ($C_{14}H_{17}N_3O_2S{\cdot}HCl{\cdot}0.25H_2O$) C, H, N.

Method J. *N*-[5-(1*H*-Imidazol-4-yl)-4-methyl-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide Maleate (29). Compound **29J** (0.069 g, 0.23 mmol) was hydrogenated in MeOH using 0.1 weight equivalent of 10% Pd/C overnight under H_2 and worked up as described in method I to provide 0.033 g (48%) of **29**, which was converted to the maleic acid salt: mp 192−195 °C; ^{1}H NMR (DMSO-d_6) δ 1.38 (m, 1H), 1.69−2.07 (m, 3H), 2.01 (s, 3H), 2.66 (m, 1H), 2.94 (m, 1H), 3.00 (s, 3H), 4.31 (m, 1H), 6.06 (s, 2H), 6.75 (s, 1H), 7.05 (d, 1H), 7.19 (d, 1H), 8.92 (s, 2H); MS (APCI+) *m*/*z* 306 $(M + H)^+$; MS (APCI-) *m*/*z* 304 $(M - H)^-$, 340 $(M + Cl)^-$. Anal. ($C_{15}H_{19}N_3O_2S{\cdot}C_4H_4O_4{\cdot}0.5H_2O{\cdot}0.25EtOAc$) C, H, N.

***N*-Benzyl-*N*-[5-(1*H*-imidazol-4-yl)-7,8-dihydronaphthalen-1-yl]methanesulfonamide (4J).** By use of method A, *N*-benzyl-*N*-(5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)methanesulfonamide[41] (**4I**) (3.0 g, 9.1 mmol) provided 1.1 g (84%) of **4J**.

(+)-*N*-[(5*R*)-5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]methanesulfonamide (7). The enantiomers of **4F** were separated by chiral chromatography on a Chiralcel OJ column (5.0 cm inner diameter, 50 cm length, 20 μm packing) using 90:10 hexanes/EtOH at a flow rate of 200 mL/min as the mobile phase. Four separate injections of 150 mg each in 95:5 EtOH/CH_2Cl_2 (6 mL) provided 320 mg of (+)-**7F** as the faster moving enantiomer and 340 mg of (−)-**8F** as the slower moving enantiomer. A solution of (+)-**7F** (130 mg, 0.33 mmol) in MeOH (10 mL) was treated with 1 N HCI (5 mL), stirred for 1.5 h, concentrated at 45 °C, and dried under vacuum for 30 min. The residue was dissolved in MeOH, filtered through cotton, concentrated, and dried under vacuum for 3 h to provide **7** as the HCl salt: mp 118−123 °C; $[\alpha]^{23}_D$ +41.8° (*c* 1.0, MeOH); MS (DCI/NH_3) *m*/*z* 292 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.70−1.82 (m, 2H), 1.92−2.04 (m, 2H), 2.83 (t, 2H), 3.03 (s, 3H), 4.34 (t, 1H), 6.82 (d, 1H), 7.14 (t, 1H), 7.23 (d, 1H), 7.26 (s, 1H), 9.03 (s, 1H), 9.07 (s, 1H), 14.36 (bs, 2H). Anal. ($C_{14}H_{17}N_3O_2S{\cdot}HCl{\cdot}0.5H_2O{\cdot}0.5MeOH$) C, H, N.

(−)-*N*-[(5S)-5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]methanesulfonamide (8). A solution of (−)-**8F** (95 mg, 0.24 mmol) in MeOH (10 mL) was treated as described for compound (+)-**7** in the above procedure to provide **8**: mp 118−123 °C; $[\alpha]^{23}_D$ −40.8° (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.70−1.82 (m, 2H), 1.92−2.04 (m, 2H), 2.83 (t, 2H), 3.03 (s, 3H), 4.34 (t, 1H), 6.82 (d, 1H), 7.14 (t, 1H), 7.23 (d, 1H), 7.26 (s, 1H), 9.03 (s, 1H), 9.07 (s, 1H), 14.36 (bs, 2H); MS (DCI/NH_3) *m*/*z* 292 $(M + H)^+$. Anal. ($C_{14}H_{17}N_3O_2S{\cdot}HCl{\cdot}0.5CH_3OH{\cdot}0.5H_2O$) C, H, N.

***N*-[5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]-*N*-methylmethanesulfonamide, Maleate (9).** A solution of **4F** (0.18 g, 0.45 mmol) in DMF (2 mL) under N_2 was treated with NaH (0.020 g, 0.50 mmol), stirred for 45 min, treated with MeI (0.031 mL, 0.50 mmol), stirred for 90 min, diluted with EtOAc (60 mL), washed with water (2 × 25 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was deprotected using method G to provide 120 mg of **9**, which was converted to the maleic acid salt: mp 142−

144 °C; ^{1}H NMR (DMSO-d_6) δ 1.67−2.07 (m, 4H), 2.70−2.86 (m, 1H), 2.87−3.01 (m, 1H), 3.08 and 3.09 (s and s, 3H), 3.12 and 3.13 (s and s, 3H), 4.24−4.35 (m, 1H), 6.05 (s, 2H), 6.94 (t, 1H), 7.13−7.24 (m, 2H), 7.37 (d, 1H), 8.85 (s, 1H); MS (DCI/NH_3) m/z 306 $(M + H)^+$. Anal. ($C_{15}H_{19}N_3O_2S \cdot C_4H_4O_4$) C, H, N.

(+)-*N*-[5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]ethanesulfonamide, Maleate (10). After substitution of $EtSO_2Cl$ for MsCl, **4E** (2.0 g, 6.4 mmol) was reacted via method F and provided 1.52 g (59%) of **10F**. The enantiomers of **10F** were separated as described for compound **7** using 95:5 hexanes/EtOH, providing (+)-**10F** as the faster moving enantiomer. Via method G, (+)-**10F** provided **10**.

(+)-*N*-[5,6,7,8-Tetrahydro-5-(1*H*-imidazol-4-yl)-1-naphthalenyl]-2,2,2-trifluoroethanesulfonamide (11). After substitution of $F_3CCH_2SO_2Cl$ for MsCl, **4E** was reacted via method F and provided **11F**. The enantiomers of compound **11F** were separated by chiral chromatography on a Chiralpak AD column (5.0 cm inner diameter, 26 cm length, 20 μDp) using 96:4 hexanes/EtOH at a flow rate of 117 mL/min as the mobile phase to provide (+)-**11F** as the slower moving enantiomer. Via method G, compound (+)-**11F** (0.20 g, 0.44 mmol) provided **11**: mp >260 °C; $[\alpha]^{23}_D$ +30.4° (*c* 0.97, AcOH); ^{1}H NMR (DMSO-d_6) δ 1.61−1.83 (m, 2H), 1.83−2.06 (m, 2H), 2.67−2.87 (m, 2H), 4.06 (t, 1H), 4.48 (q, 2H), 6.64 (s, 1H), 6.95 (d, 1H), 7.08 (t, 1H), 7.17 (d, 1H), 7.54 (s, 1H), 9.8 (bs, 1H), 11.5 (bs, 1H); MS (DCI/NH_3) m/z 360 $(M + H)^+$. Anal. ($C_{15}H_{16}N_3O_2SF_3$) C, H, N.

Example of High-Throughput Synthesis: *N*-[5-(1*H*-Imidazol-5-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]-1-propanesulfonamide (12). To a solution of 1-propanesulfonyl chloride (20.5 mg, 0.14 mmol) in CH_2Cl_2 (250 mL) was added pyridine (78 mL, 0.96 mmol) followed by a solution of **4E** (30 mg, 0.096 mmol) in CH_2Cl_2 (1 mL). The CH_2Cl_2 was removed under vacuum, and the reaction mixture was gently shaken at ambient temperature overnight. To the reaction mixture was added 1.0 mL of CH_2Cl_2 followed by 200 mg of polymer-supported trisamine (Argonaut Laboratories). The reaction mixture was shaken at room temperature for 30 min and washed with CH_2Cl_2, and the volume of the filtrate was brought to 5 mL with CH_2Cl_2. The organic layer was extracted with 10% aqueous citric acid (3 × 4 mL) and brine (2 × 4 mL) and was filtered (Varian CE1000M), and the solvent was removed under vacuum. The resulting oil was dissolved in 2 mL of CH_3CN, and 0.5 g of Amberlyst resin was added. The reaction mixture was shaken at room temperature for 72 h and filtered. The resin was washed with CH_3CN (2 × 2 mL) and MeOH (2 × 2 mL) and was suspended in 2 M methanolic NH_3 (2 mL) for 2 h. The resin was filtered, washed with 0.5 mL of MeOH, and then re-treated with 2 M methanolic NH_3 as described. The combined filtrates were concentated under vacuum, and the crude material was purified using reverse-phase preparative HPLC to provide 6.7 mg (21.9%) of **12**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.99 (t, J = 7.5 Hz, 3H), 1.67 (m, 1H), 1.74 (m, 3H), 1.88 (m, 1H), 2.02 (m, 1H), 2.74 (m, 1H), 2.79 (m, 1H), 3.06 (t, J = 7.7 Hz, 2H), 4.00 and 4.12 (2 m, 2.4:1, 1H), 6.44 and 6.54 (2 bs, 1:2.4, 1H), 6.75 and 6.91 (2 bd, 1:2.4, J = 7.7, 1H), 7.02 (m, 1H), 7.10 (m, 1H), 7.49 and 7.51 (2 bs, 1:2.4, 1H), 8.85 (bs, 1H), 11.70 and 11.84 (2 bs, 2.4:1, 1H); MS (APCI−) m/z 319 $(M - H)^-$. Anal. Calcd ($C_{16}H_{21}N_3O_2S$): C, 60.16; H, 6.63; N, 13.16. Found: C, 58.10; H, 5.32; N, 11.92.

***N*-[5,6,7,8-Tetrahydro-5-(1*H*-imidazol-4-yl)-1-naphthalenyl]-2-methylethanesulfonamide, Maleate (13).** After substitution of isopropylsulfonyl chloride (0.099 mL, 0.88 mmol) for MsCl, **4E** was reacted via method F and, without purification, the resulting intermediate was reacted via method G to provide 0.09 g (35%) of **13**, which was converted to the maleic acid salt: mp 124−125 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (d, 6H), 1.69−1.83 (m, 2H), 1.89−2.02 (m, 2H), 2.83 (t, 2H), 3.25−3.36 (m, 1H), 4.28 (t, 1H), 6.04 (s, 2H), 6.79 (d, 1H), 7.10 (t, 1H), 7.16−7.23 (m, 2H), 8.82 (bs, 1H), 8.94 (s, 1H); MS (DCI/NH_3) m/z 320 $(M + H)^+$. Anal. ($C_{16}H_{21}N_3O_2S \cdot C_4H_4O_4$) C, H, N.

***N*-[5,6,7,8-Tetrahydro-(1*H*-imidazol-4-yl)-1-naphthalenyl]cyclopropanesulfonamide, Maleate (14).** As in **13**, cyclopropylsulfonyl chloride[42] provided **14**, which was converted to the maleic acid salt: mp 156−157 °C; ^{1}H NMR (DMSO-d_6) δ 0.88 (m, 2H), 0.97 (m, 2H), 1.76 (m, 2H), 1.97 (m, 2H), 2.65 (m, 1H), 2.87 (t, 2H), 4.30 (t, 1H), 6.04 (s, 2H), 6.82 (d, 1H), 7.12 (t, 1H), 7.17 (s, 1H), 7.24 (d, 1H), 8.85 (s, 1H), 9.07 (s, 1H); MS (DCI/NH_3) m/z 318 $(M + H)^+$. Anal. ($C_{16}H_{19}N_3O_2S \cdot C_4H_4O_4$) C, H, N.

Naphthalene-2-sulfonic Acid [5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydronaphthalen-1-yl]amide Trifluoroacetate (15). As for **12**, 2-naphthalenesulfonyl chloride provided, after HPLC chromatography, the trifluoracetic acid salt of **15**. ^{1}H NMR (CD_3OD) δ 1.44 (m, 2H), 1.83 (m, 2H), 3.15 (m, 2H), 4.22 (t, J = 4.2 Hz, 1H), 6.76 (d, J = 7.7, 1H), 6.87 (d, J = 7.3 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 7.08 (d, J = 0.7 Hz, 1H), 7.65 (ddd, J = 1.1, 6.9, 8.0 Hz, 1H), 7.70 (ddd, J = 1.1, 7.0, 8.1 Hz, 1H), 7.78 (dd, J = 2.2, 8.7 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 8.12 (t, J = 8.0 Hz, 2H), 8.03 (d, J = 1.8 Hz, 1H), 8.91 (d, J = 1.1 Hz, 1H), 9.65 (s, 1H). Anal. Calcd ($C_{23}H_{21}N_3O_2S \cdot$ 2TFA): C, 51.35; H, 3.67; N, 6.65. Found: C, 52.21; H, 3.24; N, 6.22.

***N′*-[5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]-*N*,*N*-dimethylsulfamide (16).** As in **13**, dimethylsulfamoyl chloride provided 0.078 g (40%) of **16**: mp 208−210 °C; ^{1}H NMR (DMSO-d_6) δ 1.85(m, 4H), 2.75 (s, 6H), 2.81 (m, 2H), 4.05 (t, J = 9 Hz, 1H), 6.53 (s, 1H), 6.84 (d, J = 9 Hz, 1H), 7.03(t, J = 9 Hz, 1H), 7.15 (d, J = 9 Hz, 1H), 7.54 (s, 1H), 8.86 (bs, 1H), 12.0 (bs, 1H); MS (DCI/NH_3) m/z 321 $(M + H)^+$. Anal. ($C_{15}H_{20}N_4O_2S \cdot 0.094CH_2Cl_2$) C, H, N.

***N*-[5,6,7,8-Tetrahydro-5-(1*H*-imidazol-4-yl)-1-naphthalenyl]acetamide, Maleate (17).** As in **13**, Ac_2O (0.083 mL, 0.88 mmol) provided 0.20 g (100%) of **17**, which was converted to the maleic acid salt: mp 159−160 °C; ^{1}H NMR (DMSO-d_6) δ 1.67−1.86 (m, 2H), 1.88−2.04 (m, 2H), 2.06 (s, 3H), 2.68 (t, 2H), 4.30 (t, 1H), 6.05 (s, 2H), 6.73 (d, 1H), 7.19 (t, 1H), 7.21 (s, 1H), 7.30 (d, 1H), 8.86 (s, 1H), 9.22 (s, 1H); MS (DCI/NH_3) m/z 256 $(M + H)^+$. Anal. ($C_{15}H_{17}N_3O \cdot C_4H_4O_4$) C, H, N.

2,2,2-Trifluoro-*N*-[5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]acetamide, Maleate (18). As in **13**, trifluoroacetic anhydride (0.12 mL, 0.88 mmol) provided 0.21 g (86%) of **18**, which was converted into the maleic acid salt: mp 181−182 °C; ^{1}H NMR (DMSO-d_6) δ 1.67−1.85 (m, 2H), 1.92−2.06 (m, 2H), 2.65 (t, 2H), 4.33 (t, 1H), 6.05 (s, 2H), 6.93 (dd, 1H), 7.16−7.23 (m, 3H), 8.83 (s, 1H), 10.92 (s, 1H); MS (DCI/NH_3) m/z 310 $(M + H)^+$. Anal. ($C_{15}H_{14}N_3OF_3 \cdot C_4H_4O_4$) C, H, N.

Methyl 5-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenylcarbamate Trifluoroacetate (19). Polymer-supported diisopropylamine (2 equiv) was treated with CH_2Cl_2 (0.75 mL) and methyl chloroformate (25.3 mg, 0.27 mmol, 1 equiv), mixed well, treated with a solution of **4E** in CH_2Cl_2 (1 mL), shaken for 16 h, treated with polymer-bound tris(2-aminoethyl)amine (5 equiv), and shaken for 2 h. The resin was removed by filtration and washed with CH_2Cl_2 (2×, 1 mL). The combined filtrates were concentrated under reduced pressure to dryness, treated with 30% TFA in CH_2Cl_2 (1.5 mL), shaken for 16 h, and concentrated under reduced pressure. The residue was purified using reverse-phase preparative HPLC to provide 47.4 mg (69%) of **19** as the TFA salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.75 (m, 2H), 1.97 (m, 2H), 2.69 (t, J = 6.4 Hz, 2H), 3.65 (s, 3H), 4.31 (t, J = 6.6 Hz, 1H), 6.71 (d, J = 7.7 Hz, 1H), 7.10 (t, J = 7.9 Hz, 1H), 7.27 (m, 2H), 8.79 (s, 1H), 8.97 (s, 1H), 14.20 (bs, 1H); MS (ESI+) m/z 272 $(M + H)^+$. Anal. ($C_{15}H_{17}N_3O_2 \cdot 1.3$TFA) C, H, N.

4-(1*H*-Imidazol-4-yl)chroman-8-ylamine, Maleate (21). Via method G, compound **39E** (0.35 g, 1.1 mmol) provided **21** that was converted to 0.19 g (50%) of the maleic acid salt: mp 145−147 °C; MS (APCI+) m/z 216 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) δ 2.18 (m, 2H), 4.19 (m, 2H), 4.21 (t, 1H), 6.09 (m, 3H), 6.55 (m, 2H), 7.33 (s, 1H), 8.95 (d, 1H). Anal. ($C_{12}H_{13}N_3O \cdot 1.5C_4H_4O_4$) C, H, N.

***N*-[2-Hydroxy-5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]methanesulfonamide, Hydrochloride (22).** A suspension of compound **23** (320 mg, 1.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C was treated with BBr_3 (1.0 M in CH_2Cl_2, 4.0

mL) over 5 min, stirred at 0 °C for 2 h, cooled to −78 °C, treated with MeOH (10 mL), warmed to ambient temperature, and concentrated. Purification of the residue on silica gel with 20% EtOH in NH_3-saturated CH_2Cl_2 provided 0.22 g (72%) of **22** that was converted to the hydrochloride salt: mp 135−137 °C; ^{1}H NMR (DMSO-d_6) δ 1.61−1.74 (m, 2H), 1.88−2.00 (m, 2H), 2.86 (t, 2H), 3.03 (s, 3H), 4.21 (t, 1H), 6.69 (d, 1H), 6.75 (d, 1H), 7.18 (d, 1H), 8.58 (s, 1H), 9.05 (d, 1H), 9.85 (s, 1H), 14.38 (bs, 2H); MS (DCI/NH_3) *m/z* 308 $(M + H)^+$. Anal. ($C_{14}H_{17}N_3O_3S$·HCl·EtOH) C, H, N.

***N*-[5-(1*H*-Imidazol-4-yl)-2-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide, Hydrochloride (23).** 6-Methoxy-5-nitro-1-tetralone[15] (0.50 g, 2.3 mmol) was reacted via method A (80%) to **23B**, method D (80%) to **23C**, and method E (90%) to **23E** and as in **13** using MsCl to provide **23** that was converted to the HCl salt: mp 209−211 °C; ^{1}H NMR (DMSO-d_6) δ 1.65−1.72 (m, 2H), 1.88−2.01 (m, 2H), 1.88 (t, 2H), 3.00 (s, 3H), 3.79 (s, 3H), 4.27 (t, 1H), 6.88 (q, 2H), 7.20 (s, 1H), 8.66 (s, 1H), 9.03 (s, 1H), 14.33 (bs, 2H); MS (DCI/NH_3) *m/z* 322 $(M + H)^+$. Anal. ($C_{15}H_{19}N_3O_3S$·HCl) C, H, N.

***N*-[3-Fluoro-5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]ethanesulfonamide (24).** A solution of 7-fluoro-3,4-dihydro-1(2*H*)-naphthalenone[43] (2.45 g, 14.9 mmol) was treated with NH_2OH·HCl (3.13 g, 45 mmol) and NaOAc (3.7 g, 45 mmol) in water (3 mL), heated at reflux for 24 h, cooled to ambient temperature, concentrated, and triturated with water. The resulting solid was collected by filtration and dried to provide 2.4 g (100%) of the corresponding oxime. To a 85 °C solution of polyphosphoric acid (0.5 g) in toluene (5 mL) was added the oxime (0.18 g, 1 mmol). After 30 min at reflux, the mixture was allowed to cool to ambient temperature, diluted with water, and extracted with EtOAc. The EtOAc layer was dried ($MgSO_4$), filtered, and concentrated to provide 0.16 g (89%) of 8-fluoro-1,3,4,5-tetrahydrobenzo[*b*]azepin-2-one. NaH (60% dispersion) (0.72 g, 18 mmol) was washed with hexane, suspended in THF (10 mL), cooled to 0 °C, and treated dropwise with a solution of the azepinone (2.16 g, 12 mmol) in THF (40 mL). After being stirred at 0 °C for 1.5 h, the mixture was treated with $EtSO_2Cl$ (1.93 g, 15 mmol). After being stirred at ambient temperature for 2.5 h, the mixture was treated with water (5 mL) and 1 M NaOH solution (24 mL) and washed with Et_2O. The aqueous layer was acidified with 1 M HCl (25 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, and concentrated to provide 4-{2-[(ethylsulfonyl)amino]-4-fluorophenyl}butanoic acid (2.9 g, 84%). This acid (2.47 g, 8.5 mmol) in CH_2Cl_2 (25 mL) and DMF (0.025 mL) was treated with oxalyl chloride (2.16 g, 17 mmol) and stirred at ambient temperature for 24 h. This solution was added to a 0 °C suspension of $AlCl_3$ (4.53 g, 34 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred at ambient temperature for 60 h, treated with water (50 mL), and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on silica gel, eluting with 3:7 EtOAc/hexane to provide **24G**. Compound **24G** (0.38 g, 1.4 mmol) in CH_2Cl_2 (7 mL) was treated with Et_3N (0.22 mL, 1.6 mmol), DMAP (0.012 g, 0.1 mmol), and Boc_2O (0.33 g, 1.5 mmol). After being stirred for 1.5 h, the mixture was concentrated and the residue was purified by filtration through a pad of silica gel, eluting with CH_2Cl_2 to provide **24I**. Via methods A and J, **24I** was converted to **24J** and 0.085 g (29%) of **24**, respectively. ^{1}H NMR (CD_3OD) δ 1.36 (t, 3H), 1.74−1.82 (m, 1H), 1.84−1.93 (m, 1H), 2.00−2.06 (m, 2H), 2.72−2.81 (m, 2H), 3.16 (q, 2H), 4.13 (t, 1H), 6.57 (dd, 1H), 6.63 (s, 1H), 7.04 (dd, 1H), 7.59 (s, 1H); MS (APCI+) *m/z* 324 $(M + H)^+$; MS (APCI−) *m/z* 322 $(M - H)^-$. Anal. ($C_{15}H_{18}FN_3O_2S$·0.25H_2O·0.1EtOH) C, H, N.

***N*-[3-Chloro-5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]ethanesulfonamide (25).** 7-Chloro-3,4-dihydro-2*H*-naphthalen-1-one[44] was processed as described for **24** except that the reaction time for method J was 2.5 h instead of 16 h to provide **25**. ^{1}H NMR (CD_3OD) δ 1.37 (t, 3H), 1.73−1.83 (m, 1H), 1.83−1.93 (m, 1H), 1.98−2.08 (m, 2H), 2.75−2.85 (m, 2H), 3.16 (q, 2H), 4.13 (t, 1H), 6.64 (s, 1H), 6.85 (d, 1H), 7.27 (d, 1H), 7.63 (s, 1H); MS (APCI+) *m/z* 340 $(M + H)^+$; MS (APCI−) *m/z* 338 $(M - H)^-$. Anal. ($C_{15}H_{18}ClN_3O_2S$·0.3H_2O·0.2EtOH) C, H, N.

4-{7-Cyclohexyl-5-[(ethylsulfonyl)amino]-1,2,3,4-tetrahydro-1-naphthalenyl}-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (26F). 7-Cyclohexyl-3,4-dihydro-1(2*H*)-naphthalenone[45] (3.8 g, 16.6 mmol) in concentrated H_2SO_4 (35 mL) at −5 °C was treated in portions with solid $NaNO_3$ (1.7 g, 20 mmol). After being stirred at 0 °C for 2 h, the mixture was poured into ice and extracted with EtOAc. The EtOAc layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to provide 1.5 g of a mixture of **26A** and starting material (60:40 ratio) that was used without further purification. This mixture was reacted sequentially by methods C, E, and F (using $EtSO_2Cl$) to provide **26F**.

***N*-[5,6,7,8-Tetrahydro-4-hydroxy-5-(1*H*-imidazol-4-yl)-1-naphthalenyl]methanesulfonamide, Maleate (27).** Compound **28F** (0.32 g, 0.76 mmol) was treated with 1.0 M BBr_3/CH_2Cl_2 (3 mL) as described for compound **22** to provide 0.13 g (54%) of **27**, which was converted to the maleic acid salt: mp 127−131 °C; ^{1}H NMR (DMSO-d_6) δ 1.44 (m, 1H), 1.74 (m, 1H), 1.85 (m, 1H), 1.96 (m, 1H), 2.62 (m, 1H), 2.91 (m, 1H), 2.95 (s, 3H), 4.29 (d, 1H), 6.04 (s, 2H), 6.66 (d, 1H), 6.85 (s, 1H), 7.07 (d, 1H), 8.75 (s, 1H), 8.85 (s, 1H); MS (DCI/NH_3) *m/z* 308 $(M + H)^+$. Anal. ($C_{14}H_{17}N_3O_2S$·$C_4H_4O_4$) C, H, N.

***N*-[5-(1*H*-Imidazol-4-yl)-4-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide (28).** A solution of 8-methoxy-1-tetralone[46] (2.26 g, 13 mmol) in Ac_2O (11.5 mL) was cooled to 0 °C, treated with a mixture of fuming HNO_3 (0.90 mL) in AcOH (0.70 mL) dropwise over 1 h, stirred at 0 °C for 1.5 h, treated with water (150 mL), and extracted with Et_2O (300 mL). The organic layer was washed with water (150 mL), washed with $NaHCO_3$ solution (3×), washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue on silica gel using a gradient of 2:1 and then 3:2 and finally 1:1 hexanes/EtOAc provided 0.84 g (30%) of **28A** as the more polar isomer. Compound **28A** was reacted sequentially by methods B and D−F to provide **28F**, which was reacted by method G to provide **28**, which was converted to the maleic acid salt: mp 181−184 °C; ^{1}H NMR (DMSO-d_6) δ 1.43 (m, 1H), 1.75 (m, 1H), 1.85 (m, 1H), 1.97 (m, 1H), 2.66 (m, 1H), 2.93 (m, 1H), 2.98 (s, 3H), 3.64 (s, 3H), 4.34 (d, 1H), 6.04 (s, 2H), 6.82 (s, 1H), 6.86 (d, 1H), 7.24 (d, 1H), 8.85 (s, 1H), 8.87 (s, 1H); MS (DCI/NH_3) *m/z* 322 $(M + H)^+$. Anal. ($C_{15}H_{19}N_3O_3S$·$C_4H_4O_4$) C, H, N.

***N*-[5-(1*H*-Imidazol-4-yl)-4-methyl-7,8-dihydronaphthalen-1-yl]methanesulfonamide (29J).** Via method F, 5-amino-8-methyltetralone[47] (0.25 g, 1.4 mmol) provided 0.25 g (69%) of **29G**. A solution of **29G** (0.23 g, 0.90 mml) in DMF (10 mL) under N_2 was treated with NaH (40 mg of 60% dispersion, 0.99 mmol), stirred for 15 min, treated with MOMCl (0.072 mL, 0.95 mmol), stirred for 1 h, treated with water, and extracted with Et_2O (3 × 75 mL). The combined extractions were washed with water, washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 0.25 g (92%) of **29I**. Via method A, **29I** (0.25 g, 0.83 mmol) provided 0.074 g (29%) of **29J**.

***N*-[4-Fluoro-5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]methanesulfonamide, Maleate (30).** A solution of 8-fluoro-5-methoxytetralone[48] (7.0 g, 36 mmol) in 1,2-dichloroethane (150 mL) was treated with $AlCl_3$ (21 g, 157 mmol), refluxed for 3.5 h, cooled to ambient temperature, poured carefully into 4 M HCl (500 mL), stirred for 16 h, treated with CH_2Cl_2 (400 mL), and thoroughly shaken. A black solid was removed by filtration through Celite. The CH_2Cl_2 layer was isolated, combined with the black solid, and extracted with a 5% NaOH solution (3 × 150 mL). The combined NaOH extracts were acidified with 4 M HCl, and the resulting solid was collected by filtration to provide 3.7 g (57%) of the phenol as a brown solid. A solution of this phenol (1.0 g, 5.5 mmol) in pyridine (3 mL) under N_2 was cooled to 0 °C, treated dropwise with Tf_2O (1.0 mL, 6.2 mmol), stirred for 16 h at ambient temperature, treated with 2 M HCl (25 mL), stirred for 30 min, and extracted with EtOAc (3 × 70 mL). The

combined EtOAc extracts were washed with brine and concentrated. Purification of the residue on silica gel with 40% EtOAc/hexanes provided 1.2 g (67%) of the triflate: trifluoromethanesulfonic acid 4-fluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl ester. A mixture of $Pd_2(dba)_3$ (0.36 g, 0.34 mmol) under N_2 in toluene (136 mL) was treated with (*R*)-(+)-BINAP (0.96 g, 1.5 mmol), treated with NaOtBu (0.98 g, 10 mmol), treated with benzylamine (1.1 mL, 10 mmol), warmed to 85 °C, treated dropwise over 45 min with a solution of the triflate (2.1 g, 6.8 mmol) in toluene (30 mL), stirred at 85 °C for 1 h, and treated with water (50 mL). The organic layer was isolated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel with 30% EtOAc/hexanes provided 0.40 g (22%) of **30H**. A solution of **30H** (0.40 g, 1.5 mmol) in CH_2Cl_2 (9 mL) was treated with pyridine (0.36 mL, 4.4 mmol) and MsCl (0.13 mL, 1.6 mmol), stirred for 4 h, treated with pyridine (0.2 mL, 2.5 mmol) and MsCl (0.10 mL, 1.3 mmol), stirred for 16 h, refluxed for 9 h, cooled to ambient temperature, treated with water (25 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel with 1:1 EtOAc/hexanes provided 0.29 g (57%) of **30I**. Compound **30I** (0.29 g, 0.83 mmol) was reacted via method A (45%) to **30J** and via method I to provide 0.097 g (87%) of **30**, which was converted to the maleic acid salt: mp 182−186 °C; ^{1}H NMR (DMSO-d_6) δ 1.50 (m, 1H), 1.76 (m, 1H), 1.95 (m, 2H), 2.70 (m, 1H), 2.92 (m, 1H), 3.02 (s, 3H), 4.42 (m, 1H), 6.07 (s, 2H), 6.99 (s, 1H), 7.05 (t, 1H), 7.30 (dd, 1H), 8.86 (s, 1H), 9.08 (s, 1H); MS (APCI+) *m*/*z* 310 $(M + H)^+$; MS (APCI−) *m*/*z* 308 $(M - H)^-$. Anal. ($C_{14}H_{16}N_3O_2SF \cdot C_4H_4O_4$) C, H, N.

***N*-[4-Chloro-5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]methanesulfonamide, Maleate (31).** A solution of 5-amino-1-tetralone[49] (0.50 g, 3.1 mmol) in DMF (15 mL) was treated with *N*-chlorosuccinimide (0.49 g, 3.7 mmol), stirred for 60 h, treated with water, and extracted with Et_2O (4 × 30 mL). The combined Et_2O extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel with 1:1 EtOAc/hexanes provided 0.31 g (51%) of 5-amino-8-chloro-3,4-dihydro-1(2*H*)-naphthalenone. This aniline was treated as described in **29** for the conversion of 5-amino-8-methyltetralone to **29J** to provide **31J**. A mixture of **31J** (0.16 g, 0.50 mmol) and 10% Pd/C in 5:1 THF/5 M HCl (6 mL) was stirred under hydrogen (1 atm) for 1 h, filtered, and concentrated. Purification of the residue on silica gel with 10% MeOH in NH_3-saturated CH_2Cl_2 provided 0.040 g (24%) of **31** that was converted to the maleic acid salt: mp 175−178 °C; ^{1}H NMR (DMSO-d_6) δ 1.30−1.85 (m, 2H), 1.86−2.08 (m, 2H), 2.60−3.00 (m, 2H), 3.06 (s, 3H), 4.44 (m, 1H), 6.05 (s, 2H), 6.82 (s, 1H), 7.32 (s, 2H), 8.80 (s, 1H), 9.15 (s, 1H); MS (APCI+) *m*/*z* 326 $(M + H)^+$; MS (APCI−) *m*/*z* 324 $(M - H)^-$. Anal. ($C_{14}H_{16}N_3O_2SCl \cdot C_4H_4O_4$) C, H, N.

Ethanesulfonic Acid [5-Hydroxy-5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydronaphthalen-1-yl]amide (32). 5-Nitro-1-tetralone[39] (1.0 g, 5.2 mmol) was reacted by method B to provide after chromatography (5% EtOH in CH_2Cl_2) 0.83 g (63%) of the intermediate alcohol. This alcohol (0.49 g, 0.80 mmol) was dissolved in EtOH (10 mL), treated with water (5 mL), NH_4Cl (0.046 g, 0.88 mmol), and iron powder (0.34 g, 7.6 mmol), heated to reflux, cooled, filtered through Celite, concentrated, and chromatographed (2% EtOH in CH_2Cl_2) to provide 0.30 g (80%) of the corresponding aniline. Via method F, this aniline (0.22 g, 0.46 mmol) and $EtSO_2Cl$ (0.068 mL, 0.72 mmol) provided 0.23 g (89%) of the sulfonamide. The trityl group was then removed by hydrogenating this sulfonamide intermediate (0.10 g, 0.18 mmol) in EtOH (20 mL) in the presence of 90 mg of 10% Pd/C under 4 atm of H_2 for 53 h, and the mixture was filtered. The filtrate was concentrated and chromatographed (10:1:89 MeOH/NH_4OH/CH_2Cl_2) to provide 0.015 g (26%) of **32**. ^{1}H NMR (CD_3OD) δ 1.37 (t, J = 7.54 Hz, 3 H), 1.74 (m, 1 H), 2.02 (m, 2 H), 2.38 (m, 1 H), 2.89 (m, 2 H), 3.15 (q, J = 7.35 Hz, 2 H), 6.73 (d, J = 1.47 Hz, 1 H), 7.17 (d, J = 7.72 Hz, 1 H), 7.24 (dd, J = 7.72, 1.47 Hz, 1 H), 7.30 (dd, J = 7.72, 1.84 Hz, 1 H), 7.67 (d, J = 1.10 Hz, 1 H). Anal. Calcd ($C_{14}H_{17}N_3O_3S$): C, 56.06; H, 5.96; N, 13.07. Found: C, 54.98; H, 5.64; N, 11.07.

***N*-[5-(1*H*-Imidazol-4-yl)-7,8-dihydro-1-naphthalenyl]-methanesulfonamide, Maleate (33).** 5-Methanesulfonamido-1-tetralone[41] (1.0 g, 4.2 mmol) was reacted with MOMCl as described for **29I** to provide 0.87 g (73%) of *N*-methoxymethyl-*N*-(5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)methanesulfonamide (**33I**) and then via method A (86%) to provide **33**, which was converted to the maleic acid salt: mp 161−165 °C; ^{1}H NMR (DMSO-d_6) δ 2.28−2.38 (m, 2H), 2.85 (t, 2H), 2.98 (s, 3H), 6.07 (s, 2H), 6.49 (t, 1H), 7.11 (dd, 1H), 7.19−7.29 (m, 2H), 7.61 (s, 1H), 8.78 (s, 1H), 9.21 (s, 1H); MS (DCI/NH_3) *m*/*z* 290 $(M + H)^+$, 307 $(M + NH_4)^+$. Anal. ($C_{14}H_{15}N_3O_2S \cdot C_4H_4O_4$) C, H, N.

***N*-[1-(1*H*-Imidazol-4-yl)-2,3-dihydro-1*H*-inden-4-yl]-ethanesulfonamide, Maleate (34).** 4-Nitroindanone[50] (**34A**) was reacted via method B (73%) to **34B**, method D (66%) to **34C**, and method E (91%) **34E**, as for **13** with $EtSO_2Cl$, to provide (54%) the free base of **34** that was converted to the maleic acid salt: mp 148−149 °C; ^{1}H NMR (CD_3OD) δ 1.36 (t, 3H), 2.16 (m, 1H), 2.64 (m, 1H), 2.96−3.24 (m, 2H), 3.14 (q, 2H), 4.62 (t, 1H), 6.25 (s, 2H), 6.92 (d, 1H), 7.21 (t, 1H), 7.29 (m, 2H), 8.76 (d, 1H); MS (DCI/NH_3) *m*/*z* 292 $(M + H)^+$. Anal. ($C_{14}H_{17}N_3O_2S \cdot C_4H_4O_4$) C, H, N.

***N*-[5-(1*H*-Imidazol-4-yl)-6,7,8,9-tetrahydro-5*H*-benzo[*a*]-cyclohepten-1-yl]methanesulfonamide, Maleate (35).** 1-Benzosuberone (18.5 g, 11.5 mmol) was mechanically stirred at −15 °C and treated with concentrated H_2SO_4 (41 mL) over 5 min, stirred for 10 min, treated dropwise over 10 min with a mixture of fuming HNO_3 (9 mL) and concentrated H_2SO_4 (14 mL), stirred at −15 °C for 15 min, and poured carefully onto a mixture of ice (200 g) and water (200 mL). The resulting solid was collected by filtration, washed with water (2 × 100 mL), dried, and recrystallized from EtOH (200 mL). The resulting solid was removed by filtration and the filtrate was adsorbed on silica gel and purified by flash chromatography on silica gel, eluting with EtOAc/hexanes 12:88 to provide **35A** (13%) as the less polar product. Via methods B, D, E, F (using $EtSO_2Cl$), and G, **35A** provided the free base of **35**, which was converted to the maleic acid salt: mp 162−164 °C; ^{1}H NMR (CD_3OD) δ 1.58 (m, 1H), 1.83 (m, 3H), 2.06 (m, 1H), 2.17 (m, 1H), 2.97 (s, 3H), 3.00 (m, 1H), 3.18 (m, 1H), 4.54 (dd, 1H), 6.25 (s, 2H), 7.69 (d, 1H), 7.14 (t, 1H), 7.26 (dd, 1H), 7.29 (s, 1H), 8.81 (d, 1H); MS (DCI/NH_3) *m*/*z* 306 $(M + H)^+$. Anal. ($C_{15}H_{19}N_3O_2S \cdot C_4H_4O_4 \cdot 0.5EtOAc$) C, H, N.

***N*-[3-(1*H*-Imidazol-4-ylmethyl)phenyl]ethanesulfonamide, Maleate (36).** 3-Nitrobenzaldehyde (**36K**) (1.6 g, 10.6 mmol) was reacted with **5** (2.4 g, 7.9 mmol) as described in method A, part 1. The reaction mixture was not concentrated but treated with aqueous NH_4Cl and extracted with CH_2Cl_2 (2×). The combined extractions were dried ($MgSO_4$), filtered, and concentrated to provide the intermediate alcohol. This alcohol, Et_3SiH (3 mL), and TFA (30 mL) were refluxed for 16 h and concentrated. The residue was triturated with hexane and then partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed (CH_2Cl_2 and then 2:1 CH_2Cl_2/EtOAc) to provide **36L** (0.81 g, 33%). Via method E, **36L** (0.81 g, 2.6 mmol) in 3:1 THF/EtOAc provided the aniline (0.74 g, 100%). Via method F with $EtSO_2Cl$ and then method H, the aniline (0.28 g, 0.89 mmol) provided compound **36** (0.24 g, 92%), which was converted to the maleic acid salt: mp 107−109 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3H), 3.08 (q, 2H), 3.99 (s, 2H), 6.05 (s, 2H), 6.96 (d, 1H), 7.08 (m, 2H), 7.28 (m, 1H), 7.37 (d, 1H), 8.80 (d, 1H), 9.77 (s, 1H); MS (DCI/NH_3) *m*/*z* 266 $(M + H)^+$. Anal. ($C_{12}H_{15}N_3O_2S \cdot C_4H_4O_4$) C, H, N.

***N*-[3-(1*H*-Imidazol-4-ylmethyl)-2-methylphenyl]methanesulfonamide, Maleate (37).** 2-Methyl-3-nitrobenzyl alcohol[51] (2.95 g, 17.5 mmol) and oxalyl chloride (6.1 mL, 70 mmol) in CH_2Cl_2 (61 mL) at −78 °C under N_2 were treated dropwise with DMSO (8.7 mL, 123 mmol), stirred for 10 min, treated with Et_3N (25 mL, 175 mmol), stirred for 10 min, warmed to room temperature, stirred for 16 h, treated with

aqueous NH_4Cl solution, and extracted with Et_2O (2×). The combined Et_2O layers were washed with water and brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (5:1 and then 2:1 hexane/EtOAc) to provide 2.73 g (94%) of **37K**, which was treated as described for **36** to provide **37**, which was converted to the maleic acid salt: mp 146−147 °C; ^{1}H NMR (DMSO-d_6) δ 1.26 (t, 3H), 3.25 (s, 3H), 3.06 (q, 2H), 4.01 (s, 2H), 6.05 (s, 2H), 7.02 (dd, 1H), 7.17 (m, 2H), 7.24 (d, 1H), 8.80 (d, 1H), 9.07 (s, 1H); MS (DCI/NH_3) *m*/*z* 280 $(M + H)^+$. Anal. ($C_{13}H_{17}N_3O_2S\cdot C_4H_4O_4$) C, H, N.

***N*-{3-[1-(1*H*-Imidazol-4-yl)ethyl]phenyl}methanesulfonamide, Maleate (38).** 3-Nitroacetophenone (**38A**) (0.67 g, 4.0 mmol) was reacted via methods A, D, and E to provide 0.59 g (60% for three steps) of **38E**. Aniline **38E** (0.31 g, 1.1 mmol) was reacted as in **13** using MsCl to provide 0.25 g (89%) of the free base of **38**, which was converted to the maleic acid salt: mp 135−136 °C; ^{1}H NMR (DMSO-d_6) δ 1.55 (d, 3H), 2.98 (s, 3H), 4.20 (q, 1H), 6.05 (s, 2H), 6.98 (d, 1H), 7.05 (s, 1H), 7.08 (d, 1H), 7.30 (t, 1H), 7.47 (s, 1H), 8.84 (s, 1H), 9.75 (s, 1H); MS (DCI/NH_3) *m*/*z* 266 $(M + H)^+$. Anal. ($C_{12}H_{15}N_3O_2S\cdot C_4H_4O_4$) C, H, N.

***N*-[4-(1*H*-Imidazol-4-yl)chroman-8-yl]methanesulfonamide (39).** 8-Nitrochroman-4-one[52] (**39A**) (3.3 g, 17 mmol) was reacted via method B (83%) to **39B**, method D (78%) to **39C**, and method E (86%) to **39E** and as for **13** using MsCl to provide the free base of **39** (41%), which was converted to the maleic acid salt: mp 172−174 °C; ^{1}H NMR (DMSO-d_6) δ 2.22 (m, 2H), 2.99 (s, 3H), 4.25 (m, 2H), 4.40 (t, 1H), 6.06 (s, 2H), 6.78 (dd, 1H), 6.83 (t, 1H), 7.16 (dd, 1H), 7.29 (s, 1H), 8.80 (s, 1H), 8.88 (s, 1H); MS (APCI+) *m*/*z* 294 $(M + H)^+$. Anal. ($C_{13}H_{15}N_3O_3S\cdot C_4H_4O_4$) C, H, N.

Ethanesulfonic Acid [4-(1*H*-imidazol-4-yl)thiochroman-8-yl]amide (40). 8-Nitrothiochroman-4-one[40] (**40A**) (0.48 g, 2.3 mmol) was reacted via method C (37%) to **40D**, method E (91%) to **40E**, and methods F (using $EtSO_2Cl$) and H to provide **40** (47%): mp 248−251 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 3H), 2.01 (m, 1H), 2.44 (m, 1H), 2.90 (m, 2H), 3.11 (q, 2H), 4.16 (m, 1H), 6.40 (s, 1H), 6.95 (m, 2H), 7.11 (m, 1H), 7.80 (s, 1H), 9.0 (s, 1H), 11.81 (bs, 1H); MS (APCI+) *m*/*z* 324 $(M + H)^+$. Anal. ($C_{14}H_{17}N_3O_2S\cdot 0.25H_2O$) C, H, N.

Ethanesulfonic Acid [1-(1*H*-Imidazol-4-yl)-1,3-dihydroisobenzofuran-4-yl]amide (41). 4-Nitro-2-benzofuran-1(3*H*)-one[53] (**41A**) (2.4 g, 13 mmol) was reacted via method A, part 1, and the intermediate alcohol (3.2 g, 69%) was isolated after chromatography (1:1 and then 2:1 EtOAc/hexane). This alcohol (0.50 g, 1.4 mmol) was reduced by stirring in Et_3SiH (2.5 mL) and TFA (15 mL) for 1 h to provide, after concentration and chromatography (1:1 and then 2:1 EtOAc/hexane), 0.25 g (52%) of *N*,*N*-dimethyl-4-(4-nitro-1,3-dihydro-2-benzofuran-1-yl)-1*H*-imidazole-1-sulfonamide. Reduction by method E (100%) and sulfonation/deprotection by method F (with $EtSO_2Cl$) and method H (96%) provided **41**, which was converted to the maleic acid salt: mp 95−98 °C; ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H), 3.14 (q, 2H), 5.12 (d, 1H), 5.26 (dd, 1H), 6.09 (s, 2H), 6.31 (s, 1H), 6.98 (dd, 1H), 7.25−7.36 (m, 2H), 7.51 (bs, 1H), 8.67 (bs, 1H), 9.59 (s, 1H), 14.6 (bs, 1H); MS (ESI+) *m*/*z* 294 $(M + H)^+$; MS (ESI−) *m*/*z* 292 $(M - H)^-$. Anal. ($C_{13}H_{15}N_3O_3S\cdot C_4H_4O_4\cdot 0.5$EtOAc) C, H, N.

Ethanesulfonic Acid [8-(1*H*-Imidazol-4-yl)-5,6,7,8-tetrahydronaphthalen-2-yl]amide (42). The title compound was prepared according to methods A and D−G, substituting 7-nitro-1-tetralone for 5-nitro-1-tetralone and $EtSO_2Cl$ in place of MsCl: mp 187−188 °C; ^{1}H NMR (DMSO-d_6) δ 1.25 (t, J = 7 Hz, 3H), 1.70 (m, 2H), 1.94 (m, 2H), 2.71 (m, 2H), 2.94 (q, J = 7 Hz, 2H), 4.00 (t, 1H), 6.51 (s, 1H), 6.86 (s, 1H), 6.97 (dd, J = 2, 8 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 7.52 (s, 1H), 9.47 (s, 1H), 11.78 (bs, 1H). Anal. ($C_{15}H_{19}N_3O_2S\cdot 0.25H_2O$) C, H, N.

***N*-[5-(1-Methyl-1*H*-imidazol-4-yl)-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide, Hydrochloride (43).** Compound **4J** (0.49 g, 1.3 mmol) in anhydrous DMF (5 mL) under N_2 was treated with NaH (62 mg of 60% dispersion, 1.5 mmol), stirred for 15 min, treated with MeI (0.096 mL, 1.5 mmol), stirred for 1 h, and quenched with water (75 mL). The semisolid was collected by decantation/filtration, dissolved in CH_2Cl_2 (100 mL), transferred to a separatory funnel to remove the majority of the water, dried ($MgSO_4$), filtered, concentrated, and chromatographed (12:1:1 EtOAc/H_2O/HCO_2H) to provide 0.12 g (24%) of the 3-methyl-3*H*-imidazol-4-yl isomer as the less polar isomer and 0.23 g (45%) of the 1-methyl-1*H*-imidazol-4-yl isomer as the more polar isomer. The more polar 1-methyl-1*H*-imidazol-4-yl isomer from above (0.22 g) was hydrogenated via method I to provide the free base of **43**, which was converted to the HCl salt: mp 130−135 °C; ^{1}H NMR (DMSO-d_6) δ 1.68−1.79 (m, 2H), 1.93−2.03 (m, 2H), 2.88 (t, 2H), 3.03 (s, 3H), 3.79 (s, 3H), 4.33 (t, 1H), 6.87 (d, 1H), 7.15 (t, 1H), 7.20−7.26 (m, 2H), 9.01 (s, 1H), 9.06 (s, 1H), 14.57 (bs, 1H); MS (DCI/NH_3) *m*/*z* 306 $(M + H)^+$. Anal. ($C_{15}H_{19}N_3O_2S\cdot HCl\cdot 0.5H_2O$) C, H, N.

***N*-[5-(3-Methyl-3*H*-imidazol-4-yl)-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide, Hydrochloride (44).** The 3-methyl-3*H*-imidazol-4-yl isomer (0.12 g) from the above procedure was hydrogenated via method I to provide the free base of **44**, which was converted to the HCl salt. MS (DCI/NH_3) *m*/*z* 306 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.67−1.91 (m, 3H), 1.94 (m, 1H), 2.71−2.94 (m, 2H), 3.03 (s, 3H), 3.83 (s, 3H), 4.45 (t, 1H), 6.85 (d, 1H), 7.03 (s, 1H), 7.14 (t, 1H), 7.24 (d, 1H), 9.05 (s, 1H), 9.07 (s, 1H), 14.32 (bs, 1H). Anal. ($C_{15}H_{19}N_3O_3S\cdot HCl\cdot EtOH\cdot 0.25H_2O$) C, H, N.

Ethanesulfonic Acid [5-(2-Methyl-1*H*-imidazol-4-yl)-5,6,7,8-tetrahydronaphthalen-1-yl]amide, Maleate (45). 5-Nitro-1-tetralone[39] (0.38 g, 2 mmol) and 4-iodo-2-methyl-1-triphenylmethylimidazole[54] (0.99 g, 2.2 mmol) were reacted via methods B and D to provide 0.63 g (89%) of **45C** after chromatography (10:1 and then 5:1 hexane/EtOAc). Via method E, **45C** (0.63 g, 1.8 mmol) provided 0.40 g (100%) of **45E**. As in **13** using $EtSO_2Cl$, **45E** (0.40 g, 1.8 mmol) provided 0.27 g (69%) of **45**, which was converted to the maleic acid salt: mp 73−77 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (t, 3H), 1.66−1.86 (m, 2H), 1.86−2.06 (m, 2H), 2.83 (t, 2H), 3.12 (q, 2H), 4.24 (t, 1H), 6.02 (s, 2H), 6.82 (d, 1H), 7.08 (s, 1H), 7.12 (t, 1H), 7.19 (dd, 1H), 8.99 (s, 1H), 13.60 (bs, 1H). Anal. ($C_{16}H_{21}N_3O_2S\cdot C_4H_4O_4\cdot 0.25H_2O$) C, H, N.

Ethanesulfonic Acid (5-Aminomethyl-5,6,7,8-tetrahydronaphthalen-1-yl)amide, Maleate (46). In step 1, following the reported procedure[15] described for the conversion of 3,4-dihydro-6-methoxy-5-nitro-1(2*H*)-naphthalenone to *N*-(5-cyano-5,6,7,8-tetrahydro-2-methoxy-1-naphthalenyl)methanesulfonamide and substitution of $EtSO_2Cl$ in place of MsCl, 5-nitro-1-tetralone[39] (5.0 g, 26 mmol) was converted to 5.3 g (77%) of ethanesulfonic acid (5-cyano-5,6,7,8-tetrahydro-naphthalen-1-yl)-amide. In step 2, a solution of this intermediate (1.0 g, 3.8 mmol) in THF (45 mL) was added dropwise to a suspension of LAH (0.58 g, 15 mmol) in THF (15 mL) at room temperature. The mixture was then heated to reflux for 2 h and cooled and the reaction mixture was quenched with the addition of acetone. After being stirred for 1 h, the mixture was concentrated, acidified with 1 M HCl, and extracted with EtOAc to remove impurities. The aqueous layer was basified with $NaHCO_3$ and extracted with EtOAc (4×) and with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to provide 0.50 g (49%) of **46** that was converted to the maleic acid salt. MS (APCI+) *m*/*z* 269 $(M + H)^+$, MS (APCI−) *m*/*z* 267 $(M - H)^-$; ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H), 1.73 (m, 4H), 2.40−2.50 (m, 1H), 2.77−2.90 (m, 1H), 2.90−3.02 (m, 1H), 3.02−3.10 (m, 2H), 3.10 (q, 2H), 6.01 (s, 2H), 7.16 (m, 3H), 7.80 (s, 3H), 8.91 (s, 1H). Anal. ($C_{13}H_{20}N_2O_2S\cdot C_4H_4O_4$) C, H, N.

Ethanesulfonic Acid (5-Methylaminomethyl-5,6,7,8-tetrahydronaphthalen-1-yl)amide, Hydrochloride (47). A solution of the free base of **46** (0.67 g, 2.5 mmol) and ethyl formate (7.7 mL) in toluene (20 mL) was refluxed for 1.5 h, cooled, and concentrated. The residue was taken up in THF (20 mL), treated with BH_3·THF complex (7.5 mL of 1 M solution THF), heated to reflux for 2 h, cooled, treated with MeOH (20 mL), concentrated, treated with MeOH (20 mL) and MeOH saturated with HCl (20 mL), refluxed for 1 h, cooled, and concentrated. The residue was taken up in water, adjusted to pH ∼8 with $NaHCO_3$, extracted with EtOAc (3×), and

extracted with THF (3×). The EtOAc extractions were discarded, the combined THF extractions were concentrated, and the residue was redissolved in CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated to provide 0.22 g (32%) of **47**, which was converted to the HCl salt: mp 195−198 °C; MS (APCI+) *m/z* 283 $(M + H)^+$; MS (APCI−) *m/z* 281 $(M - H)^-$; ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H), 1.71 (m, 3H), 1.88 (m, 1H), 2.59 (t, 3H), 2.69−2.70 (m, 1H), 2.82 (m, 1H), 3.00−3.19 (m, 2H), 3.08 (q, 2H), 3.23 (m, 1H), 7.16 (m, 3H), 8.78−9.08 (s, 2H), 8.93 (s, 1H). Anal. ($C_{14}H_{22}N_2O_2S\cdot HCl\cdot 0.25H_2O$) C, H, N.

***N*-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide (48).** In step 1, a solution of *N*-benzyl-*N*-(5-cyano-7,8-dihydronaphthalen-1-yl)-methanesulfonamide[39] (10 g, 30 mmol) in EtOH (200 mL) was treated with $NaBH_4$ (10 g, 260 mmol), stirred for 6 h, concentrated, treated with water (200 mL), and extracted with Et_2O (2×) and EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered, concentrated, and chromatographed (1:1 hexane/EtOAc) to provide 8.0 g (77%) of *N*-benzyl-*N*-(5-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)methanesulfonamide. In step 2, a solution of this intermediate (2.0 g, 5.9 mmol) in CH_2Cl_2 (30 mL) and MeOH (5 mL) at 0 °C was treated with a stream of HCl gas for 30 min, sealed, stirred overnight at ambient temperature, concentrated to dryness, treated with EtOH (25 mL), treated with ethylenediamine (3 mL), stirred under N_2 over the weekend, brought to pH 1 with the addition of 1 M HCl, and extracted with Et_2O. The aqueous layer was basified to pH 11 with a mixture of NH_4OH solution and ice and extracted with CH_2Cl_2 (3 × 200 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and concentrated to provide 2.3 g of *N*-benzyl-*N*-[5-(4,5-dihydro-1*H*-imidazol-2-yl)-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide. In step 3, this intermediate (1.5 g, 3.9 mmol) was hydrogenated in MeOH (250 mL) using wet 20% Pd/C (1.5 g) under 4 atm of H_2, filtered, and concentrated to provide 1.06 g (92%) of **48**, which was converted to the HCl salt. ^{1}H NMR (DMSO-d_6) δ 1.68 (m, 1 H), 1.95 (m, 3 H), 2.80 (m, 2 H), 3.02 (s, 3 H), 3.84 (s, 4 H), 4.25 (t, J = 6.99 Hz, 1 H), 7.00 (d, J = 7.35 Hz, 1 H), 7.21 (t, J = 7.72 Hz, 1 H), 7.28 (d, J = 6.99 Hz, 1 H), 9.18 (s, 1 H), 10.29 (s, 2 H). Anal. ($C_{14}H_{20}ClN_3O_2S\cdot 0.25H_2O$) C, H, N.

Ethanesulfonic Acid [3-(1*H*-imidazol-4-yl)phenyl]amide (49). In step 1, a mixture of 3-aminophenylboronic acid monohydrate (0.23 g, 1.5 mmol) and **6** (0.50 g, 1.1 mmol) in EtOH (4 mL) and toluene (8 mL) was treated with 0.85 M Na_2CO_3 (4 mL) and $Pd(PPh_3)_4$ (0.095 g, 0.082 mmol), stirred at 60 °C for 1 h, stirred at 100 °C for 7 h, cooled, concentrated, and partitioned between EtOAc and water. The EtOAc layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed (2.5−4% MeOH in CH_2Cl_2) to provide 0.16 g (35%) of 3-(1-trityl-1*H*-imidazol-4-yl)-phenylamine. In step 2, via method F using $EtSO_2Cl$, this intermediate (0.085 g, 0.21 mmol) provided 0.17 g of ethanesulfonic acid [3-(1-trityl-1*H*-imidazol-4-yl)phenyl]-amide. In step 3, via method H, this intermediate (0.13 g, 0.26 mmol) provided 0.033 g (50%) of **49**. ^{1}H NMR (DMSO-d_6) δ 1.20 (t, J = 7.35 Hz, 3 H), 3.08 (q, J = 7.35 Hz, 2 H), 7.04 (dd, J = 8.09, 1.47 Hz, 1 H), 7.27 (t, J = 7.91 Hz, 1 H), 7.47 (d, J = 7.72 Hz, 1 H), 7.56 (s, 1 H), 7.69 (m, 2 H), 9.74 (s, 1 H), 12.19 (broad s, 1 H). Anal. Calcd ($C_{11}H_{13}N_3O_2S$): C, 52.57; H, 5.21; N, 16.72. Found: C, 51.89; H, 5.20; N, 14.96.

Ethanesulfonic Acid [3-(4,5-Dihydro-1*H*-imidazol-2-ylamino)phenyl]amide (50). In step 1, via method F using $EtSO_2Cl$, 3-nitroaniline (4.0 g, 29 mmol) provided 5.4 g of ethanesulfonic acid (3-nitrophenyl)amide. In step 2, via method E, this intermediate provided 4.8 g (83%) of ethanesulfonic acid (3-aminophenyl)amide. In step 3, this intermediate (1.2 g, 6.0 mmol) was refluxed with 2-methylthio-2-imidazoline hydrochloride[55] (1.6 g, 6.6 mmol) in pyridine (8 mL) for 4.5 h, cooled, concentrated, chromatographed (10% MeOH in CH_2Cl_2), and rechromatographed (10% EtOH in NH_3-saturated CH_2Cl_2) to provide 0.37 g (23%) of **50**: mp 98−101 °C; MS (APCI+) *m/z* 269 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.17 (t, 3H), 3.04 (q, 2H), 3.31 (s, 4H), 6.68 (dd, 2H), 6.82 (s, 1H), 7.07 (dd, 1H). Anal. ($C_{11}H_{16}N_4O_2S\cdot EtOH\cdot 0.25H_2O$) C, H, N.

Ethanesulfonic Acid (3-Pyrrolidin-2-ylmethylphenyl)-amide (51). In step 1, a mixture of 3-nitrobenzaldehyde (10 g, 66 mmol), methyl 4-nitrobutyrate (8.8 mL, 69 mmol), and DBU (1.0 mL, 6.7 mmol) in THF (12 mL) was stirred for 1 day, treated with more methyl 4-nitrobutyrate (8.8 mL, 69 mmol), stirred an additional day, and partitioned between NH_4Cl solution and EtOAc. The EtOAc layer was washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (20% EtOAc in hexane) to provide 16.6 g (79%) of 5-hydroxy-4-nitro-5-(3-nitrophenyl)pentanoic acid methyl ester. In step 2, this intermediate (16.4 g, 55 mmol) and NaOAc (5.0 g, 61 mmol) in Ac_2O (140 mL) were heated to 50 °C for 4 h, concentrated, and partitioned between $NaHCO_3$ solution and EtOAc. The EtOAc layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to provide 15.0 g of 4-nitro-5-(3-nitrophenyl)pent-4-enoic acid methyl ester. In step 3, this intermediate (15.0 g, 534 mmol) in 340 mL of EtOH was cooled to 0 °C, treated with $NaBH_4$ (2.0 g), stirred at ambient temperature for 35 min, concentrated, treated with NH_4Cl solution, and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to provided 12.6 g (83%) of 4-nitro-5-(3-nitrophenyl)pentanoic acid methyl ester as a yellow oil. In step 4, this intermediate (6.3 g, 22 mmol) in MeOH (45 mL) and concentrated HCl (45 mL) was treated with a suspension of zinc (14.6 g, 22 mmol) in MeOH (25 mL), stirred at ambient temperature for 1 h, treated carefully with 6 M NaOH (300 mL), stirred for 1.5 h, neutralized to pH 7 with HCl, and extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and concentrated to provide 1.49 g (35%) of 5-(3-aminobenzyl)pyrrolidin-2-one. In step 5, via method F using $EtSO_2Cl$, this intermediate (1.49 g, 7.8 mmol) provided 1.14 g (52%) of ethanesulfonic acid [3-(5-oxo-pyrrolidin-2-ylmethyl)-phenyl]amide. In step 6, the product from above (0.40 g, 1.4 mmol) in THF (8 mL) was added over 15 min to a 0 °C slurry of LAH (0.16 g, 4.2 mmol) in THF (1 mL). After 4 h at ambient temperature, the mixture was carefully treated with excess acetone and stirred for 1 h. The resulting salts were removed by filtration and washed with THF. The combined filtrates were concentrated and chromatographed (10% EtOH in NH_3-saturated CH_2Cl_2) to provide 0.095 g (25%) of **51**: mp 55−58 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3H), 1.25 (m, 1H), 1.50−1.75 (m, 3H), 2.52−2.73 (m, 3H), 2.85 (m, 1H), 3.05 (q, 2H), 3.08 (m, 1H), 6.92 (d, 1H), 7.00−7.09 (m, 2H), 7.20 (dd, 1H). Anal. ($C_{13}H_{20}N_2O_2S\cdot 0.25H_2O$) C, H, N.

Ethanesulfonic Acid [3-(1*H*-Imidazol-4-ylsulfanyl)phenyl]amide (52). In step 1, a solution of **5** (2.0 g, 6.6 mmol) in THF (50 mL) under N_2 at −78 °C was treated with EtMgBr (3.0 M in Et_2O, 2.5 mL), stirred for 15 min, treated with a solution of 3-nitrophenyl disulfide (2.1 g, 6.6 mmol) in THF (5 mL), warmed to 0 °C, stirred for 45 min, quenched with NH_4Cl solution, and diluted with Et_2O. The organic layer was isolated, washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 1.1 g (48%) of 4-(3-nitrophenylsulfanyl)imidazole-1-sulfonic acid dimethylamide. In step 2, a mixture of this intermediate (1.0 g, 3.1 mmol), iron powder (1.2 g, 21 mmol), and NH_4Cl (0.18 g, 3.3 mmol) in EtOH (30 mL) and H_2O (15 mL) was refluxed for 16 h, cooled, and filtered through Celite. The filtrate was diluted with EtOAc, washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 0.95 g of 4-(3-aminophenylsulfanyl)imidazole-1-sulfonic acid dimethylamide. In step 3, via method F using $EtSO_2Cl$, this intermediate (0.90 g, 3.0 mmol) provided 0.95 g (81%) of 4-(3-ethanesulfonylaminophenylsulfanyl)imidazole-1-sulfonic acid dimethylamide. In step 4, via method H, this intermediate (0.4 g, 1.0 mmol) provided 0.12 g (41%) of **52**. ^{1}H NMR (DMSO-d_6) δ 1.15 (t, J = 7.35 Hz, 3 H), 3.03 (q, J = 7.35 Hz, 2 H), 6.76 (d, J = 7.72 Hz, 1 H), 6.94 (m, 2 H), 7.18 (t, J = 7.91 Hz, 1 H), 7.54 (s, 1 H), 7.85 (s, 1 H), 9.80 (s, 1 H), 12.51 (s, 1 H). Anal. Calcd ($C_{11}H_{13}N_3O_2S_2$): C, 46.62; H, 4.62; N, 14.83. Found: C, 46.09; H, 3.78; N, 13.74.

Ethanesulfonic Acid [3-(1*H*-Imidazole-4-sulfonyl)phenyl]amide (53). A 0 °C solution of the product from step 3 of **52** (0.42, 1.1 mmol) in CH_2Cl_2 (30 mL) was treated with

peracetic acid (32 wt % solution in AcOH, 2.5 mL), stirred for 1 h at ambient temperature, washed with $NaHCO_3$ solution, dried ($MgSO_4$), filtered, concentrated, treated with 1 M HCl (10 mL), heated to reflux for 2 h, neutralized with 1 M NaOH, treated with silica gel (5 g), concentrated to dryness, and chromatographed (10% MeOH in CH_2Cl_2) to provide 0.14 g (40%) of **53**. ^{1}H NMR (DMSO-d_6) δ 1.18 (t, J = 7.46 Hz, 3 H), 3.14 (q, J = 7.46 Hz, 2 H), 7.45 (dt, J = 7.12, 2.20 Hz, 1 H), 7.55 (m, 2 H), 7.76 (m, 1 H), 7.87 (d, J = 1.36 Hz, 1 H), 8.01 (d, J = 1.36 Hz, 1 H), 10.22 (s, 1 H), 12.97 (s, 1 H). Anal. ($C_{11}H_{13}N_3O_4S_2$) C, H, N.

Ethanesulfonic Acid (3-Pyrrolidin-3-ylphenyl)amide (54). In step 1, 3-(3-nitrophenyl)acrylic acid methyl ester (6.0 g, 29 mmol) was treated with nitromethane (50 mL) and 1,1,3,3-tetramethylguanidine (1 mL), heated to 80 °C for 30 min, concentrated, and chromatographed (2:1 and then 1:1 hexane/EtOAc) to provide 3.7 g (48%) of 4-nitro-3-(3-nitrophenyl)butyric acid methyl ester. In step 2, this intermediate (3.7 g, 14 mmol) and RaNi 2800 (0.4 g) in MeOH (40 mL) were stirred at 60 °C for 16 h under 4 atm of H_2, cooled, filtered, concentrated, and chromatographed (5% and then 10% MeOH in NH_3-saturated CH_2Cl_2) to provide 1.6 g (57%) of 4-(3-aminophenyl)pyrrolidin-2-one. In step 3, via method F using $EtSO_2Cl$, this intermediate (1.0 g, 5.7 mmol) provided 1.3 g (87%) of ethanesulfonic acid [3-(5-oxopyrrolidin-3-yl)phenyl]-amide. In step 4, a solution of this intermediate (1.28 g, 4.8 mmol) in THF was treated with 1 M BH_3·THF in THF (24 mL), heated to reflux overnight, cooled, treated with 1 M HCl (30 mL), heated to reflux for 1 h, cooled, concentrated, and chromatographed (10% and then 20% MeOH in NH_3-saturated CH_2Cl_2) to provide 0.49 g of recovered starting material and 0.71 g (59%) of **54**. ^{1}H NMR (DMSO-d_6) δ 1.19 (t, J = 7.29 Hz, 3 H), 1.88 (m, 1 H), 2.31 (m, 1 H), 2.98 (t, J = 10.85 Hz, 1 H), 3.09 (q, J = 7.57 Hz, 2 H), 3.19 (m, 1 H), 3.36 (m, 2 H), 3.57 (dd, J = 11.02, 7.97 Hz, 1 H), 7.11 (m, 3 H), 7.30 (t, J = 7.97 Hz, 1 H), 9.36 (broad s, 2 H); MS (DCI/NH_3) m/z $(M + H)^+$ 255. Anal. ($C_{12}H_{18}N_2O_2S$·0.5H_2O·0.5CH_2Cl_2) C, H, N.

Ethanesulfonic Acid [3-(4,5-Dihydro-1*H*-imidazol-4-ylmethyl)phenyl]amide (55). In step 1, a solution of 2-amino-3-(3-nitro-phenyl)propionic acid hydrochloride[56] (2.1 g, 8.4 mmol) in EtOH (40 mL) was treated with 100 mL of 1 M HCl in Et_2O. The Et_2O was removed under reduced pressure and the remaining mixture was refluxed for 8 h, cooled, and concentrated to provide 2-amino-3-(3-nitrophenyl)propionic acid ethyl ester hydrochloride. In step 2, this intermediate was taken up in NH_3-saturated MeOH (40 mL), stirred for 3 days in a sealed vessel, and concentrated to provide 2.1 g (100% for two steps) of 2-amino-3-(3-nitrophenyl)propionamide as the HCl salt. In step 3, this intermediate (1.5 g, 6.1 mmol) was dissolved in THF (75 mL), treated with 10 M BH_3·Me_2S complex (15 mL), refluxed overnight, cooled, treated carefully with 100 mL of 6 M HCl, refluxed overnight, cooled, concentrated, neutralized to pH 9, treated with brine, and extracted with THF (5 × 200 mL). The combined THF layers were dried (Na_2SO_4), filtered, concentrated, and chromatographed (10% MeOH in NH_3-saturated CH_2Cl_2) to provide 0.27 g (23%) of 3-(3-nitrophenyl)propane-1,2-diamine as the less polar product and 0.11 g (11%) of 3-(3-aminophenyl)propane-1,2-diamine as the more polar product. In step 4, the 3-(3-nitrophenyl)propane-1,2-diamine (0.27 g, 1.4 mmol) in DMF (6 mL) was treated with Boc_2O (0.68 g, 3.1 mmol) stirred for 2 h, diluted with water, and stirred for 30 min. The resulting precipitate was collected by filtration and dried to provide 0.16 g (29%) of [2-*tert*-butoxycarbonylamino-3-(3-nitrophenyl)propyl]carbamic acid *tert*-butyl ester. In step 5, via method E, this intermediate (0.16 g, 0.40 mmol) provided 0.14 g (94%) of [2-(3-aminophenyl)-1-(*tert*-butoxycarbonylaminomethyl)ethyl]-carbamic acid *tert*-butyl ester. In step 6, via steps F and G, this aniline (0.13 g, 0.37 mmol) and $EtSO_2Cl$ provided 0.13 g of ethanesulfonic acid [3-(2,3-diaminopropyl)phenyl]amide. In step 7, this intermediate in EtOH (1.4 mL) was treated with formamidine acetate (0.048 g, 0.46 mmol) under N_2 at ambient temperature, stirred overnight, concentrated, dissolved in 1 M HCl, washed with EtOAc, basified to pH 9 with 25% NaOH solution, treated with brine, and extracted with THF (5×). The combined THF layers were concentrated and chromatographed (10% MeOH in NH_3-saturated CH_2Cl_2) to provide 10.2 mg (10% for two steps) of **55**: mp 80−83 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3H), 2.56 (m, 1H), 2.72 (m, 1H), 3.07 (m, 3H), 3.37 (m, 1H), 3.91 (m, 1H), 6.95 (d, 1H), 6.98 (s, 1H), 7.04 (m, 1H), 7.06 (s, 1H), 7.22 (t, 1H); MS (APCI+) m/z 268 $(M + H)^+$. Anal. ($C_{12}H_{17}N_3O_2S$) C, H, N.

Supporting Information Available: Table 6 (α_2 binding and functional data), X-ray crystallographic data for compound **8**, and spectral data of intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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