2-(Anilinomethyl)imidazolines as α_1 Adrenergic Receptor Agonists: the Discovery of α_{1a} Subtype Selective 2′-Alkylsulfonyl-Substituted Analogues

Stephen J. Hodson,* Michael J. Bishop,† Jason D. Speake,† Frank Navas, III,† Deanna T. Garrison,† Eric C. Bigham,† David L. Saussy, Jr.,‡ James A. Liacos,‡ Paul E. Irving,‡ M. Jeffrey Gobel,‡ and Bryan W. Sherman‡

GlaxoSmithKline Research Laboratories, P.O. Box 13398, Research Triangle Park, North Carolina 27709-3398

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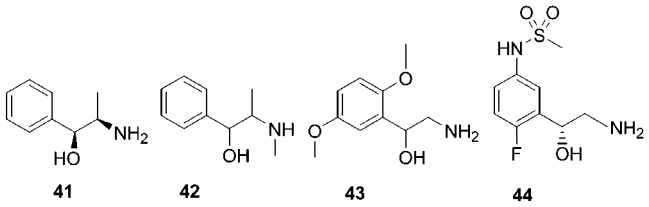
A series of 2′-alkylthio-2-(anilinomethyl)imidazolines were prepared to examine the effect of the alkyl group size, sulfur oxidation state, and phenyl ring substitution on ligand binding and agonism of α-adrenergic receptor subtypes α_{1a}, α_{1b}, α_{1d}, α_{2a}, and α_{2c}. Binding at all receptor subtypes decreased for compounds in the sulfone oxidation state as compared to their sulfide analogues. While sulfides were generally potent, nonselective agonists, sulfones exhibited α_{1a} subtype selectivity in a cell-based functional assay. Sulfone (**32**) was 250−7000-fold selective for α_{1a} vs all other subtypes.

Introduction

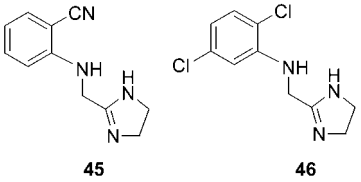
Adrenergic receptor agonists selective for the α_1 family have been used to prevent or reverse the hypotensive state associated with a variety of medical conditions. They have also been used to treat nasal congestion, mydriasis, and disorders of the lacrimal gland.[1] While compounds with selectivity for α_1 vs α_2 adrenergic receptors have long been known, the more recent cloning and expression of α_{1a}, α_{1b}, and α_{1d} receptor subtypes have allowed the search for compounds with selectivity for individual subtypes within the α_1 family. Our interest in identifying selective α_{1a} agonists was derived from the limited success of α adrenergic agonists phenylpropanolamine (**41**) (Figure 1), pseudoephedrine (**42**), and α-(aminomethyl)-2,5-dimethoxybenzyl alcohol (**43**) (the active metabolite of midodrine) in treating stress urinary incontinence and the hypothesis that undesired cardiovascular effects seen with these compounds might be diminished in compounds with high functional selectivity for the α_{1a} receptor.[2] Differential expression of α_1 subtypes in various tissues is well-documented,[3] and while the role of each α_1 receptor subtype in urethral smooth muscle tone and contraction is not fully understood, data suggest that α_{1a} selective agonists have an increased likelihood of achieving an acceptable therapeutic index.[4] *N*-[3-[(1*R*)-2-amino-1-hydroxyethyl]-4-fluorophenyl] methanesulfonamide (**44**), an α_{1a} selective agonist, has been reported to provide selectivity for contraction of urethral smooth muscle vs the cardiovascular effects in animals and was recently evaluated in clinical trials for stress urinary incontinence.[5]

Screening of our in-house compound collection using cloned human α_{1a} adrenoceptor in a cell-based functional assay identified simple 2-(anilinomethyl)imidazolines as α_{1a} adrenergic agonists.[6] Some of these compounds (for example, **45** and **46**; Figure 2) were originally patented as pesticides,[7] but 2-(anilinomethyl) imidazolines are known to be adrenergic agonists.[8]



41 42 43 44

Figure 1.



45 46

Figure 2.

In an effort to identify structurally novel compounds in this series, a medium throughput parallel synthesis approach was developed. Commercially available anilines were reacted with 2-chloromethylimidazoline hydrochloride in a Stemblock,[9] and the crude products were purified using a MultElute chromatography system to give the desired products in a single step. From this set, 2′-methylthio-2-(anilinomethyl)imidazoline (**1**) was identified as a potent though nonselective α adrenergic agonist (Table 1). Starting with this compound, variations of alkyl group size, sulfur oxidation state, and phenyl ring substituents were examined in an effort to identify α_{1a} selective compounds.

Chemistry

Sulfoxide (**2**) and sulfones (**3**, **6**, **10**, **13**, **17**, **20**, **23**, **25**, **28**, **32**, **36**, and **40**) were prepared via oxidation of the corresponding sulfides (Scheme 1) typically using *meta*-chloroperoxybenzoic acid as the oxidant.[10] The sulfides (**1**, **5**, **9**, **12**, **16**, **19**, **22**, **24**, **27**, **31**, and **35**) in turn were prepared by alkylation of the corresponding alkylthioanilines with 2-chloromethylimidazoline hy-

* To whom correspondence should be addressed. Stephen J. Hodson, Proctor and Gamble Health Care Research Center, P.O. Box 8006, Mason, OH 45040.
† Medicinal Chemistry Department.
‡ Receptor Biochemistry Department.

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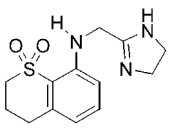
Table 1. In Vitro Binding and Functional Data[a]

				α receptor binding (pK_i)						functional agonism (pEC_{50}) (% max)				
no.	R	X	*n*	α_{1a}	α_{1b}	α_{1d}	α_{2a}	α_{2b}	α_{2c}	α_{1a}	α_{1b}	α_{1d}	α_{2a}	α_{2c}
1	CH_3	H	0	7.36	7.18	7.95	7.32	6.11	6.84	8.34 105	8.66 105	8.05 55	7.4 76	8.25 82
2	CH_3	H	1	5.89	6.10	5.92	6.01	<5.2	<5.3	6.31 91	<4	<4	<5 21	<5 74
3	CH_3	H	2	6.23	5.89	5.42	5.25	<5.2	<5.3	7.25 103	<4	<4	<5 11	5.5 68
5	Et	H	0	7.36	7.12	7.24	7.09	5.79	6.57	8.47 109	7.86 82	7.29 34	6.60 67	7.55 101
6	Et	H	2	5.92	6.04	5.65	5.88	<5.2	5.60	6.62 115	<4	<4	<5 10	5.3 64
7	*n*-Pr	H	2	5.66	6.08	5.86	<5.1	<5.2	5.58	7.16 115	<4	<4	<5 23	5.5 56
9	*i*-Pr	H	0	7.24	6.77	6.65	7.09	5.63	6.78	8.30 115	7.21 29	<5.3	6.38 64	7.55 91
10	*i*-Pr	H	2	5.57	6.00	5.55	5.53	<5.2	<5.3	5.71 70	<5	<5.3	<5 14	<5 50
12	CH_3	3-F	0	6.83	6.62	6.52	6.78	5.40	6.66	8.11 91	7.07 48	7.47 59	7.00 102	7.8 104
13	CH_3	3-F	2	6.26	5.64	5.46	<5.1	<5.2	6.59	7.62 93	<4	<4	<5 64	6.3 93
16	CH_3	4-F	0	7.68	7.82	8.30	7.23	6.07	6.66	8.11 93	8.22 78	8.04 75	6.5 47	7.00 82
17	CH_3	4-F	2	6.18	6.29	5.79	6.40	<5.2	<5.3	6.36 61	<4	<4	<5 19	<5 32
19	CH_3	5-F	0	7.48	7.39	8.21	7.74	6.48	6.94	8.64 90	8.73 92	7.66 107	7.60 96	8.25 97
20	CH_3	5-F	2	6.09	5.88	5.58	5.35	<5.2	<5.3	7.78 96	<4	<4	<5 18	5.7 91
23	CH_3	6-F	2	6.38	6.42	6.04	6.06	<5.2	6.16	7.38 106	<4	<4	<5 38	6.35 93
24	CH_3	5-CF_3	0	6.23	5.69	6.32	6.70	5.78	6.22	7.98 111	8.22 114	7.36 58	<5 40	8.1 45
25	CH_3	5-CF_3	2	<4.9	<5.0	<4.8	<5.1	<5.2	<5.3	5.96 95	<4	<4	<5 33	<5 25
27	CH_3	5-CH_3	0	7.68	6.91	7.76	7.20	6.01	6.70	9.96 101	9.38 96	9.04 107	7.60 87	8.05 81
28	CH_3	5-CH_3	2	6.11	5.46	5.32	5.41	<5.2	<5.3	8.71 98	6.85 91	<5.7	<5 24	5.95 76
31	CH_3	5-OCH_3	0	6.76	6.16	6.97	6.66	<5.2	6.22	8.80 101	8.44 92	8.30 91	6.35 52	6.70 74
32	CH_3	5-OCH_3	2	5.79	5.34	5.12	5.44	<5.2	<5.3	7.85 102	<4	<4	<5 16	5.48 49
35	CH_3	5-Cl	0	7.73	7.16	8.33	7.38	6.17	6.77	9.36 82	9.30 103	8.57 106	8.20 93	8.55 92
36	CH_3	5-Cl	2	6.27	5.53	5.62	<5.1	<5.2	5.32	8.55 91	7.21 103	<4	<5 42	6.10 81
37	CH_3	4-Cl	2	6.34	6.19	6.06	5.30	<5.2	5.40	6.29 41	<4	<4	<5 38	<5 54
40				6.21	5.67	<4.8	6.10	<5.2	5.57	<4	<4	<4	<5 29	5.2 69
44				5.95	4.95					6.80 109	<4.0	<4.0	<5.0 34	5.7 87
oxymetazoline				7.80	6.08	5.87	7.79	5.27	7.23	7.69 74	<4.6	<4.6	8.48 88	

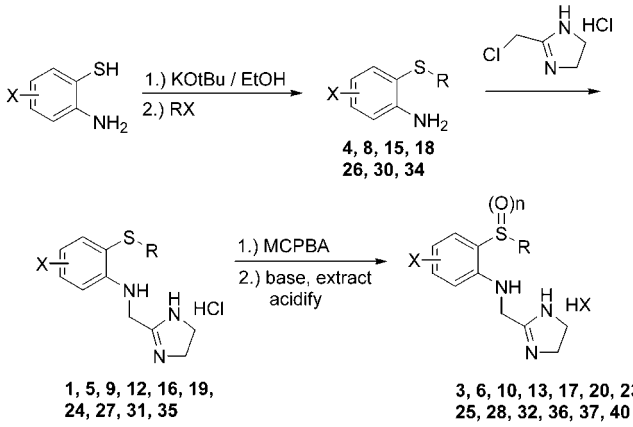
[a] Each entry represents the mean of at least two experiments, with α_1 pK_i values having an average SEM of ±0.08, α_2 pK_i values having an average SEM of ±0.13, α_1 pEC_{50} values having an average SEM of ±0.15, and α_2 pEC_{50} values having an average SEM of ±0.10. "% max" refers to the maximum response observed for the compound expressed as a percentage of the maximum response observed for a nonselective α_1 (phenylephrine) or α_2 (UK14 304) agonist and is indicative of the efficacy of the compounds relative to these full agonists.

drochloride in the presence of phenol.[7a] An excess of the aniline served as an acid scavenger, or in some cases, 2,6-lutidine was used as a base. Isolation of the product imidazolines was accomplished by chromatography on silica gel or alumina. Some compounds could be isolated by partitioning the crude reaction mixture in water/CH_2Cl_2 and adjusting the pH to 7.0 with NaOH to allow extraction of the excess aniline. Adjusting the pH to 12 allowed extraction of the free base into the organic phase, and addition of HCl or fumaric acid precipitated the product as its salt.

The aniline used for the preparation of **1** was commercially available. Anilines **4**, **8**, **15**, **18**, **26**, **30**, and **34** were made by alkylation of the corresponding thiophenols with the appropriate alkyl halide. The aniline used for the preparation of **12** was obtained by deprotection of its trifluoroacetamide derivative.[11]

The anilines used for the preparation of **16**, **19**, **27**, **31**, and **35** were made by hydrolysis of the appropriate commercially available benzothiazole derivatives (Scheme 2) followed by alkylation with methyl iodide.[12] The aniline used for the preparation of **23** was prepared by

Scheme 1

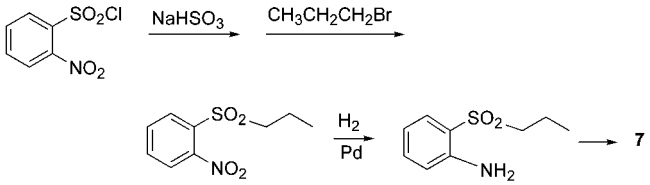


alkylation of 2,6-difluoronitrobenzene with sodium methylmercaptide followed by reduction of the nitro group.[13] 8-Aminothiochroman (**39**),[14] used for the preparation of **40**, was made by conversion of 8-nitrothiochroman-4-one to the enol-triflate followed by hydrogenation of the nitro group and hydrogenolysis of the enol triflate. Compound **7** was prepared via alkylation of the *o*-nitrophenylsulfinate, derived from the corresponding sulfonyl chloride, with bromopropane (Scheme 3).[15]

Discussion

To model the potential ability of ligands to activate the individual α adrenergic subtypes in humans, all compounds were evaluated in a cell-based functional assay using the cloned human receptors. Human α_{1a}, α_{1b}, and α_{1d} receptors were expressed in rat-1 fibroblasts, and agonist activity was evaluated via calcium mobilization through the Gq-coupled PLC pathway using calcium sensitive fluorescent dyes. Human α_{2a} and α_{2c} receptors were expressed in Chinese hamster ovary (CHO) cells, and agonist activity was evaluated via cyclic adenosine 5′-monophosphate (cAMP) accumulation (lack of a reliable high-throughput assay for the human α_{2b} receptor prevented us from evaluating all compounds for α_{2b} activity). The agonist potency (expressed as the pEC_{50}) and efficacy (expressed as a percent of the maximal effect of phenylephrine for α_1 adrenoceptors or UK 14 304 for α_2 adrenoreceptors) of select analogues of 2′-methylthio-2-(anilinomethyl)imidazoline are listed in Table 1. α_{1a}, α_{1b}, α_{1d}, α_{2a}, and α_{2c} receptor binding affinities for these compounds are also listed in Table 1.[16]

Scheme 3

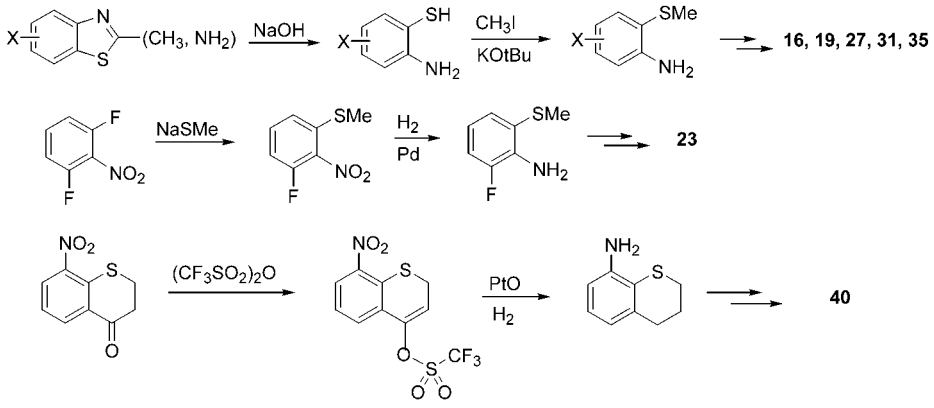


Effect of Alkyl Group Size in Sulfides. Lengthening the methyl group of **1** to give ethyl-substituted compound (**4**) caused almost no change in affinity (pK_i). The largest effect, a 5-fold reduction, was seen at α_{1d}. Branching (as in isopropyl compound **9**) also caused little change in affinity at any receptor except at α_{1d}, where a 20-fold reduction was seen. Potency (pEC_{50}) at α_{1a}, α_{1b}, α_{2a}, and α_{2c} was also little affected by lengthening or branching (compounds **5** and **9**). Changes of less than 10-fold were observed. Lengthening (as in compound **5**) reduced potency at α_{1d} by only 6-fold, but branching (**9**) caused a nearly 1000-fold reduction in potency. This parallels the observed affinity data in that α_{1d} suffers the largest affinity loss on alkyl group enlargement and suggests that α_{1d} has a significantly different binding cavity than the other subtypes. This cavity is unable to accommodate branching in the space filled by the alkyl group of **9** resulting in 20-fold decreased affinity. Moreover, the resulting complex fails to induce the correct conformational change required for receptor activation.

Effect of Sulfur Oxidation State. 2-(Anilinomethyl)imidazolines with amide or ketone substituents in the 2′-position exhibit interesting structure−activity relationships (SAR) with respect to α_1 subtype selectivity.[17] Hydrogen bonding between the 2′-amide or ketone carbonyl and the aniline proton may affect the conformation of these molecules in the receptor (Figure 3), serving to restrict movement of the imidazoline and/or the 2′-substituent. On the basis of the selectivity data, it appears that the α_{1a} receptor can generally accommodate this conformational restriction better than α_{1b} or α_{1d}. We hypothesized that a sulfoxide or sulfone in the 2′-position might also form a hydrogen bond and lead to similar effects.

We oxidized the methylthio group of **1**, giving sulfone **3**, to look for similar hydrogen-bonding effects. Methyl sulfone **3** lost 15-fold affinity and 12-fold potency at α_{1a}, as compared to methyl sulfide **1**, but still strongly activated the receptor ($pEC_{50} = 7.25$). While affinity at

Scheme 2



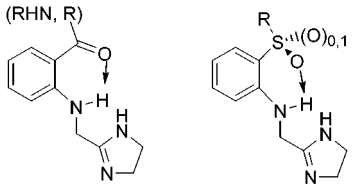


Figure 3.

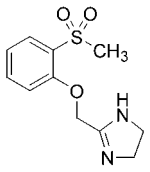


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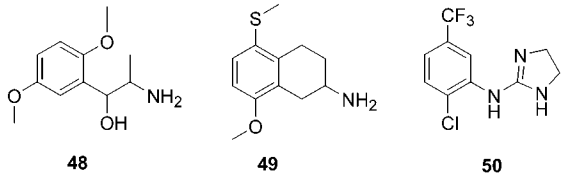
Figure 4.



48 **49** **50**

Figure 5.

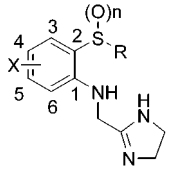


Figure 6.

α_{1b} decreased comparably (20-fold), potency at the α_{1b} receptor decreased remarkably, leaving **3** inactive at α_{1b}. This difference holds for the other subtypes as well. Affinity for **3** at α_{1d}, α_{2a}, and α_{2c} decreased between 9 and 340-fold, while potency decreased from 250- to greater than 10 000-fold. The result is that sulfone **3** is 50- to greater than 10 000-fold selective for α_{1a} vs α_{1b}, α_{1d}, α_{2a}, α_{2b}, and α_{2c}. Sulfide **1**, while 12-fold more potent at α_{1a}, was only 1.5−9-fold selective for α_{1a} vs the other subtypes. While **3** did retain some activity at α_{2c}, it was a weak partial agonist (pEC_{50} = 5.5, 68% maximum potency of UK 14 304). Racemic sulfoxide **2** had half of the affinity of sulfone **3** and was 9-fold less potent at α_{1a}. This suggests that both enantiomers of sulfoxide **2** are less potent agonists at α_{1a} than sulfone **3**. Compound **2** had similar affinity at α_{1b}, α_{1d}, and α_{2a}. In **3**, the hydrogen bond formed by the sulfone induces a favorable receptor-bound conformation leading to α_{1a} selectivity. The hydrogen bond formed by sulfoxide **2** induces a less favorable bound comformation, and selectivity for α_{1a} decreases. This hypothesis is further supported by the observation that an analogue of **3** in which the aniline NH was replaced by an oxygen (**47**; Figure 4) was a very weak agonist at all receptors tested with pEC_{50} = 5.3 at α_{1b} and less than 5.0 at the other subtypes (unpublished data).

Effect of Alkyl Group Size on Sulfones. Enlarging the alkyl group in the sulfide series generally had little effect on affinity or potency (except for branching at α_{1d}), and the trend was similar in the sulfone series. Comparison of sulfones **3**, **6**, **7**, and **10** shows that linear or branched alkyl group extension changed affinity by a factor of 7 or less. Potency at α_{1a} decreased by 8-fold with a one carbon extension to **6**, while *n*-propyl-substituted **7** was nearly identical to **3** in potency. Branching in compound **10** caused a 35-fold loss of potency at α_{1a} relative to methyl sulfone **3**. Potency at the other subtypes, already nearly absent in **3**, remained so with **6**, **7**, and **10**. The weak partial agonism of **3** at α_{2c} was finally eliminated by branching in **10**. Compound **40**, which can be thought of as a constrained analogue of **7**, had greater affinity at α_{1a} than **7**, nearly equal to that of methyl sulfone **3**, but lost all functional activity except for weak agonism at α_{2c}. These observations again suggest that a hydrogen bond involving the sulfone group induces a bound conformation in **3**, **6**, **7**, and (to a lesser extent) **10**, which activates the α_{1a} receptor. The constrained analogue (**40**) is unable to assume this conformation.

Effect of Phenyl Ring Substitution. Compounds **1** and **3** were modified with a fluorine in most positions on the aryl ring and with a variety of electron-donating or -withdrawing substituents in the 5′-position. Our focus on 2′,5′-substitution of the aniline ring was based on the existence of a number of known α_{1a} agonists with similar substitution patterns, such as methoxamine (**48**), 1,2,3,4-tetrahydro-8-methoxy-5-(methylthio)-2-naphthaleneamine (**49**), and 2-(2-chloro-5-trifluoromethylphenylamino)-2-imidazoline (**50**) (Figure 5).[18]

Addition of a 5′-methyl group (**27** and **28**) resulted in less than 5-fold changes in affinity as compared to the unsubstituted compounds. Potency however was enhanced by 50-fold for the sulfide (α_{1a} pEC_{50} = 10.66) and 30-fold for the sulfone. In contrast, addition of a 5′-trifluoromethyl group to the sulfide (**24**) resulted in a 20-fold reduction in potency at α_{1a} and a 250-fold reduction in potency at α_{2a}. The 5′-trifluoromethyl-substituted sulfone **25** lost affinity and potency as compared to **3**, except at α_{2a}. In general, electron-withdrawing groups at the 5′-position of sulfoxide **3** had a small negative impact on binding (up to 20-fold) that was not subtype selective. The effect of the 5′-substituent on potency appears to depend both on size and on electron-withdrawing/donating ability and is not always selective for α_{1a} vs the other subtypes. This further suggests the role of hydrogen bonding in determining the conformation of the bound molecule. Electron-withdrawing substituents para to the sulfonyl group would reduce the ability of the sulfone to participate in hydrogen bond formation. The highest composite functional selectivity for α_{1a} vs all receptor subtypes was seen for the 5′-methoxy-substituted sulfone (**32**). It is notable that **32** was one of the weakest binding compounds at α_{1a} (pK_i = 5.79) but was still a potent full agonist (α_{1a} pEC_{50} = 7.85, 102% maximum potency of phenylephrine; Figure 6).

Conclusion

The receptor affinity and functional data presented point to the importance of hydrogen bonding in determining the conformation of the receptor-bound sulfones. The complex formed by the sulfones with the α_{1a} receptor strongly activates the α_{1a} receptor. The other receptor subtypes interact with this conformation less favorably, and the resulting complex fails to induce the

conformational change required for strong activation. The constrained sulfone (**40**) is unable to assume the favorable conformation and loses potency at all receptors. The sulfides, unconstrained by this hydrogen bonding, are potent but generally nonselective agonists at all α subtypes. From the existing data, it is not possible to discern whether the hydrogen bond-induced orientation of the 2′-subsitituent, the imidazoline ring, or both are important in eliciting selective activation of the receptor subtypes. Studies by Perez and co-workers suggest that α adrenergic agonists containing a basic nitrogen (such as an imidazoline) interact with the receptor to interrupt an interhelical salt bridge.[19] The α_{1d} receptor behaves quite differently than the other subtypes toward the sulfides and tolerates almost no steric volume in the 2-position. Several of the compounds reported herein offer significant in vitro selectivity advantages over **44**. These selective α_{1a} adrenoceptor agonists are useful tools to test the relationship between α_{1a} subtype selectivity and uroselectivity in animal models. Progress toward a clinical candidate for stress urinary incontinence from this series will be reported in due course.

Experimental Section

Determination of Affinity for α Adrenoceptors. Affinity of compounds at α_1 adrenoceptor subtypes was determined by radioligand binding techniques using membranes prepared from Rat-1 fibroblasts expressing human α_{1a}, α_{1b}, or α_{1d} adrenoceptors as previously described.[17] Affinity of compounds at α_2 adrenoceptor subtypes was determined by radioligand binding techniques using membranes prepared from CHO cells expressing human α_{2A}, α_{2B}, or α_{2C} adrenoceptors as previously described.[17]

Determination of Functional Activity at α_1 Adrenoceptors. Functional activity of compounds at α_1 adrenoceptors was assayed by determining their ability to induce an increase in intracellular free calcium concentration in Rat-1 fibroblasts expressing human α_{1A}, α_{1B}, or α_{1D} adrenoceptors. Intracellular free calcium concentrations were determined using the calcium sensitive fluorescent dye Calcium Green (Molecular Probes) and measured in a fluorescence imaging plate reader (FLIPR, Molecular Devices). For these assays, cells were grown in 225 cm^2 flasks in DMEM (GIBCO) supplemented with 10% heat-inactivated fetal bovine serum (Hyclone), and 0.6 mg/mL G418 (Genetecin, GIBCO). Adhered cells were released with 1 mL of trypsin solution (0.25%, Sigma), diluted in media, and added to 96 well culture plates in a volume of 100 μL to give 6000 cells/well, and incubated for 48 h at 37 °C prior to loading and assay.

On the day of assay, cells were washed once with assay buffer (145 mM NaCl, 5 mM KCl, 0.5 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, and 10 mM glucose, pH 7.4). The washed cells were then loaded with Calcium Green by incubating for 2 h at 37 °C in assay buffer containing Calcium Green (4 μM), pluronic acid (0.2%), and probenecid (2.5 mM). After they were loaded, the plates were washed twice with assay buffers and allowed to come to room temperature. Plates were then transferred to the FLIPR, and baseline fluorescence was recorded for 10 s, followed by addition of compounds and continuous monitoring of fluorescence for 50 s. The maximum response observed in the presence of compound was corrected for the baseline measurement and expressed as a percent of the corrected response to a maximal concentration of the nonselective α_1 agonist phenylephrine. Nonlinear regression of these normalized data was performed to estimate the potency (pEC_{50}) of the compounds.

Determination of Functional Activity at α_2 Adrenoceptors. Functional activity of compounds at α_2 adrenoceptor subtypes was assayed by determining their ability to inhibit forskolin-stimulated accumulation of cAMP in CHO cells expressing human α_{2A} or α_{2C} adrenoceptors. For these assays, cells were grown to 90% confluence in DMEM/F-12 supplemented with pyroxidine·HCl, 15 mM HEPES, and 2 mM L-glutamine, supplemented with heat-inactivated fetal bovine serum (10%), G418 (500 μg/mL, GIBCO), L-glutamine (2 mM, GIBCO), penicillin G (100 units/mL), and streptomycin sulfate (100 μg/mL, GIBCO). The day prior to the assay, cells were harvested using 0.05% trypsin, resuspended in culture media, and plated in 96 well plates (100 μL, 40 000 cells/well). On the day of the assay, the cells were washed in an assay buffer comprised of DMEM/F-12 with pyroxidine·HCl, HEPES (15 mM), L-glutamine (2 mM), and isobutylmethylxanthine (300 μM). Compounds or a nonselective α_2 agonist, UK14 304 (RBI) were added to the wells and incubated at 37 °C for 30 min. Following this preincubation, forskolin (5 μM) was added to the wells and the plates were incubated at 37 °C for an additional 90 min. The assay was stopped by the removal of media from the wells. cAMP levels were determined by assay of the samples using standard Flashplate (DuPont/NEN) techniques. Data were corrected for baseline accumulation and expressed as percent inhibition of the response to forskolin alone. Nonlinear regression of these normalized data was performed to estimate the potency (pEC_{50}) of the compounds.

2′-Methylthio-2-(anilinomethyl)imidazoline Hydrochloride (1). 2-Methylmercaptoaniline (Aldrich Chemical Co.) (166.6 g, 1.2 mol) and 2-chloromethylimidazoline hydrochloride (75 g, 0.48 mol) were stirred at reflux in 2-propanol (375 mL) for 21 h. The reaction mixture was allowed to cool, and the solid was filtered. The solid was washed with ethyl acetate and then stirred in 800 mL of 1:1 water:ethyl acetate. Sodium hydroxide (1.0 N) (270 mL) was added to the heterogeneous mixture, and the organic phase was discarded. To the aqueous mixture was added 1 N NaOH (50 mL) followed by ethyl acetate (300 mL). The layers were separated, and the pH of the aqueous phase was adjusted to 10 with 1 N NaOH. The basic aqueous phase was extracted with ethyl acetate (2 × 300 mL). The extracts were reduced to 100 mL under vacuum and filtered. Ethyl acetate (1 L) was added to the filtrate, and hydrogen chloride (4 N in 1,4-dioxane) (120 mL) was added with stirring. A solid formed as the mixture was allowed to cool to room temperature. The resulting product was collected to give **1** (97 g, 73%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 10.0 (br s, 2H), 7.3 (d, J = 8.0 Hz, 1H), 7.2 (dd, J = 8.0 Hz, 1H), 6.7 (dd, J = 8.5 Hz, 1H), 6.45 (d, J = 8.5 Hz, 1H), 5.95 (t, J = 5.5 Hz, 1H), 4.3 (d, J = 5.5 Hz, 2H), 3.8 (s, 4H), 2.35 (s, 3H). MS (ESI): 222 (M + H). Anal: CHNSCl.

2′-Methylsulfinyl-2-(anilinomethyl)imidazoline Hydrochloride (2). Compound **1** (2.3 g, 8.9 mmol) was dissolved in water (20 mL) and cooled to 0 °C. A solution of OXONE (3.4 g, 5.5 mmol) in 30 mL of water was added dropwise (28 mL used) until conversion of starting material was complete as seen by HPLC (Luna C_{18} 3 μm × 50 mm × 2 mm; 1 mL/min 0−95% CH_3CN:H_2O/8 min; 220 nm detection). Ethyl acetate was added (50 mL), and the pH was adjusted to 12 with 5 N KOH. The organic phase was separated, filtered through Celite, and evaporated in vacuo. The resulting resin was dissolved in 2-propanol (10 mL) and treated dropwise with a solution of concentrated HCl (0.6 mL) in 2-propanol (5 mL) until precipitation was complete. The resulting white powder was recrystallized twice from hot 2-propanol to give **2** (1.1 g, 44%) as a white powder. ^{1}H NMR (400 MHz; DMSO-d_6): δ 10.2 (br s, 2H), 7.47 (d, J = 6.9 Hz, 1H), 7.32 (dd, J = 8.0 Hz, 1H), 6.87 (dd, J = 7.5 Hz, 1H), 6.6 (d, J = 8.2 Hz, 1H), 6.5 (t, J = 5.8 Hz, 1H), 4.3 (m, 2H), 3.8 (s, 4H), 2.8 (s, 3H). MS (ESI): 238 (M + H). Anal: CHNSCl.

2′-Methylsulfonyl-2-(anilinomethyl)imidazoline Hydrochloride (3). Compound **1** (5.0 g, 19.4 mmol) was dissolved in water (18 mL) and cooled to −8 °C in an ice bath. The resulting stirred slurry was treated with a solution of OXONE (15.8 g, 25.7 mmol) in water (55 mL) in a slow stream while the temperature was maintained below 10 °C. The mixture was allowed to warm to room temperature and stirred for 30 min. 1-Butanol (50 mL) was added to the reaction mixture

followed by 20 mL of 5 N KOH. The layers were separated, and the aqueous layer was extracted with 1-butanol (50 mL). The 1-butanol extracts were combined and treated with 1 N HCl until the pH was ~2.0. The mixture was heated to reflux to reduce the volume until crystals appeared. The mixture was allowed to cool and stir for 1 h, and the resulting crystals were collected and dried in vacuo at 50 °C to give **3**, (4.0 g, 71%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 10.3 (br s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 7.8 Hz, 1H), 6.9 (ddd, J = 7.5 Hz, 2.7 Hz, 1H), 6. 7 (m, 2H), 4.42 (d, J = 5.7 Hz, 2H), 3.8 (s, 4H), 3.2 (s, 3H). MS (ESI): 254 (M + H). Anal: CHNSCl.

2-Ethylthioaniline (4).[23] 2-Aminothiophenol (Lancaster Chemical Company) (5.0 g, 40 mmol) was stirred in dry ethanol (100 mL) and cooled in an ice bath. Potassium *t*-butoxide (4.5 g, 40 mmol) was added portionwise to the solution over 15 min, and the mixture was stirred for an additional 45 min. Ethyl iodide (3.3 mL, 41 mmol) was added dropwise to the reaction mixture over 15 min. The mixture was allowed to warm to room temperature and then stirred for 45 min. The reaction mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The resulting residue was treated with methylene chloride (100 mL) and filtered, and the filtrate was evaporated to dryness under vacuum to give **4** (5.2 g, 85%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.2 (dd, J = 7.7 Hz, 1.2 Hz, 1H), 7.0 (ddd, J = 7.7 Hz, 1.4 Hz, 1H), 6.7 (dd, J = 7.7 Hz, 1.0 Hz, 1H), 6.5 (ddd, J = 7.4 Hz, 1.1 Hz, 1H), 5.2 (br s, 2H), 2.7 (q, J = 7.3 Hz, 2H), 1.1 (t, J = 7.3 Hz, 3H). The product was used in the subsequent reaction without further analysis or purification.

2′-Ethylthio-2-(anilinomethyl)imidazoline Fumarate (5). Compound **4** (1.0 g, 6.53 mmol), 2-chloromethylimidazoline hydrochloride (0.9 g, 5.8 mmol), 2,6-lutidine (0.7 mL, 5.8 mmol), and phenol (0.6 g) were mixed and heated in a 120 °C oil bath under nitrogen for 30 min. The mixture was stirred with water (10 mL) and washed twice with methylene chloride (5 mL). Sodium hydroxide (1.0 N) (2.9 mL) was added to the reaction mixture, and the solution was washed with methylene chloride (2 × 5 mL). The layers were separated, and the aqueous phase was evaporated in vacuo to give 0.54 g of the crude product. A second reaction was run similarly to give 0.69 g of the crude product. The crude products obtained from these reactions were combined and treated with methylene chloride (60 mL), water (20 mL), and 1.0 N NaOH (5 mL). The organic phase was dried ($MgSO_4$) and filtered. The filtrate was added rapidly to a stirred solution of fumaric acid (0.52 g, 4.5 mmol) in methanol (10 mL), and the mixture was allowed to stand for 1 h. The resulting crystals were collected and dried under vacuum to provide **5** (0.73 g, 29%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 10.0 (br s, 2H), 7.35 (dd, J_{AB} = 7.3 Hz, J_{AC} = 1.2 Hz, 1H), 7.15 (dd, J = 7.7 Hz, 1H), 6.63 (dd, J = 7.8 Hz, 1H), 6.55 (d, J = 7.8 Hz,1H), 6.45 (s, 2H), 6.1 (t, J = 6.1 Hz, 1H), 4.2 (d, J = 6.1 Hz, 2H), 3.7 (s, 4H), 2.75 (q, J = 7.3 Hz, 2H), 1.1 (t, J = 7.4 Hz, 3H). MS (ESI): 236 (M + H). Anal: CHNS.

2′-Ethylsulfonyl-2-(anilinomethyl)imidazoline Fumarate (6). Compound **5** (0.42 g, 1.2 mmol) was dissolved in methylene chloride (20 mL) and methanol (6 mL) and treated with 3-chloroperoxybenzoic acid (0.5 g of 85 wt %). After 1 h, the mixture was concentrated and diluted with methylene chloride (20 mL), water (3 mL), and 10 N sodium hydroxide (1 mL). The mixture was agitated, and the methylene chloride layer was separated. The organic solution was dried ($MgSO_4$) and filtered, and the filtrate was poured into a solution of fumaric acid (0.15 g, 0.13 mmol) in methanol (4 mL). The resulting crystals were collected and dried under vacuum to give **6** (0.28 g, 60%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 10.95 (br s), 7.60 (d, J = 7.5 Hz, 1H), 7.50 (dd, J = 7.5 Hz, 1H), 6.85 (dd, J = 7.5 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 6.73 (t, J = 5.8 Hz, 1H), 6.46 (s, 2H), 4.23 (d, J = 5.8 Hz, 2H), 3.70 (s, 4H), 3.28 (q, J = 7.5 Hz, 2H), 1.08 (t, J = 7.5 Hz, 3H). MS (ESI): 268 (M + H). Anal: CHNS.

2′-Propylsulfonyl-2-(anilinomethyl)imidazoline Hydrochloride (7). Sodium hydrogensulfite (50 g, 480 mmol), sodium bicarbonate (35 g, 416 mmol), and water (200 mL) were combined, and the mixture was heated to 80 °C. 2-Nitrobenzenesulfonyl chloride (47 g, 212 mmol) was added to the aqueous mixture in several portions over 90 min, and the mixture was stirred for 2 h at 80 °C. The reaction mixture was allowed to cool to ambient temperature. The resulting solid was collected, washed with ice water, and dried in vacuo to give the intermediate sulfinic acid (crude yield 28.6 g). The crude sulfinic acid (9.5 g) was treated with sodium bicarbonate (11 g), water (5 mL), and 1-bromopropane (9.8 mL). The mixture was stirred, and an additional 15 mL of water was added over 1 h. The mixture was heated to 90 °C under nitrogen and stirred for 16 h. After it was cooled, the mixture was extracted with toluene (3 × 100 mL) and the combined extracts were concentrated in vacuo to give crude 2-propylsulfonyl nitrobenzene (0.6 g). Silica gel chromatography (7:1 hexane:CH_2Cl_2) gave pure product (0.34 g). Reduction with hydrogen (50 psi) and 5% Pd on carbon (0.1 g) in ethanol (50 mL) for 1 h gave 2-propylsulfonyl aniline (0.29 g, 1.45 mol). This solid was mixed with 2-chloromethylimidazoline-hydrochloride (0.45 g, 2.9 mmol) in 2-propanol (2 mL) and immersed in a 130 °C oil bath under a stream of nitrogen. Additional 2-propanol was added twice over 2 h to remix the resulting resin. The reaction mixture was dissolved in methanol and adsorbed onto basic alumina. The crude product was purified on basic alumina using CH_2Cl_2:MeOH (9:1). Fractions containing the desired product were combined and concentrated to 5 mL. Treatment with 4 N HCl in dioxane (1 mL) gave **7** (17 mg). ^{1}H NMR (300 MHz; CD_3OD): δ 7.75 (d, J = 7.8 Hz, 1H), 7.55 (dd, J = 6.6 Hz, 1H), 6.95 (dd, J = 7.3 Hz,-1H), 6.8 (d, J = 7.1 Hz, 1H), 4.45 (br s, 2H), 4.4 (s, 4H), 3.2 (t, J = 7.5 Hz, 2H), 1.7 (tq, J = 7.3 Hz, 2H), 1.0 (t, J = 7.3 Hz, 3H). MS (ESI): 282 (M + H). Anal: CHNSCl.

2-Isopropylthioaniline (8).[24] 2-Aminothiophenol (Lancaster Chemical Company) (2.34 g, 18.7 mmol) was stirred in dry ethanol (50 mL) and cooled in an ice bath. Potassium *t*-butoxide (2.1 g, 18.7 mmol) was added portionwise over 5 min, and the mixture was stirred for an additional 5 min. Isopropyl iodide (1.9 mL, 19 mmol) was added dropwise to the reaction mixture. After 1 h, the mixture was diluted with 50 mL of CH_2Cl_2 and filtered to remove KI. The filtrate was concentrated in vacuo to give **8** (2.02 g, 59%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.2 (d, J = 7.7 Hz, 1H), 7.05 (dd, J = 7.7 Hz, 1H), 6.7 (d, J = 7.7 Hz, 1H),), 6.5 (dd, J = 7.7 Hz, 1H), 5.3 (br s, 2H), 2.7 (dq, J = 6.8 Hz, 1H), 1.15 (t, J = 6.8 Hz, 6H). The product was used in the subsequent reaction without further analysis or purification.

2′-Isopropylthio-2-(anilinomethyl)imidazoline Hydrochloride (9). Compound **8** (0.4 g, 2.4 mmol), 2-chloromethylimidazoline hydrochloride (0.33 g, 2.15 mmol), 2,6-lutidine (0.28 mL, 2.4 mmol), and 2-propanol (1 mL) were mixed and immersed in a 120 °C oil bath under nitrogen for 5 h. The resulting resin was allowed to cool and then stirred with methylene chloride (10 mL). The suspension was filtered to give an off-white solid, which was dissolved in methanol (2 mL) and treated with 4.0 N HCl in dioxane (125 μL) and concentrated under vacuum to give **7**, (212 mg, 31%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 10.2 (br s, 2H), 7.35 (dd, J = 7.5 Hz, 1.2 Hz, 1H), 7.2 (dd, J = 7.0 Hz, 1H), 6.65 (dd, J = 7.3 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.2 (br s, 2H), 4.4 (br s, 2H), 3.6 (s, 4H), 3.2 (dq, J = 6.8 Hz, 1H), 1.2 (d, J = 6.6 Hz, 6H). MS (ESI): 250 (M + H). Anal: CHNSCl.

2′-Isopropylsulfonyl-2-(anilinomethyl)imidazoline Fumarate (10). Compound **9** (0.2 g, 0.7 mmol) was stirred in methylene chloride (10 mL) and treated with *meta*-chloroperoxybenzoic acid (0.21 g, of 70 wt %) and methanol (1 mL). After 1 h, the solvent was evaporated and the crude product was chromatographed on basic alumina (1−20% methanol/methylene chloride). The desired fractions were combined and concentrated to give 0.13 g of the free base. The amine was dissolved in methylene chloride (6 mL) and treated with fumaric acid (0.055 g) in methanol (1.5 mL). The resulting crystals were collected and dried under vacuum to give **10** (0.14 g, 54%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.5 (m, 2H), 6.75 (m, 3H), 6.5 (s, 2H), 5.8 (br s, 2H), 4.3 (br s, 2H), 3.6 (s, 4H),

3.4 (dq, J_{AB} = 6.8 Hz, 1H), 1.2 (d, J = 6.8 Hz, 6H). MS (ESI): 282 (M + H). Anal: CHNS.

3-Fluoro-2-(methylthio)aniline (11). *N*-(2-Methylthio-3-fluorophenyl)trifluoroacetamide[11] (2.36 g crude, 9.33 mmol) was taken up in methanol (40 mL), and solid potassium hydroxide (1.57 g, 28.0 mmol) was added portionwise at room temperature. The mixture was heated to reflux. After 1.5 h, the mixture was cooled to room temperature, and the solvent volume was reduced to 5 mL by evaporation under reduced pressure. The residue was taken up in deionized water (30 mL) and extracted with diethyl ether (3 × 40 mL). The extracts were combined, washed with saturated sodium chloride solution, dried over sodium sulfate, and filtered, and the filtrate was concentrated by evaporation under reduced pressure. The crude product was purified by silica gel chromatography using 10% ethyl acetate in hexanes to give 1.2 g of **11**. ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.04 (dd, J = 14.9 Hz, 8.1 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H) 6.36 (dd, J = 8.2 Hz, 8.2 Hz, 1H), 5.71 (s, 2H), 2.22 (s, 3H). The product was used in the subsequent reaction without further analysis or purification.

2′-Methylthio-3′-fluoro-2-(anilinomethyl)imidazoline Fumarate (12). Compound **11** (1.03 g, 6.56 mmol), 2-chloromethylimidazoline hydrochloride (0.508 g, 3.28 mmol), and phenol (0.75 g) were heated at 145 °C for 1.5 h under a nitrogen atmosphere. After it was cooled, the residue was taken up in deionized water (100 mL) and diethyl ether (75 mL). The aqueous layer was separated, and the pH was adjusted to approximately 8 with 1 N sodium hydroxide. The aqueous mixture was washed with diethyl ether, and the pH was adjusted to 12 with 10 N sodium hydroxide. The product was extracted with diethyl ether (2 × 50 mL) and ethyl acetate (2 × 50 mL). The organic extracts were combined, dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The free base (0.40 g) was dissolved in ethyl acetate and treated with fumaric acid (0.194 g) in methanol to produce a precipitate. Filtration gave **12** (0.49 g, 42%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.22 (dd, J = 15.3 Hz, 7.8 Hz, 1H), 6.55 (dd, J = 8.6 Hz, 1H), 6.37−6.50 (m, 4H), 4.21 (d, J = 5.8 Hz, 2H), 3.72 (s, 4H), 2.26 (s, 3H). MS (ESI): 240 (M + H). Anal: CHNS.

2′-Methylsulfonyl-3′-fluoro-2-(anilinomethyl)imidazoline Fumarate (13). Compound **12** (0.465 g, 1.31 mmol) was dissolved in methanol (20 mL) and dichloromethane (10 mL) under a nitrogen atmosphere, and *m*-chloroperoxybenzoic acid (0.75 g of 57−86% pure material) was added portionwise. The mixture was stirred at room temperature for 16 h. The volatiles were removed by evaporation under reduced pressure. The residue was slurried in deionized water (40 mL) and washed with ethyl acetate (2 × 30 mL). The aqueous layer was adjusted to pH 12 using 3 N sodium hydroxide. The product was extracted with ethyl acetate (2 × 60 mL), dried over magnesium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to give 0.118 g of the free base. The sulfone was taken up in ethyl acetate and treated with fumaric acid (0.050 g) in methanol to produce a precipitate. Filtration gave **13** (0.121 g, 24%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.67 (t, J = 5.6 Hz, 1H); 7.47 (dd, J = 15.1 Hz, 8.4 Hz, 1H); 6.63 (dd, J = 11.3 Hz, 8.1 Hz, 1H), 6.46−6.65 (m, 3H); 4.26 (d, J = 5.6 Hz, 2H); 3.69 (s, 4H); 3.36 (s, 3H). MS (ESI): 272 (M + H). Anal: CHNS.

2-Mercapto-4-fluoroaniline (14). 2-Amino-6-fluorobenzothiazole (5.0 g, 29.7 mmol) (Aldrich Chemical Co.) was stirred in 120 mL of 10 N NaOH in a 500 mL three-necked round-bottomed flask, which was fitted with a reflux condenser. The reaction mixture was heated at 120 °C under a slow stream of nitrogen. After 2 h, the nitrogen stream was no longer basic to wet litmus paper. The reaction mixture was allowed to cool, treated with 1 g of decolorizing carbon, and filtered. The filtrate was treated with acetic acid (70 mL) to adjust the pH to 5.0. The resulting precipitate was collected, washed with water, and dried under vacuum to give **14** (5.5 g, 130%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.9 (d, J = 9 Hz, 1H), 6.6 (m, 3H), 6.1 (br s, 2H), 3.35 (br s, 1H), 1.9 (s, 2H) (residual acetic acid). The product was used in the subsequent reaction without further purification or analysis.

2-Methylthio-4-fluoroaniline (15). Compound **14** (5.5 g, 30 mmol) was stirred in ethanol (250 mL) and treated with potassium *t*-butoxide (3.9 g, 35 mol) portionwise over 10 min. Methyl iodide (1.9 mL, 30 mmol) was added dropwise, and the reaction was stirred for 2 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was triturated with CH_2Cl_2 (200 mL), and the solid was filtered. The crude product was chromatographed on silica gel (CH_2Cl_2/MeOH, 9:1) to give **15** (2.25 g, 43%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.95 (dd, J_{AB} = 9.5 Hz, J_{AC} = 2.9 Hz 1H), 6.77 (ddd, J = 8.8 Hz, 3.0 Hz, 1H), 6.66 (d, J = 5.3 Hz, 1H), 6.63 (d, J = 5.3 Hz 1H), 4.95 (br s, 2H), 2.35 (s, 3H). The product was used in the subsequent reaction without further purification or analysis.

2′-Methylthio-4′-fluoro-2-(anilinomethyl)imidazoline Fumarate (16). Compound **15** (2.25 g, 13.31 mmol) was mixed with 2-chloromethylimidazoline hydrochloride (1.86 g, 12 mmol), 2,6-lutidine (1.63 mL, 14 mmol), and phenol (1.5 g). The reaction mixture was immersed in a 120 °C oil bath under nitrogen for 20 min. The mixture was diluted with methylene chloride (20 mL) and water (20 mL). The layers were separated, and the aqueous phase was washed with methylene chloride (2 × 10 mL). Sodium hydroxide (10 N) (2 mL) was added to the aqueous phase, and the mixture was extracted with methylene chloride (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo to give 2.29 g of the crude product. The crude product was dissolved in methylene chloride (100 mL) and added to a solution of fumaric acid (1.04 g) in methanol (25 mL) and stored at 4 °C overnight. The resulting product was filtered and dried under vacuum to give **16** (2.12 g, 65%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.1 (dd, J = 9.1 Hz, 2.9 Hz 1H), 6.91 (ddd, J = 8.8 Hz, 3.0 Hz, 1H), 6.5 (d, J = 5.3 Hz, 1H), 6.46 (d, J = 5.3 Hz 1H), 6.42 (s, 2H), 5.7 (t, J = 5.9 Hz, 1H), 4.15 (d, J = 5.8 Hz, 2H), 2.40 (s, 3H). MS (ESI): 240 (M + H). Anal: CHNS.

2′-Methylsulfonyl-4′-fluoro-2-(anilinomethyl)imidazoline Fumarate (17). Compound **16** (1.9 g, 5.35 mmol) was stirred in methanol (30 mL) and methylene chloride (100 mL) and treated with 3-chloroperoxybenzoic acid (3.25 g of 85 wt %). After 1 h, the mixture was concentrated in vacuo. To the crude product was added methylene chloride (70 mL), water (20 mL), and 10 N sodium hydroxide (2 mL). The organic phase was separated, dried ($MgSO_4$), and filtered, and the filtrate was concentrated under vacuum to give 1.16 g of the free. The free base was dissolved in methylene chloride (60 mL) and added to a solution of fumaric acid (0.495 g) in methanol (12 mL). The resulting crystals were collected and dried in vacuo to give **17** (0.95 g, 46%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.4 (d, J = 8.1 Hz, 2H), 6.8 (m, 1H), 6.58 (t, J = 5.6 Hz, 1H), 6.45 (s, 2H), 4.3 (d, J = 5.6 Hz, 2H), 3.7 (s, 4H), 3.3 (s, 3H). MS (ESI): 272 (M + H). Anal: CHNS.

5-Fluoro-2-(methylthio)aniline (18). 5-Fluoro-2-methylbenzothiazole (10.03 g, 60 mmol) was slurried in a mixture of ethylene glycol (45 mL) and 10 N sodium hydroxide (45 mL) and heated to reflux under a nitrogen atmosphere. After 2 h, the solution was cooled to 0 °C and treated with concentrated hydrochloric acid to pH 7. The product was extracted with ethyl acetate (3 × 75 mL), dried over magnesium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to yield 3.28 g of crude 2-amino-4-fluorothiophenol. The crude 2-amino-4-fluorothiophenol was dissolved in absolute ethanol (50 mL) and cooled to 0 °C under a nitrogen atmosphere. Potassium *tert*-butoxide (2.83 g, 25.23 mmol) was added portionwise to the thiophenol solution, and the reaction mixture was stirred for 15 min. Iodomethane (3.34 g, 23.5 mmol) in tetrahydrofuran (15 mL) was added dropwise to the cold solution, and a thick precipitate formed. After the addition was complete, the slurry was stirred for 30 min. The volatiles were removed by evaporation under reduced pressure. The residue was taken up in deionized water (30 mL) and 10 N sodium hydroxide. (5 mL). The mixture was extracted with diethyl ether (3 × 50 mL). The extracts were combined, washed

with saturated sodium chloride solution, dried over magnesium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The product was purified by silica gel chromatography using 5% ethyl acetate in hexanes to give 1.37 g of **18**. ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.21 (dd, J = 8.6 Hz, 6.9 Hz, 1H); 6.46 (dd, J = 11.5 Hz, 2.8 Hz, 1H); 7.21 (ddd, J = 8.6 Hz, 2.8 Hz, 1H); 5.55 (s, 2H); 2.22 (s, 3H). The product was used in the subsequent reaction without further analysis or purification.

2′-Methylthio-5′-fluoro-2-(anilinomethyl)imidazoline Fumarate (19). Compound **18** (1.01 g, 6.44 mmol), 2-chloromethylimidazoline hydrochloride (0.499 g, 3.22 mmol), and phenol (0.80 g) were heated at 145 °C for 1.5 h under a nitrogen atmosphere. After it was cooled, the residue was taken up in deionized water (100 mL) and diethyl ether (75 mL). The aqueous layer was separated and treated with 1 N sodium hydroxide to adjust the pH to 8. The aqueous layer was washed with ethyl acetate, and the layers were separated. The pH of the aqueous phase was adjusted to 12 with 10 N sodium hydroxide. The product was extracted with ethyl acetate (3 × 50 mL). The extracts were combined, dried over magnesium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to give 0.53 g of the desired free base. The free base was dissolved in ethyl acetate and treated with a solution of fumaric acid (0.256 g) in methanol to produce a precipitate. Filtration gave **19** (0.66 g, 22%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.37 (dd, J = 6.8 Hz, 8.2 Hz, 1H), 6.43−6.50 (m, 3H), 6.41 (dd, J = 12.0 Hz, 2.6 Hz, 1H), 6.29 (t, J = 6.0 Hz, 1H), 4.19 (d, J = 6.0 Hz, 2H), 3.72 (s, 4H), 2.29 (s, 3H). MS (ESI): 240 (M + H). Anal: CHNS.

2′-(Methylsulfonyl-5′-fluoro-2-(anilinomethyl)imidazoline Fumarate (20). Compound **19** (0.465 g, 1.31 mmol) was dissolved in methanol (20 mL) and dichloromethane (10 mL) under a nitrogen atmosphere, and *m*-chloroperoxybenzoic acid (0.532 g of 57−86% pure material) was added portionwise. The mixture was stirred at room temperature for 1.5 h. The volatiles were removed by evaporation under reduced pressure. The residue was slurried in deionized water (40 mL) and washed with ethyl acetate (2 × 30 mL). The pH of the aqueous layer was adjusted to 12 with 3 N sodium hydroxide. The product was extracted with ethyl acetate (2 × 60 mL), dried over magnesium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to give 0.340 g of the desired sulfone. The free base was taken up in ethyl acetate and treated with fumaric acid (0.145 g) in methanol to produce a precipitate. Filtration gave **20** (0.375 g, 74%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.70 (dd, J = 8.8 Hz, 6.6 Hz, 1H); 6.91 (br s, 1H); 6.63−6.68 (m, 2H); 6.48 (s, 2H); 4.23 (d, J = 5.3 Hz, 2H); 3.67 (s, 4H); 3.19 (s, 3H). MS. (ESI): 272 (M + H). Anal: CHNS.

6-Fluoro-2-methylthioaniline (21). 2,6-Difluoronitrobenzene (1.0 g, 6.3 mmol) was stirred in ethanol (10 mL) and treated with sodium methylmercaptan (0.44 g, 6.3 mmol) in several portions over 5 min. After it was stirred for 2 h, the mixture was concentrated in vacuo and the crude product was chromatographed on silica gel (hexane:ethyl acetate (7:3) to give 2-methylmercapto-6-fluoro-nitrobenzene (1.0 g). The nitrobenzene intermediate was reduced in ethanol (30 mL) using 5% palladium on carbon (0.3 g) and hydrogen at 50 psi for 2 h. The catalyst was removed by filtration through Celite, and the solvent was evaporated to give **21** (0.69 g, 70%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.06 (d, J = 7.8 Hz, 1H), 7.0 (dd, J = 11.2 Hz, 8.2 Hz, 1H), 6.6 (m, 1H), (5.1, br s, 2H), 2.35 (s, 3H). The product was used in the subsequent reaction without further analysis or purification.

2′-Methylthio-6′-fluoro-(anilinomethyl)imidazoline Fumarate (22). Compound **21** (0.69 g, 4.37 mmol), 2-chloromethylimidazoline hydrochloride (0.6 g, 3.87 mL), 2,6-lutidine (0.6 mL, 5.1 mmol), and phenol (0.5 g) were combined under a nitrogen atmosphere, and the mixture was immersed in a 120 °C oil bath for 20 min. The mixture was diluted with water (5 mL) and washed with methylene chloride (3 × 5 mL). Sodium hydroxide (10 N) (2 mL) was added to the aqueous phase, and the mixture was extracted with methylene chloride (3 × 5 mL). The extracts were combined, dried ($MgSO_4$), and filtered, and the filtrate was concentrated to 40 mL. The free base was treated with a solution of fumaric acid (0.4 g, 3.5 mmol) in methanol (10 mL). The resulting precipitate was collected to give **22** (0.15 g, 0.42 mmol). ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.2 (d, J = 8.1 Hz, 1H), 7.05 (dd, J = 7.8 Hz, 5.1 Hz, 1H), 6.7 (m, 1H), 5.5 (br s, 1H), 4.2 (s, 2H), 3.8 (s, 4H), 2.4 (s, 3H). The product was used in the subsequent reaction without further analysis or purification.

2′-Methylsulfonyl-6′-fluoro-2-(anilinomethyl)imidazoline Fumarate (23). Compound **22** (0.15 g, 0.42 mmol) was dissolved in methanol (5 mL) and treated with *meta*-chloroperoxybenzoic acid (100 mg, 70 wt %). After 30 min, the mixture was concentrated under vacuum and diluted with methylene chloride (6 mL) and 1 N sodium hydroxide (2 mL). The organic phase was separated, dried (Na_2SO_4), and filtered, and the filtrate was added to a solution of fumaric acid (45 mg, 0.38 mmol) in methanol (1 mL). The resulting solid was collected and dried under vacuum to give **23** (0.145 g, 88%). ^{1}H NMR (400 MHz; CD_3OD): δ 7.65 (d, J = 8.0 Hz, 1H), 7.4 (dd, J = 8.1 Hz, 5.6 Hz, 1H), 7.0 (ddd, J = 8.1 Hz, 4.5 Hz, 1H), 6.65 (s, 2H), 4.5 (d, J = 4.8 Hz, 2H), 4.0 (s, 4H), 3.2 (s, 3H). MS (ESI): 272 (M + H). Anal: CHNS.

2′-Methylthio-5′-trifluoromethyl-2-(anilinomethyl)imidazoline Fumarate (24). 3-Amino-4-(methylthio)benzotrifluoride (1.0 g, 4.83 mmol., Lancaster Chemical Company), 2-chloromethylimidazoline hydrochloride (0.372 g, 2.4 mmol), and phenol (0.3 g) were heated under a nitrogen atmosphere at 140 °C for 2 h. After it was cooled, the residue was taken up in deionized water (75 mL) and diethyl ether (75 mL). The aqueous layer was separated and treated with 1 N sodium hydroxide to pH 7. The solution was washed with diethyl ether (75 mL). The aqueous layer was separated and treated with 1 N sodium hydroxide to pH 12. The product was extracted with ethyl acetate (3 × 25 mL). The extracts were combined, dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up in ethyl acetate and treated with fumaric acid (1 equiv) in methanol to produce a precipitate. Filtration gave **24** (0.69 g, 71%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.44 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H); 6.77 (s, 1H); 6.48 (s, 2H), 6.06 (br s, 1H), 4.20 (d, J = 5.4 Hz, 2H), 3.69 (s, 4H), 2.47 (s, 3H). MS (ESI): 290 (M + H). Anal: CHNS.

2′-Methylsulfonyl-5′-trifluoromethyl-2-(anilinomethyl)-imidazoline Fumarate (25). Compound **24** (0.614 g, 1.5 mmol) was dissolved in methanol (10 mL) under a nitrogen atmosphere. *m*-Chloroperoxybenzoic acid (0.610 g of 57−86% pure material) was added portionwise. The mixture was stirred at room temperature for 1.5 h. The mixture was poured into deionized water (35 mL) and diethyl ether (45 mL). The aqueous layer was separated, and the pH of the aqueous phase was adjusted to approximately 12 with NaOH (10 N). The product was extracted with diethyl ether (2 × 50 mL) and ethyl acetate (2 × 30 mL). The extracts were combined, dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to give 0.37 g of the desired sulfone. The free base was taken up in ethyl acetate and treated with a solution of fumaric acid in methanol to produce a precipitate. Filtration gave **25** (0.305 g, 46%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.86 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H); 7.09 (s, 1H); 7.01 (t, J = 5.5 Hz, 1H), 6.49 (s, 2H); 4.34 (d, J = 5.5 Hz, 2H), 3.66 (s, 4H); 3.26 (s, 3H). MS (ESI): 322 (M + H). Anal: CHNS.

5-Methyl-2-(methylthio)aniline (26). 2,5-Dimethylbenzothiazole (10.44 g, 63.95 mmol) was slurried in ethylene glycol (75 mL) and 10 N sodium hydroxide (75 mL). The reaction mixture was heated to reflux under a nitrogen atmosphere. After 4 h, the solution was cooled to 0 °C and treated with concentrated hydrochloric acid to pH 7. The product was extracted with diethyl ether (3 × 75 mL), dried over magnesium sulfate, and filtered, and the filtrate was concentrated in vacuo to give 2.61 g of crude 2-amino-4-methylthiophenol. The crude product (2.58 g) was dissolved in absolute ethanol (50 mL), and the solution was cooled to 0 °C under a nitrogen

atmosphere. Potassium *tert*-butoxide (2.29 g, 20.42 mmol) was added portionwise, and the solution was stirred for 15 min. Iodomethane (2.7 g, 19.02 mmol) in tetrahydrofuran (15 mL) was added dropwise to the cold solution. After the addition was complete, the slurry was stirred for 45 min. The volatiles were removed by evaporation under reduced pressure. The residue was taken up in deionized water (30 mL) and 10 N sodium hydroxide (5 mL). The mixture was extracted with diethyl ether (3 × 50 mL). The extracts were combined, washed with saturated sodium chloride solution, dried over magnesium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to give 2.64 g of **26**. ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.11 (d, J = 7.7 Hz, 1H), 6.54 (s, 1H), 6.38 (d, J = 7.7 Hz, 1H); 5.14 (s, 2H), 2.26 (s, 3H), 2.16 (s, 3H). The product was used in the subsequent reaction without further analysis and purification.

2′-Methylthio-5′-methyl-2-(anilinomethyl)imidazoline Fumarate (27). Compound **26** (1.03 g, 6.74 mmol), 2-chloromethylimidazoline hydrochloride (0.522 g, 3.37 mmol), and phenol (1.0 g) were combined, and the mixture was heated at 145 °C for 1 h under a nitrogen atmosphere. After it was cooled, the residue was taken up in deionized water (100 mL) and ethyl acetate (75 mL). The aqueous layer was separated and treated with 1 N sodium hydroxide to pH 12. The product was extracted with ethyl acetate (3 × 40 mL). The extracts were combined, dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up in ethyl acetate and treated with a solution of fumaric acid (1 equiv) in methanol to produce a precipitate. Filtration gave **27** (0.67 g, 57%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.24 (d, J = 7.5 Hz, 1H), 6.41−6.58 (m, 4H), 5.98 (s, 1H), 4.21 (br s, 2H), 3.76 (s, 4H), 2.30 (s, 3H), 2.24 (s, 3H). MS (ESI): 236 (M + H).

2′-Methylsulfonyl-5′-methyl-2-(anilinomethyl)imidazoline Fumarate (28). Compound **27** (0.560 g, 1.6 mmol) was dissolved in methanol (20 mL) under a nitrogen atmosphere. *m*-Chloroperoxybenzoic acid (0.736 g of 70−75% pure material) was added portionwise. The mixture was stirred at room temperature for 2 h. The mixture was poured into deionized water (40 mL) and ethyl acetate (50 mL). The layers were separated, and the pH of the aqueous layer was adjusted to 12 with 10 N NaOH. The product was extracted with diethyl ether (2 × 75 mL), dried over magnesium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to give 0.420 g of the free base. The free base was dissolved in ethyl acetate and treated with a solution of fumaric acid in methanol to produce a precipitate. Filtration gave **28** (0.458 g, 75%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.53 (d, J = 8.0 Hz, 1H), 6.62−6.68 (m, 3H), 6.47 (s, 2H), 4.26 (br s, 2H), 3.71 (s, 4H), 3.17 (s, 3H), 2.30 (s, 3H). MS (ESI): 268 (100%) (M + H). Anal: CHNS.

2-Amino-4-methoxy-benzenethiol (29).[22] To a 300 mL round-bottom flask were added 5-methoxy-2-methylbenzothiazole (9.7 g, 54.1 mmol), sodium hydroxide (60 mL), and ethylene glycol (60 mL). The reaction mixture was heated at reflux with stirring under a nitrogen atmosphere for 3 h. The oil bath was removed, and the reaction mixture was allowed to cool at room temperature. The reaction mixture was washed twice with diethyl ether and then cooled in an ice−water bath. The pH of the cold aqueous phase was adjusted to approximately 3 (litmus paper) with concentrated hydrochloric acid. The acidic aqueous phase was extracted twice with diethyl ether. The combined organic extracts were washed with water followed by saturated sodium chloride, dried over magnesium sulfate, and filtered, and the filtrate was concentrated under vacuum to give 7.0 g (83%) of **29**. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.33 (d, J = 8.5 Hz, 1H) 6.34 (m, 2H), 4.42 (br s, 2H), 3.79 (s, 3H).

5-Methoxy-2-(methylthio)aniline (30). A solution of **29** (7.0 g, 45.1 mmol) in ethanol (100 mL) was cooled in an ice−water bath and potassium *tert*-butoxide (5.6 g, 49.9 mmol, 1.1 equiv) was added portionwise via a powder addition funnel. The reaction mixture was stirred under a nitrogen atmosphere for 15 min. To the cold reaction mixture was added iodomethane (6.5 g, 45.8 mmol, 1.02 equiv). The ice−water bath was removed, and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give 9.6 g of the crude product. Approximately one-half of the crude product was purified by flash chromatography over silica gel with hexanes:ethyl acetate (95:5) followed by hexanes:ethyl acetate (3:1) as eluant to give 2.6 g of **30** as a yellow liquid. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.16 (d, J = 8.5 Hz, 1H), 6.31 (d, J = 2.5 Hz, 1H), 6.14 (dd, J = 8.4 Hz, 2.6 Hz, 1H), 5.32 (br s, 2H), 3.67 (s, 3H), 2.20 (s, 3H).

2′-(Methylthio)-5′-methoxy-2-(anilinomethyl)imidazoline Fumarate (31). To a 25 mL round-bottom flask were added 2-chloromethylimidazoline hydrochloride (93%) (0.6 g, 3.6 mmol), **30** (1.35 g, 7.19 mmol, 2.0 equiv), and phenol (0.88 g). The reaction mixture was heated at 135−145 °C with stirring under a nitrogen atmosphere for 45 min. The oil bath was removed, and the reaction mixture was allowed to cool at room temperature. The reaction mixture was partitioned between dichloromethane and water. The layers were separated, and the pH of the aqueous phase was adjusted to approximately 8 (litmus paper) with 1 N sodium hydroxide. The basic aqueous phase was washed with dichloromethane. The layers were separated, and the pH of the aqueous phase was adjusted to 12 with 1 N sodium hydroxide. The aqueous phase was extracted with diethyl ether (2×). The combined diethyl ether extracts were dried over magnesium sulfate and filtered, and the filtrate was concentrated in vacuo to give 0.544 g of the crude product as a gold-yellow oil. The free base was purified by flash chromatography over silica gel with dichloromethane:methanol:ammonium hydroxide (94:5:1) as eluant to give 0.307 g of the free base as an oil, which partially solidified to a white solid. The free base (0.307 g, 1.22 mmol) and fumaric acid (0.142 g, 1.22 mmol, 1.0 equiv) were combined and dissolved in hot methanol. The hot solution was filtered, and the filtrate was allowed to cool at room temperature. The title compound (**31**) (0.233 g; 18%) was filtered as a pale yellow solid. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.30 (d, J = 8.4 Hz, 1H), 6.47 (s, 2H), 6.27 (dd, J = 8.4, 2.4 Hz, 1H), 6.19 (br t, J = 5.9 Hz, 1H), 6.12 (d, J = 2.3 Hz, 1H), 4.25 (d, J = 6.0 Hz, 2H), 3.76 (s, 4H), 3.72 (s, 3H), 2.24 (s, 3H). MS (ESI): 252 (M^+).

2′-Methylsulfonyl-5′-methoxy-2-(anilinomethyl)imidazoline Fumarate (32). 3-Chloroperoxybenzoic acid (57−86%, assumed 86%) (0.22 g, 1.1 mmol, 2.0 equiv) was added portionwise to a mixture of **31** (0.202 g, 0.55 mmol) and methanol (20 mL) at room temperature with stirring under a nitrogen atmosphere. Evaluation of the reaction by thin-layer chromatography (dichloromethane:methanol:ammonium hydroxide (88:10:2) indicated the reaction was incomplete. Additional 3-chloroperoxybenzoic acid was added to the reaction mixture portionwise until thin-layer chromatography indicated the reaction was complete. The reaction mixture was partially concentrated under vacuum and diluted with water. The aqueous mixture was washed twice with ethyl acetate. The pH of the aqueous phase was adjusted to approximately 12 with 1 N sodium hydroxide. The basic aqueous phase was extracted with ethyl acetate. The organic extract was dried over magnesium sulfate and filtered, and the filtrate was concentrated in vacuo to give 0.31 g of the free base as an off-white solid. The free base (0.13 g, 0.46 mmol) and fumaric acid (0.053 g, 0.46 mmol, 1.0 equiv) were dissolved in methanol, and diethyl ether was added. The precipitated solid was filtered, washed with diethyl ether, and dried under vacuum at 70 °C to give 0.073 g (33%) of the title compound (**32**) as an off-white solid. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.59 (d, J = 8.9 Hz, 1H), 6.74 (br t, J = 5.3 Hz, 1H), 6.49 (s, 2H), 6.45 (br dd, J = 8.9, 2.1 Hz, 1H), 6.23 (br d, J = 2.0 Hz, 1H), 4.25 (d, J = 5.2 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 4H), 3.15 (s, 3H). MS (ESI): 284 (M^+).

2-Amino-4-chloro-benzenethiol (33). This compound was prepared according to the procedure described for 2-amino-4-methoxy-benzenethiol by employing 5-chloro-2-methylbenzothiazole (5.0 g, 27.2 mmol), 30% sodium hydroxide (30 mL),

and ethylene glycol (30 mL). The reaction mixture was heated at reflux for 2.5 h and worked up to give 4.0 g (92%) of **33** as an off-white solid. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.14 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1 H), 6.48 (dd, J = 8.2, 2.2 Hz, 1H), 5.17 (br s, 2H). The product was used in the subsequent reaction without further analysis or purification.

5-Chloro-2-(methylthio)aniline (34). To a 250 mL round-bottom flask were added **33** (3.75 g, 23.5 mmol) and ethanol (50 mL). The mixture was cooled in an ice−water bath, and potassium *tert*-butoxide (2.9 g, 25.8 mmol, 1.1 equiv) was added portionwise via a powder addition funnel. The cold reaction mixture was stirred for 75 min. Iodomethane (3.5 g, 24.7 mmol, 1.05 equiv) was slowly added to the cold reaction mixture and stirred for 30 min. The ice−water bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give 2.5 g (61%) of **34** as a yellow liquid. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.19 (d, J = 8.2 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 6.55 (dd, J = 8.2, 1.9 Hz, 1H), 5.49 (br s, 2H), 2.31 (s, 3H). The product was used in the subsequent reaction without further analysis or purificaion.

2′-(Methylthio)-5′-chloro-2-(anilinomethyl)imidazoline Fumarate (35). To a 50 mL round-bottom flask were added chloromethylimidazoline hydrochloride (93%) (0.80 g, 4.8 mmol), **34** (2.0 g, 11.7 mmol, 2.4 equiv), and phenol (0.60 g). The reaction mixture was heated at 140 °C with stirring under a nitrogen atmosphere for 50 min. The reaction mixture was allowed to cool and then partitioned between water and ethyl acetate. The layers were separated, and the pH of the aqueous phase was adjusted to 9 with 1 N sodium hydroxide. The basic aqueous phase was washed with ethyl acetate. The layers were separated, and the pH of the aqueous phase was adjusted to approximately 12 with 1 N sodium hydroxide. The aqueous phase was extracted with ethyl acetate. The organic solution was dried over magnesium sulfate and filtered, and the filtrate was concentrated in vacuo to give 0.78 g of the free base as a white solid. The free base (0.78 g, 3.05 mmol), fumaric acid (0.354 g, 3.05 mmol, 1.0 equiv), and methanol were combined, and the mixture was heated until the solids fully dissolved. The hot solution was filtered, and the filtrate was allowed to cool at room temperature and then placed in the refrigerator. A white solid was filtered and rinsed with diethyl ether to give 0.392 g (22%) of the title compound (**35**). ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.30 (d, J = 8.2 Hz, 1H) 6.68 (dd, J = 8.1, 2.0 Hz, 1H), 6.57 (d, J = 1.9 Hz, 1H), 6.45 (s, 2 H), 6.11 (br t, J = 5.5 Hz, 1H), 4.14 (d, J = 5.5 Hz, 2H), 3.69 (s, 4H), 2.33 (s, 3H). MS (ESI): 256 (M^+). Anal: CHN.

2′-Methylsulfonyl-5′-chloro-2-(anilinomethyl)imidazoline Fumarate (36). Methanol (10 mL) and **35** (0.373 g, 1.0 mmol) were combined in a round-bottom flask. To the stirred suspension was added 3-chloroperoxybenzoic acid (57−86%, assumed 86%) (0.40 g, 2.0 mmol, 2.0 equiv) portionwise at room temperature. Thin-layer chromatography on silica gel (dichloromethane:methanol:ammonium hydroxide, 88:10:2) indicated that the reaction was incomplete. 3-Chloroperoxybenzoic acid was added portionwise until the reaction was complete. The reaction mixture was partitioned between water and ethyl acetate. The layers were separated, and the aqueous phase was washed with ethyl acetate. The pH of the aqueous phase was adjusted to approximately 12 with 1 N sodium hydroxide. The basic aqueous phase was extracted with ethyl acetate. The organic solution was dried over magnesium sulfate and filtered, and the filtrate was concentrated under vacuum to give 0.215 g of the free base as a white solid. The free base (0.215 g, 0.75 mmol) and fumaric acid (0.086 g, 0.74 mmol, 1.0 equiv) were dissolved in methanol, and diethyl ether was added to the solution until it became turbid. A white solid was filtered, rinsed with diethyl ether, and dried under vacuum. The product was recrystallized from ethanol, rinsed with diethyl ether, and dried under vacuum to give 0.045 g (11%) of the title compound (**36**) as a white solid. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.65 (d, J = 9.0 Hz, 1H), 6.89 (m, 3 H), 6.51 (s, 2H), 4.22 (d, J = 5.2 Hz, 2H), 3.66 (s, 4H), 3.21(s, 3H). MS (ESI): 288 (M^+). Anal: CHN.

2′-Methylsulfonyl-4′-chloro-2-(anilinomethyl)imidazoline Fumarate (37). This compound was obtained as a contaminant from a preparation of **3** in which sodium chloride (at about 25 mol %) was present prior to oxidation. Oxone oxidation of chloride to chlorine is well-documented.[20] The free base was isolated using reverse phase chromatography and converted to the fumaric acid salt. The structure of the title compound was determined via high-resolution mass spectrometry (HRMS) and ^{1}H NMR techniques. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.62 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 8.9 Hz, 2.2 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H), 6.79 (d, J = 5.9 Hz, 1H), 6.5 (s, 2H), 4.2 (d, 5.0 Hz, 2H), 3.65 (s, 4H), 3.26 (s, 3H). HRMS: 288.0559 (M + H).

8-Nitrothiochroman-4-one (38). 3-[(2-Nitrophenyl)thio]-propanoic acid[21] (4.2 g, 18.5 mmol) was heated in $POCl_3$ (21 mL) at 80 °C for 7 h. The mixture was concentrated in vacuo to give an oil. The crude product was diluted with 30 mL of CH_2Cl_2 and adsorbed onto silica gel. Chromatography on silica using hexane/CH_2Cl_2 (1:2) gave **38** (1.8 g, 46%). The product was used in the subsequent reaction without further purification or analysis.

8-Aminothiochroman (39).[14] A solution of **38** (1.8 g, 8.6 mmol) in CH_2Cl_2 (40 mL)was treated with triflic anhydride (1.8 mL, 10.6 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (2.2 g, 11 mmol) under nitrogen. The reaction mixture was heated to reflux for 16 h. The mixture was washed with 1.0 N HCl, and the layers were separated. The organic phase was dried with sodium sulfate and filtered, and the filtrate was concentrated in vacuo. Chromatography on silica gel using hexane/CH_2Cl_2 (1:1) gave the enol-triflate (1.0 g, 35%), which was used without further purification. The enol-triflate was dissolved in dry ethanol (60 mL) and treated with Pt oxide (140 mg) and hydrogenated at 30 psi for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give **39** (0.3 g, 60%). The product was used without further purification.

***N*-(4,5-Dihydro-1H-imidazol-2-ylmethyl)-8-aminothiochroman, 1,1-Dioxide Fumarate (40).** Compound **39** (0.3 g, 1.8 mmol), chloromethylimidazoline hydrochloride (0.28 g, 1.7 mmol), 2,6-lutidine (0.21 mL, 1.8 mmol), and phenol (0.2 g) were combined, and the mixture was heated for 15 min at 130 °C. The mixture was chromatographed on alumina (8:2 CH_2Cl_2:MeOH) to give 0.12 g of the *N*-alkylated intermediate. The intermediate was dissolved in CH_2Cl_2 (4 mL) and treated with *meta*-chloroperoxybenzoic acid (0.19 g of 85%). After 30 min, the mixture was stirred with water (2 mL) and 1 N NaOH (1 mL). The organic phase was separated, dried ($MgSO_4$), and filtered. Fumaric acid (60 mg, 0.5 mmol) was added to the filtrate. The solid that crystallized from solution was filtered and dried in vacuo to give 90 mg (12%) of the desired product (**40**). ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.25 (t, J = 8.0 Hz, 1H), 6.55 (t, J = 9.0 Hz, 2H), 6.45 (s, 2H), 4.1 (d, J = 5.5 Hz, 2H), 3.8 (s, 4H), 3.45 (dt, J = 6.2 Hz, 2.3 Hz, 2H), 2.9 (t, J = 6.2 Hz, 2H), 2.22 (dt, J = 6.2 Hz, 2.3 Hz, 2H). MS (ESI): 280 (M + H^+). Anal: CHNS.

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