α_2 Adrenoceptor Agonists as Potential Analgesic Agents. 3. Imidazolylmethylthiophenes

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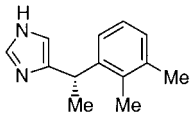
A series of imidazolylmethylthiophenes has been prepared and evaluated as ligands for the α_2 adrenoceptor. These compounds were tested in two animal models that are predictive of analgesic activity in humans. The 3-thienyl compounds were generally the most potent, particularly those with substitution in the 4-position. A subset of the most active compounds was further evaluated for adverse cardiovascular effects in the anesthetized rat model. In addition to excellent binding at the α_{2D} adrenoceptor, the 4-bromo analogues **20e** and **21e** were very active in the rat abdominal irritant test (RAIT) with ED_{50} doses of 0.38 and 0.31 mg/kg, respectively. We constructed a pharmacophore model based on the biological activity of the present series, dexmedetomidine (**1**), and conformationally restrained analogues **3** and **4**.

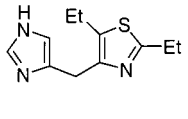
Introduction

Adrenergic receptors belong to the superfamily of seven-transmembrane G-protein coupled receptors (GPCR) and are implicated in a variety of pharmacological functions. The α and *β* subtypes of this receptor were characterized by Alquist over 50 years ago.[1] Since that time the pharmacology of adrenoceptors has been investigated in many laboratories throughout the world. The molecular biology of the α and *β* adrenoceptor subtypes has recently been reviewed.[2] It has been known for many years that an α_2 agonist such as dexmedetomidine (**1**) can produce antinociception in laboratory animals and analgesia in humans.[3] The α_2 adrenoceptor has been further divided into the α_{2A}, α_{2B}, and α_{2C} subtypes. A fourth subtype, the α_{2D}, is believed to be a rat homologue of the α_{2A}. More recently, Bylund and co-workers have used genetically engineered mice to demonstrate that it is primarily the α_{2A} subtype that is responsible for antinociception, while hypertensive responses are believed to be mediated through the α_{2B} subtype, and several other CNS responses are attributed to the α_{2C}.

In two previous communications we have described the synthesis and pharmacological profile of a series of imidazolylmethylthiazoles and -oxazoles[4] and imidazolyldihydrothianaphthenes[5] as potent α_2 agonists. One active compound from the imidazolylmethylthiazole series was RWJ 37210 (**2**), which showed good binding at the α_{2D} adrenergic receptor (K_i = 18 nM) and was a potent antinociceptive agent with an ED_{50} = 1.8 mg/kg po in the mouse abdominal irritant test (MAIT). Similarly, imidazotetrahydrothianaphthene **3** displayed good binding at the α_{2D} receptor (K_i = 2.9 nM) and was also active in the mouse and rat antinociception model (RAIT



1



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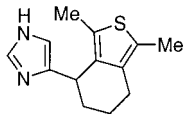
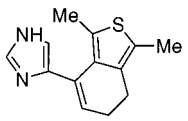


3



4

ED_{50} = 7.9 mg/kg). On the other hand, unsaturated compound **4** showed 2000-fold better binding at the α_{2D} receptor (K_i = 0.0086 nM) and yet was inactive in the MAIT paradigm. For comparative purposes, dexmedetomidine (**1**) has an α_2 adrenergic receptor binding affinity (K_i = 0.39 nM) and good oral activity in the mouse and rat antinociception models (ED_{50} = 0.05 and 0.1 mg/kg, respectively).[6] Thiophene has long been known to be an effective isostere for benzene with surprising differences between the 2- and 3-positional substituents.[7] We therefore decided to synthesize a number of imidazolylalkylthiophenes and evaluate these compounds for α_{2D} receptor binding and antinociceptive activity in rodent models.

Cardiovascular effects are quite often problematic with α_2 ligands, and the more potent compounds from this series were evaluated by means of electrocardiograph (ECG) in an anesthetized rat model. A subset of the active and inactive compounds was examined in modeling experiments to better understand the conformational requirements of α_2 adrenergic ligands for biological activity. Herein are reported the results of those studies.

Chemistry

The synthesis of the imidazomethyl-2-thiophene compounds is shown in Scheme 1. Weinreb amides **6b**−**d** were readily prepared in good yield from the corresponding acid chloride and *N*,*O*-dimethylhydroxylamine

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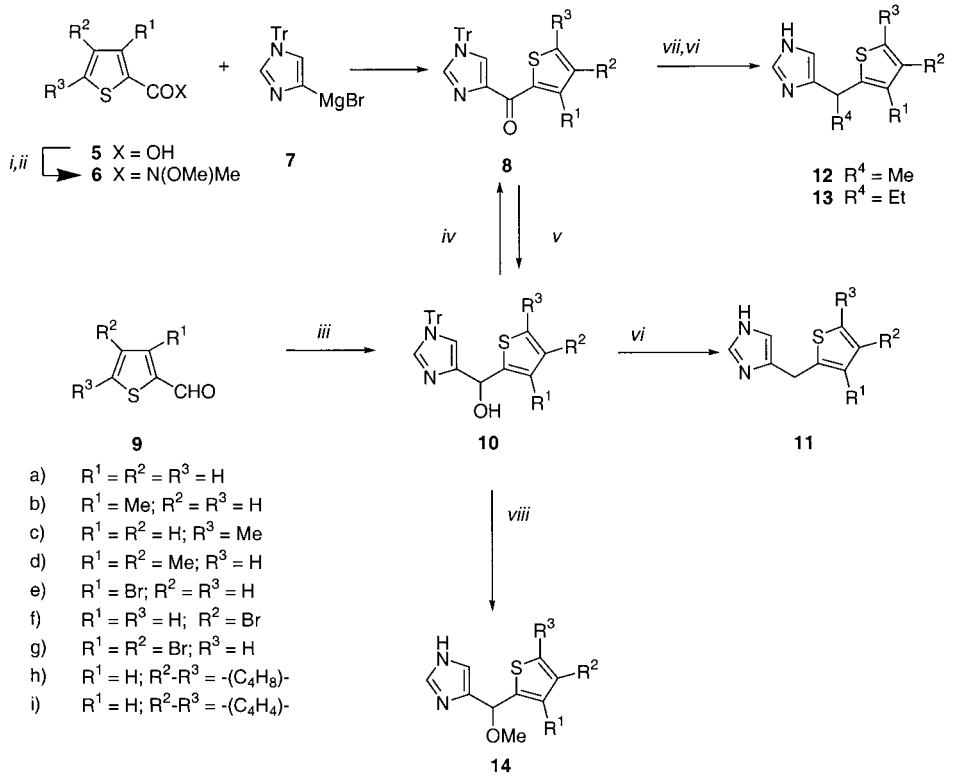
Scheme 1[a]



[a] Reagents: (i) $SOCl_2$; (ii) HNMe(OMe); (iii) **7**; (iv) MnO_2; (v) $NaBH_4$; (vi) [H]; (vii) R^4MgX; (viii) MeOH, HCl.

hydrochloride. Reaction of these intermediates with *N*-tritylimidazole magnesium bromide[8] (**7**) afforded thiophene ketones **8b**−**d**. These compounds are shown in Table 1. The ketones were reduced with $NaBH_4$ to give the intermediate carbinol and then deoxygenated and deprotected to give the unsubstituted methylene targets **11b**−**d**. Carbinol intermediates **10e**−**i** (Table 1)-were obtained from **7** and the appropriately substituted thiophenecarboxaldehyde. A number of methods for the deoxygenation of the carbinol intermediates were explored. Catalytic hydrogenation using Pearlman's catalyst was the most straightforward. However this procedure was only applicable to substrates which did not contain halogen substituents and in general gave only modest yields. Reduction with $BH(TFA)_2$[9] was applicable for substrates that contained halogens and gave acceptable results in most cases. To optimize results with this reagent, however, longer reaction times were often required and BH_3·THF was unsuitable due to polymerization of the THF. The use of BH_3·Me_2S[10] and $NaBH_4$[11] proved to offer alternative sources of borane that allowed for longer reaction times and therefore higher yields. Finally, the deoxygenation of the benzothiophene **10i** with Et_3SiH/TFA[12] gave an excellent yield of target compound **11i**.

Compounds of general structure **12** and **13** were prepared by addition of the appropriate Grignard reagent to the protected imidazole ketone **8** to give the tertiary carbinol. These intermediates were directly deoxygenated and deprotected using the methodology described above. Acid-catalyzed solvolysis of carbinol **10e** in methanol gave the corresponding methoxy-substituted product **14e**. The synthesis of imidazolylmethyl-3-thiophene compounds is shown in Scheme 2 and is analogous to the chemistry described for the 2-thiophene targets. The ketone and carbinol intermediates are shown in Table 2.

The preparation of the cyclopropane compound **25** is shown in Scheme 3. Addition of MeMgBr to imidazole ketone **8b** followed by dehydration gave olefin **24**. Cyclopropanation of this olefin using Simmons−Smith conditions[13] gave **25**, albeit in modest yield. This intermediate was deprotected using MeOH and HCl to give target compound **26**.

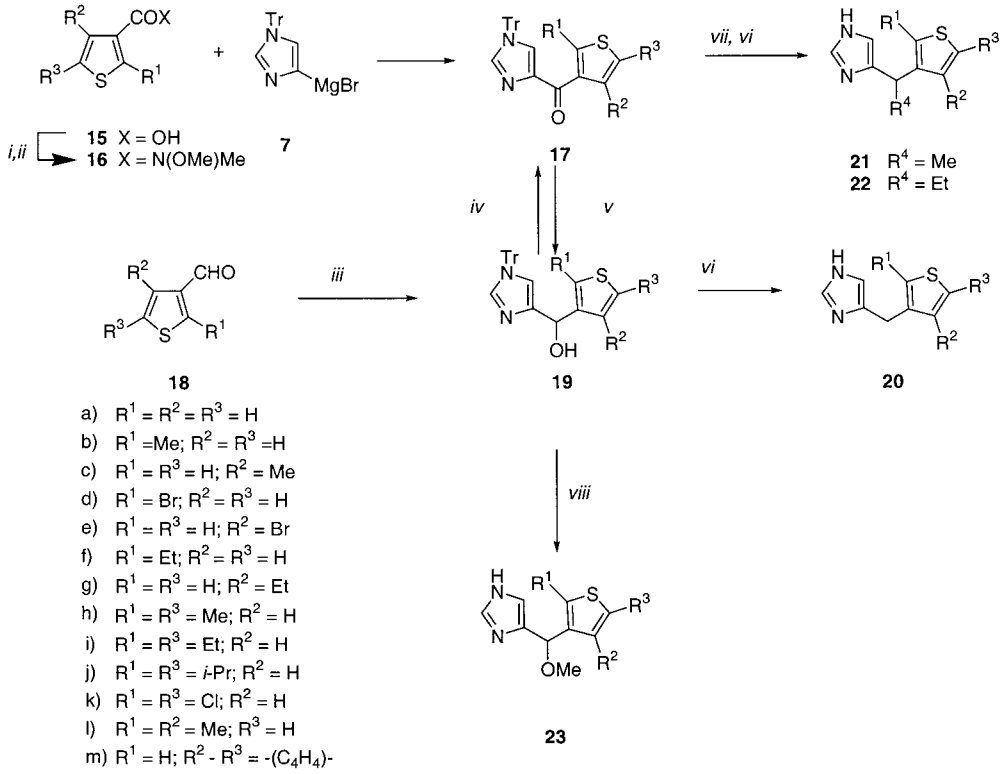
The enantiomers of **12b,e** were prepared by a classical resolution of the corresponding dibenzoyltartaric acid salts. In general 2−3 recrystallizations from 2-PrOH were required to obtain material of >95% ee (a single enantiomer was detected by ^1H NMR using 1 equiv of Mosher's acid in $CDCl_3$). The enantiomers of **21e** were obtained by HPLC using a Chiralpak AD column (99.9/0.1 MeCN/$HNEt_2$). The enantiomeric purity was determined to be >98% by HPLC. Attempts to resolve **21g** by classical resolution or chiral chromatography were unsuccessful.

Biological Results and Discussion

The compounds were prepared and tested in vitro in an α_2 adrenergic receptor binding assay. They were also screened in vivo in the mouse abdominal irritant test (MAIT) for antinociceptive activity. Compounds with >80% inhibition in this model were then evaluated in the rat abdominal irritant test (RAIT), and an ED_{50} was determined for those compounds with significant activity. The data for 2-thiophene and 3-thiophene compounds are presented in Tables 3 and 4, respectively.

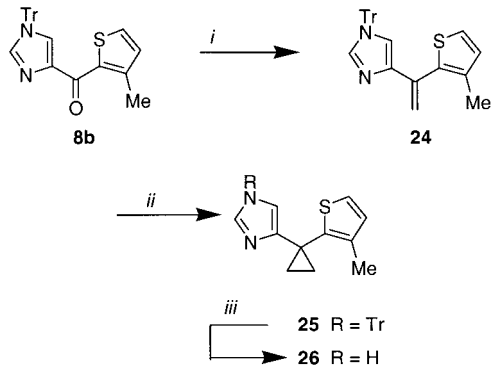
In the 2-thiophene series of compounds, the unsubstituted thiophene compound **11a** as well as those bearing a substituent in the 5-position such as **11c**,**h**,**i**

Scheme 2[a]



[a] Reagents: (i) $SOCl_2$; (ii) HNMe(OMe); (iii) **7**; (iv) MnO_2; (v) $NaBH_4$; (vi) [H]; (vii) R^4MgX; (viii) MeOH, HCl.

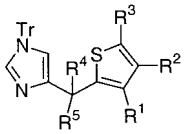
Scheme 3[a]



[a] Reagents: (i) 1. MeMgBr, 2. TsOH; (ii) CH_2I_2, Et_2Zn; (iii) MeOH, HCl.

showed only modest binding at the α_2 receptor (K_i = 1.1−8.7 nM) and were inactive in the mouse model. Compounds with a substituent (Me or Br) ortho to the benzylic carbon such as **11b,e** were 1 order of magnitude more potent in binding (K_i = 0.45 and 0.35 nM, respectively) and significantly more active in the in vivo models (RAIT ED_{50} = 0.87 and 2.0 mg/kg, respectively). A lone 3-substituent as in the case of **11f** was intermediate in both receptor binding and biological activity. The 3,4-disubstituted compounds **11d,g** had the highest affinity at the α_{2D} adrenergic receptor (K_i = 0.17 and 0.07 nM, respectively) but had only modest antinociceptive activity. Alkyl substitution on the benzylic carbon such as compounds **12b,d,e,g** and **13b** led to a modest decrease in receptor binding relative to their unsubstituted analogues. In addition, compounds **12b,e** had in vivo activity that was comparable to that of their unsubstituted analogues. It was interesting to find that compounds **12d**,**g** and **13b** were inactive in the rat

Table 1. *N*-Tritylimidazoalkyl-2-thiophene Intermediates



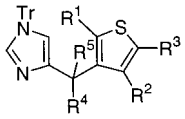
compd	R^1	R^2	R^3	R^4	R^5	method/yield	formula
8b	Me	H	H	=O		A/52	$C_{28}H_{22}N_2O_S$
8c	H	H	Me	=O		A/50	$C_{28}H_{22}N_2OS$
8d	Me	Me	H	=O		A/73	$C_{29}H_{24}N_2OS$
8e	Br	H	H	=O		C/91	$C_{27}H_{19}BrN_2OS$
10e	Br	H	H	OH	H	B/70	$C_{27}H_{21}BrN_2OS$
10f	H	Br	H	OH	H	B/66	$C_{27}H_{21}BrN_2OS$
10g	Br	Br	H	OH	H	B/69	$C_{27}H_{20}Br_2N_2OS$
10h	H	−(C_4H_8)−		OH	H	B/80	$C_{31}H_{28}N_2OS$[a]
10i	H	−(C_4H_4)−		OH	H	B/65	$C_{31}H_{24}N_2OS$

[a] Product was somewhat labile, and attempts to recrystallize resulted in some decomposition.

model despite the fact that there was some activity in the mouse. The methoxy-substituted compound **14e** showed very little binding at the receptor and had almost no antinociceptive activity. Finally, the cyclopropane analogue **26** had no significant binding to the receptor and was inactive in vivo.

The 3-substituted thiophene analogues were generally more potent, and even the unsubstituted thiophene compound **20a** had modest receptor affinity and antinociceptive activity (K_i = 3.1 nM; RAIT ED_{50} = 0.97 mg/kg). We examined the effects of substitution at either of the two possible ortho positions in this molecule (compounds **20b**−**g**) and found that for the Et analogues both isomers were equally active. However for Me and Br substituents, the 4-substituted isomer was the more active. The 2,5-dimethyl and 2,5-diethyl analogues **20h,i** were equipotent relative to their corresponding mono-

Table 2. *N*-Tritylimidazoalkyl-3-thiophene Intermediates



compd	R^1	R^2	R^3	R^4	R^5	method/ yield	formula
17b	Me	H	H	=O		C/93	$C_{28}H_{22}N_2OS$
17c	H	Me	H	=O		C/75	$C_{28}H_{22}N_2OS$
17e	H	Br	H	=O		C/64	$C_{27}H_{19}BrN_2OS$
17g	H	Et	H	=O		C/90	$C_{29}H_{24}N_2$
17k	Cl	H	Cl	=O		A/74	$C_{27}H_{18}Cl_2N_2OS$
19a	H	H	H	OH	H	B/50	$C_{27}H_{22}N_2OS$
19b	Me	H	H	OH	H	B/55	$C_{28}H_{24}N_2OS$
19c	H	Me	H	OH	H	B/59	$C_{28}H_{24}N_2OS$
19d	Br	H	H	OH	H	B/64	$C_{27}H_{21}BrN_2OS$
19e	H	Br	H	OH	H	B/56	$C_{27}H_{21}BrN_2OS{\cdot}0.25H_2O$
19f	Et	H	H	OH	H	B/62	$C_{29}H_{26}N_2OS{\cdot}0.25H_2O$
19g	H	Et	H	OH	H	B/62	$C_{29}H_{26}N_2OS{\cdot}0.5H_2O$
19h	Me	H	Me	OH	H	B/93	$C_{29}H_{26}N_2OS{\cdot}0.25H_2O$
19i	Et	H	Et	OH	H	B/79	$C_{31}H_{30}N_2OS{\cdot}0.25H_2O$
19j	*i*-Pr	H	*i*-Pr	OH	H	B/66	$C_{33}H_{34}N_2OS{\cdot}0.25H_2O$
19k	Cl	H	Cl	OH	H	E/72	$C_{27}H_{20}Cl_2N_2OS$
19l	Me	Me	H	OH	H	B/66	$C_{29}H_{26}N_2OS{\cdot}0.5H_2O$
19m	H	$-(C_4H_4)-$		OH	H	B/45	$C_{31}H_{24}N_2OS{\cdot}H_2O$

substituted compounds. However the 2,5-dichloro compound **20k** had a significant loss in activity, and the diisopropyl compound **20j** was inactive. The 2,4-dimethyl compound **20l** was among the most potent in binding to the α_2 receptor (K_i = 0.1 nM) and was fully effective in the MAIT screen (100% inhibition @ 30 mg/kg). However we were unable to obtain an ED_{50} in the rat as a consequence of some behavioral side effects. The benzothiophene compound **20m** showed excellent binding at the receptor (K_i = 0.09 nM) and was also very potent in the RAIT (ED_{50} = 0.44 mg/kg). A methyl substituent on the benzylic carbon, such as **21b,c,e,g**, had only minor effects on receptor binding and antinociceptive activity relative to the unsubstituted compounds. However an ethyl (**22c**) or methoxy (**23c,e**) substituent at the benzylic carbon resulted in a significant decrease in biological activity.

The potential for cardiovascular side effects is an important issue for compounds that bind to adrenergic receptors. We employed an anesthetized rat model as a way of evaluating some of the more potent compounds in this series for cardiovascular liability. After id administration of compound at a dose of 3× ED_{50} value, the ECG of the animal was monitored and changes in the QT interval (ΔQT) were recorded. These data are shown in Table 5. We used dexmedetomidine (**1**) as a standard in this procedure which produced only an 8% change in the QT interval.

For the imidazolylmethyl-2-thiophene compounds, **11b** was the most potent in vivo. However the ΔQT was significantly higher at 22%. Compounds **12b,e** were resolved, and only the more active enantiomer was evaluated in CV tests. Again these two compounds produced a significant QT prolongation. In the imidazolylmethyl-3-thiophene series, compounds **20c,e,f,g** were tested and only the 4-bromo compound **20e** had a ΔQT (11%) close to that of dexmedetomidine (**1**). Compound **21e** is the α-methyl analogue of **20e** and was comparable in α_2 binding and antinociceptive activity. Unfortunately the more active enantiomer of this compound (**(−)21e**) actually had a higher QT prolongation than the unsubstituted compound.

Modeling. While it is certainly possible that pharmacodynamics and bioavailability could play a significant role in vivo, we decided to construct models of low-energy conformations of some of the biologically active compounds and compare these results with the data obtained for the RAIT assay. Initially we chose compounds **1**, **20e**, and (−)**21e**[14] with RAIT ED_{50} values of 0.12, 0.38, and 0.19 mg/kg respectively, for modeling studies. The overlay of these structures is shown in Figure 1a,b. It is quite clear from these models that these 3-thiophene compounds fit quite well with dexmedetomidine (**1**). We attempted to fit 2-thienyl compounds **11b**,**g** to this model. The overlay of these structures is shown in Figure 2a,b. Compound **11b** also fits quite well into this model and is quite active in the antinociceptive assay (ED_{50} = 0.87 mg/kg). On the other hand compound **11g** is quite different in the position of the thiophene ring and is 10-fold less active in the RAIT assay (ED_{50} = 7.1 mg/kg) despite being among the most potent ligands for the α_{2D} receptor. Substitution of the methylene bridge such as OMe (**14e**) and cyclopropyl (**26**) resulted in no antinociceptive activity and very little receptor affinity, and as expected **14e** and **26** have almost no overlap with **1** (Figure 3).

Finally we wanted to see if this model would explain the vast difference between receptor binding and antinociceptive activity that was observed between analogues **3** and **4**. These structures are shown in Figure 4. In fact unsaturated compound **4** which is inactive in the RAIT forces the thiophene ring into a much different region of space than the aromatic ring of **1**. The reduced compound **3** however does in fact hold the thiophene ring in much the same orientation as the phenyl ring of **1** and consequently retains significant biological activity.

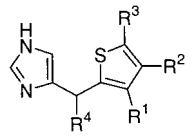
In conclusion, we have prepared some 2-thienyl- and 3-thienyl-4-methylimidazoles that show excellent binding at the α_{2D} receptor and are quite potent in assays predictive of analgesic activity. The 3-thienyl compounds that contained a substituent in the 4-position, such as **20c,e,g** and **21c,e,g**, were the most active in the RAIT assay. In addition, those compounds with a 4-Br substituent, such as in **20e** and **21e**, have the lowest cardiovascular side effect potential of all compounds in this series. Finally molecular modeling techniques provided insight to better understand these results.

Experimental Section

Chemistry. All melting points are uncorrected and were taken on a Thomas-Hoover capillary melting point apparatus or similar device. ^{1}H NMR spectra were obtained on a 90-MHz Varian EM-390 NMR spectrometer or a 360-MHz Brucker AM-360 NMR spectrometer with $SiMe_4$ as the internal standard. The spectral data for each compound supported the assigned structure, and all elemental analyses were within 0.4% of the calculated value, except where indicated. The examples below represent typical experimental conditions for the preparation of compounds shown in Schemes 1−3.

General Procedures for Thiophene Aldehydes and Weinreb Amides. *N,O*-Dimethyl-(3-methylthiophene-2-yl)carboxamide (6b). To a solution of 3-methylthiophene-2-carboxylic acid (26.0 g, 0.182 mol) in $CHCl_3$ (150 mL) was added $SOCl_2$ (15.9 mL, 0.22 mol) and the reaction mixture was heated at reflux for 2 h and then cooled to room temperature. This solution was then added dropwise to a mixture of *N,O*-dimethylhydroxylamine hydrochloride (26.6 g, 0.273 mol) and NEt_3 (68 mL, 0.49 mol) in $CHCl_3$ (400 mL) cooled in an ice

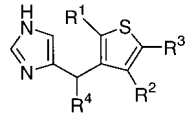
Table 3. Imidazoalkyl-2-thiophenes



compd	R^1	R^2	R^3	R^4	method/yield	formula	mp (°C)/solvent[a]	α_{2D} K_i[b] (nM)	MAIT[c] (%)	RAIT[d]
11a	H	H	H	H	D/18	$C_8H_8N_2S\cdot HCl$	128−129/Acn	8.7	60	NT
11b	Me	H	H	H	E/20	$C_9H_{10}N_2S\cdot HCl$	127.5−129/Ac	0.45	100	0.87 (0.4, 1.5)
11c	H	H	Me	H	F/20	$C_9H_{10}N_2S\cdot HCl$	131−133/Ac	3.6	33	NT
11d	Me	Me	H	H	E/12	$C_{10}H_{12}N_2S\cdot HCl$	180−182/Acn	0.17	100	4.7 (2.3, 9.0)
11e	Br	H	H	H	G/44	$C_8H_7BrN_2S\cdot HCl$	211.5−213.5/Acn	0.35	100	2.0 (0.9, 4.2)
11f	H	Br	H	H	H/30	$C_8H_7BrN_2S\cdot HCl$	186−189.5/Acn	1.4	80	5.2 (2.3, 8.7)
11g	Br	Br	H	H	G/68	$C_8H_6Br_2N_2S\cdot HCl$	224−227/Acn	0.07	93	7.1 (3.4, 13.6)
11h	H	$-(C_4H_8)-$		H	H/41	$C_{12}H_{14}N_2S\cdot HCl$	181−183/Acn	3.7	7	NT
11i	H	$-(C_4H_4)-$		H	I/93	$C_{12}H_{10}N2S\cdot HCl$	187−188/−	1.1	20	NT
12b	Me	H	H	Me	J/40	$C_{10}H_{12}N_2S\cdot HCl$	163−165/Ac	2.1	100	2.2 (0.8 4.7)
12d	Me	Me	H	Me	K/25	$C_{11}H_{14}N_2S\cdot C_4H_4O_4$	127−129/Ac	0.75	87	IA
12e	Br	H	H	Me	L/55	$C_9H_9BrN_2S\cdot HCl$	185−188/Acn	0.96	100	0.97 (0.4, 2.6)
12g	Br	Br	H	Me	L/25	$C_9H_8Br_2N_2S\cdot C_4H_4O_4$[e]	120−123.5/Ac	0.43	80	NT
13b	Me	H	H	Et	K/8	$C_{11}H_{14}N_2S\cdot C_4H_4O_4$	108.5−109.5/Ac	8.3	100	IA
14e	Br	H	H	OMe	N/35	$C_9H_9BrN_2OS\cdot C_4H_4O_4$	127.5−129.5/Ac	39	53	NT
26	Me	H	H	$-CH_2CH_2-$	−/44	$C_{11}H_{12}N_2S\cdot C_4H_4O_4$	151−155/Ac	1000	40	NT

[a] Solvents: Ac = acetone; Acn = acetonitrile. [b] Receptor binding K_i's were determined using 5−8 concentrations in triplicate. [c] Values reported are % inhibition at the screening dose of 30 mg/kg po. [d] Values expressed are ED_{50} (95% confidence limits); NT = not tested; IA = inactive. [e] C: calcd, 34.54; found, 35.08.

Table 4. Imidazomethyl-3-thiophenes



compd	R^1	R^2	R^3	R^4	method/yield	formula	mp (°C)/solvent[a]	α_{2D} K_i[b] (nM)	MAIT[c] (%)	RAIT[d]
20a	H	H	H	H	D/32	$C_8H_8N_2S\cdot C_4H_4O_4$	115−118/Ac	3.1	100	0.97 (0.51, 1.8)
20b	Me	H	H	H	D/24	$C_9H_{10}N_2S\cdot C_4H_4O_4$	140−141/Ac	0.44	100	0.89 (0.43, 1.7)
20c	H	Me	H	H	D/48	$C_9H_{10}N_2S\cdot C_4H_4O_4$	142−144/Ac	0.47	100	0.35 (0.17, 0.84)
20d	Br	H	H	H	H/65	$C_8H_7BrN_2S\cdot C_4H_4O_4$	148−150/Ac	ND	100	1.1 (0.53, 2.4)
20e	H	Br	H	H	G/34	$C_8H_7BrN_2S\cdot C_4H_4O_4$	135−137/Ac	0.23	100	0.38 (0.20, 0.81)
20f	Et	H	H	H	D/53	$C_{10}H_{12}N_2S\cdot C_4H_4O_4$	148−150/Ac	0.07	100	0.27 (0.14, 0.51)
20g	H	Et	H	H	D/47	$C_{10}H_{12}N_2S\cdot C_4H_4O_4$	146−148/Ac	.29	100	0.32 (0.18, 0.49)
20h	Me	H	Me	H	D/47	$C_{10}H_{12}N_2S\cdot C_4H_4O_4$	146−148/Ac	0.69	100	0.9 (0.43, 1.75)
20i	Et	H	Et	H	G/70	$C_{12}H_{16}N_2S\cdot C_4H_4O_4$	123−124/Ac	0.4	100	0.31 (0.17, 0.58)
20j	*i*-Pr	H	*i*-Pr	H	G/46	$C_{14}H_{20}N_2S\cdot C_4H_4O_4$	160−161/Ac	12	40	NT
20k	Cl	H	Cl	H	H/52	$C_8H_6Cl_2N_2S\cdot C_4H_4O_4$	164−166/Ac	0.88	100	3.2 (1.74, 5.03)
20l	Me	Me	H	H	G/22	$C_{10}H_{12}N_2S\cdot C_4H_4O_4$	160−162/Ac	0.1	100	*e*
20m	H	$-(C_4H_4)-$		H	H/62	$C_{12}H_{10}N_2S\cdot C_4H_4O_4$	154−156/Ac	0.09	100	0.44 (0.19, 0.93)
21b	Me	H	H	Me	K/34	$C_{10}H_{12}N_2S\cdot C_4H_4O_4$	131−133/Ac	2.3	100	1.6 (0.9, 3.5)
21c	H	Me	H	Me	K/23	$C_{10}H_{12}N_2S\cdot C_4H_4O_4$	125−128/Ac	0.39	100	0.27 (0.14, 0.49)
21e	H	Br	H	Me	J/40	$C_9H_9BrN_2S\cdot C_4H_4O_4$	137−139/Ac	0.08	100	0.31 (0.19, 0.51)
21g	H	Et	H	Me	K/39	$C_{11}H_{14}N_2S\cdot C_4H_4O_4$	145−147/Ac	0.28	100	0.48 0.23, 0.97)
22c	H	Me	H	Et	K/19	$C_{11}H_{14}N_2S\cdot C_4H_4O_4$	101−105Ac	0.97	100	2.6 (1.5, 4.4)
23c	H	Me	M	OMe	N/47	$C_{10}H_{12}N_2OS\cdot C_4H_4O_4$[f]	99−102/Ac	15.9	100	4.4 (2.4, 7.8)
23e	H	Br	H	OMe	N/21	$C_9H_9BrN_2OS\cdot C_4H_4O_4$	111−112/Ac	ND	100	3.6 (1.7, 8.5)

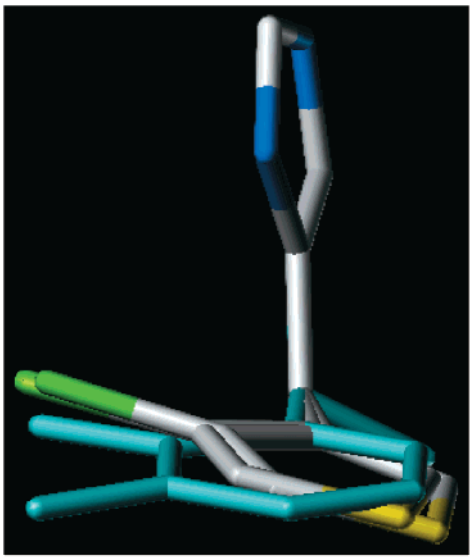
[a] See Table 3 for solvents. [b] Receptor binding K_i's were determined using 5−8 concentrations in triplicate. [c] Values reported as % inhibition at the screening dose of 30 mg/kg po. [d] Values expressed are ED_{50} (95% confidence limits); NT = not tested. [e] Unable to determine an ED_{50}. [f] N: calcd, 8.64; found, 8.12.

Table 5. Cardiovascular Data for Selected Compounds

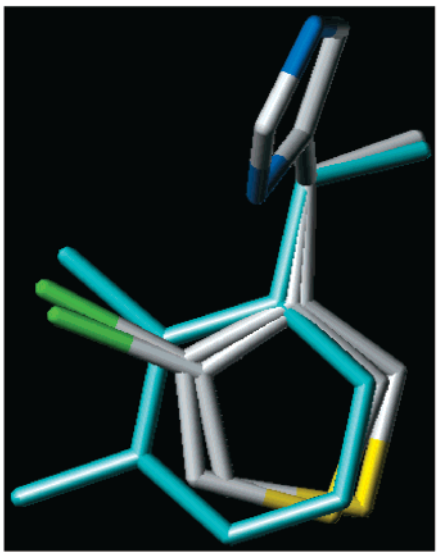
compd	α_{2_D} (nM)	RAIT ED_{50} (mg/kg)	ΔQT (%)
11b	0.45	0.87 (0.4, 1.5)	22
(+)12b	0.78	1.18 (0.45, 2.6)	24
(+)12e	0.18	0.97 (0.56, 1.59)	23
20c	0.47	0.35 (0.17, 0.84)	34
20e	0.23	0.38 (0.20, 0.81)	11
20f	0.07	0.27 (0.14, 0.51)	28
20g	0.29	0.32 (0.18, 0.49)	48
(−)21e	ND	0.19 (0.13, 0.26)	20
21g	40	0.48 (0.23, 0.97)	32
1	0.015	0.12 (0.04, 0.17)	8

bath. After the addition was complete, the reaction was allowed to warm to room temperature, and then transferred to a separatory funnel. The organic layer was washed with water (2×) and then dried over $MgSO_4$. The solution was filtered and the solvent was evaporated in vacuo. The resulting liquid was vacuum distilled (109.5−110.5 °C, 0.75 mmHg) to give a clear oil (28.8 g, 85%): ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 3.33 (s, 3H), 3.71 (s, 3H), 6.9 (d, 1H, J = 5 Hz), 7.35 (d, 1H, J = 5 Hz). Anal. ($C_8H_{11}O_2S$) C,H,N.

2-Methylthiophene-3-carboxaldehyde (18b). To a solution of 3-bromo-2-methylthiophene (11.8 g, 67.0 mmol) in dry Et_2O (50 mL) cooled to −78 °C was added *n*-BuLi (1.6 M, 42.0 mL) dropwise. After the addition was complete, the reaction was stirred at −78 °C for an additional 45 min. A solution of DMF (9.8 g, 134.0 mmol) in dry Et_2O was also cooled to −78 °C and then added via cannula to the reaction mixture. The reaction was allowed to slowly warm to room temperature and then quenched with water. The mixture was transferred to a separatory funnel and the aqueous layer extracted with an additional portion of Et_2O. The combined organic layers were washed with water and brine and then dried over Na_2SO_4. The solution was filtered and the solvent was evaporated in vacuo to give a yellow oil. Chromatography on silica (2.5 to 5% Et_2O



(a)

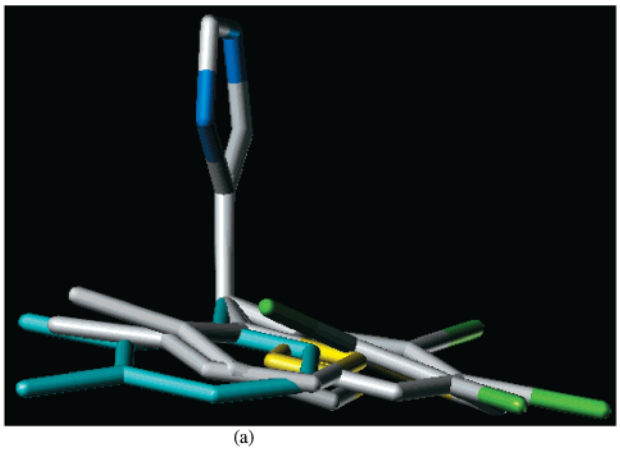


(b)

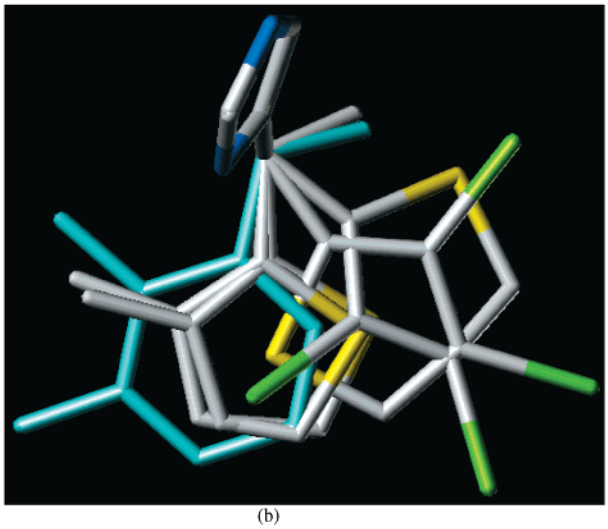
Figure 1. Overlay of **1**, **20e**, and **21e**: (a) side view; (b) top view.

in hexane) gave the title compound as a pale yellow oil (4.2 g, 50%). This material would decompose at room temperature but could be stored 2−3 days in the refrigerator: ^{1}H NMR ($CDCl_3$) δ 2.85 (s, 3H), 7.1 (d, 1H, J = 5 Hz), 7.7 (d, 1H, J = 5 Hz), 10.1 (s, 1H).

General Procedures for Addition of Imidazole Grignard Reagent to Thiophene Carbonyl Compounds. *N*-Triphenylmethyl-(3-methylthiophene-2-yl)-1*H*-imidazole-4-methanone (8b). Method A. To a solution of **5** (21.8 g, 50 mmol) in CH_2Cl_2 (150 mL) under Ar was added 3.0 M EtMgBr in Et_2O (17.0 mL). This solution was stirred at room temperature for 1 h at which point halogen metal exchange was complete as judged by TLC analysis of an aliquot. A solution of *N*,*O*-dimethyl-(3-methylthiophene-2-yl)carboxamide (**6b**; 9.3 g, 50 mmol) in CH_2Cl_2 was added dropwise, and the reaction was stirred overnight at room temperature. The reaction was quenched by the addition of aqueous NH_4Cl and extracted with CH_2Cl_2 (2×). The combined organic layers were washed with water and then dried over Na_2SO_4. After filtering the solvent was evaporated in vacuo and the residue was recrystallized from acetone to give the title compound as a pale yellow solid (11.1 g, 52%): mp 195−197 °C; ^{1}H NMR ($CDCl_3$)



(a)



(b)

Figure 2. Overlay of **1** and **11b,g:** (a) side view; (b) top view.

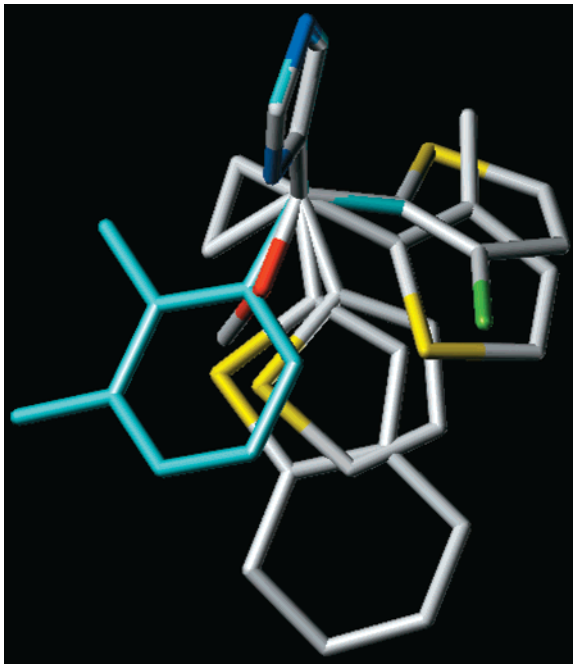


Figure 3. Overlay of compounds **1**, **11a**,**h**, **14e**, and **26**.

δ 2.65 (s, 3H), 6.9 (d, 1H, J = 5 Hz), 7.15 (m, 6H), 7.35 (m, 9H), 7.5 (m, 2H), 7.75 (d, 1H, J = 2 Hz). Anal. ($C_{28}H_{22}N_2OS$) C,H,N.

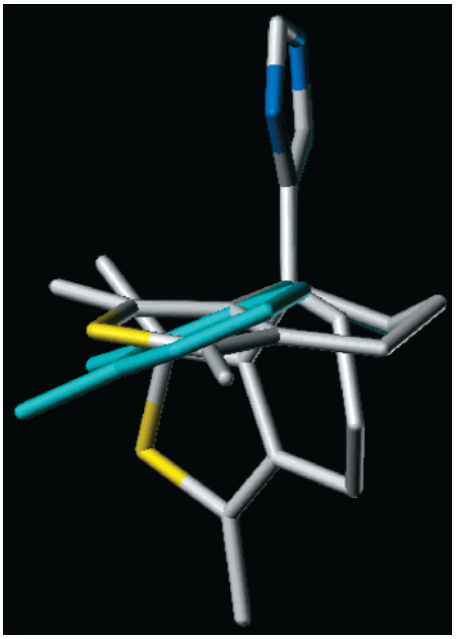


Figure 4. Overlay of compounds **1**, **3**, and **4**.

***N*-Triphenylmethyl-(4-bromothiophene-2-yl)-1*H*-imidazole-4-methanol (10f)**. **Method B**. This is essentially the same procedure as described above except 4-bromothiophene-2-carboxaldehyde (**9f;** 3.5 g, 18.3 mmol) was used in place of Weinreb amide **8b.** The crude carbinol product is purified by chromatography on silica ($CHCl_3$) to give the title compound as a light yellow solid (6.0 g, 66%): ^{1}H NMR ($CDCl_3$) δ 4.5 (br s, 1H ex), 5.9 (s, 1H), 6.75 (s, 1H), 6.85 (s, 1H), 7.15 (m, 7H), 7.3 (m, 9H), 7.45 (s, 1H). Anal. ($C_{27}H_{21}BrN_2OS$) C,H,N.

***N*-Triphenylmethyl-(3-bromothiophene-2-yl)-1*H*-imidazole-4-methanone (8e)**. **Method C**. A mixture of **10e** (17.3 g, 34.5 mmol) and MnO_2 (50 g) in CH_2Cl_2 (300 mL) was stirred overnight at room temperature. The solution was filtered through Dicalite and the solvent was evaporated in vacuo to give a white solid (15.6 g, 91%). An analytical sample could be obtained by recrystallization from CH_2Cl_2/MeOH: ^{1}H NMR ($CDCl_3$) δ 7.15 (m, 7H), 7.3 (m, 9H), 7.5 (m, 1H), 7.55 (m, 1H), 7.8 (s, 1H). Anal. ($C_{27}H_{19}BrN_2OS$) C,H,N.

General Procedures for Deoxygenation and Deprotection of Imidazolylthiophene Carbinols. 4-[(Thiophene-2-yl)methyl]-1*H*-imidazole Hydrochloride (11a). **Method D**. A solution of bromothiophene **10f** (5.0 g, 10.0 mmol) was combined with $Pd(OH)_2$ in EtOH and hydrogenated at 50 °C, 50 psi overnight. The catalyst was removed by filtration and the filtrate was evaporated in vacuo. The residue was dissolved in dilute HCl and washed with Et_2O, and then basified with Na_2CO_3 and extracted with EtOAc (2×). The organic layer was separated and dried over K_2CO_3, filtered and the solvent evaporated in vacuo. The residue was chromatographed on silica (2.5% to 5% of MeOH containing 10% NH_4OH in $CHCl_3$). The appropriate fractions were combined and the solvent was evaporated in vacuo. The residue was dissolved in acetone and treated with Et_2O·HCl. The product was collected and recrystallized from MeCN to give a white solid: mp 128−129 °C; ^{1}H NMR (DMSO-d_6) δ 4.3 (s, 2H), 7.0 (s, 2H), 7.4 (m, 1H), 7.5 (s, 1H), 9.05 (s, 1H), 14.7 (br s, 1H). Anal. ($C_8H_8N_2S$·HCl) C,H,N.

4-[(3-Methylthiophene-2-yl)methyl]-1*H*-imidazole Hydrochloride (11b). **Method E**. A mixture of **8b** (7.7 g, 18.0 mmol) and $NaBH_4$ (1.0 g, 27.0 mmol) in 2-PrOH was heated at reflux for 2 h at which point the starting material had been consumed. The reaction was quenched by the cautious addition of cold 3 N HCl. Most of the 2-PrOH was evaporated from the reaction. The residue was diluted with water, basified with solid Na_2CO_3 and extracted with $CHCl_3$ (2×). The extracts were combined and dried over Na_2SO_4, and then filtered and the solvent was evaporated in vacuo. The residue was triturated with EtOAc to give an off-white solid that was used directly without further purification. To a solution of TFA (50.8 mL, 0.66 mol) in CH_2Cl_2 cooled in an ice bath was added BH_3·THF (330 mL, 0.33 mol) dropwise. After the addition was complete, a solution of the carbinol in CH_2Cl_2 (50 mL) was added in one portion. The reaction mixture was stirred for 2 h at 0 °C and then quenched with water and 3 N HCl. The solution was basified with solid Na_2CO_3 and extracted with CH_2Cl_2 (2×). The extracts were combined and dried over K_2CO_3, filtered and the solvent evaporated in vacuo. The residue was dissolved in MeOH and filtered. To this solution was added 3 N HCl (10 mL) and the mixture heated at reflux 2−3 h until starting material had been consumed. The solvent was evaporated in vacuo. The residue was dissolved in water and washed with Et_2O (2×), then basifed and extracted with EtOAc (2×). The extracts were combined and dried over Na_2SO_4, filtered and the solvent evaporated in vacuo. The residue was purified by chromatography on silica (99:0.5:0.5 EtOAc/MeOH/NH_4OH). The appropriate fractions were combined and the solvent was evaporated in vacuo. The residue was treated with Et_2O·HCl and the salt was recrystallized from acetone and to give the title compound as white needles (1.2 g, 20%): mp 127.5−129 °C; ^{1}H NMR (DMSO-d_6) δ 2.2 (s, 3H), 4.15 (s, 2H), 6.85 (d, 1H, J = 5 Hz), 7.3 (d, 1H, J = 5 Hz), 7.4 (s, 1H), 9.0 (s, 1H), 14.6 (br s, 2H). Anal. ($C_9H_{10}N_2S$·HCl) C,H,N.

4-[(5-Methylthiophene-2-yl)methyl]-1*H*-imidazole Hydrochloride (11c). **Method F**. A mixture of **8c** (3.9 g, 9.0 mmol) and $NaBH_4$ (0.52 g, 14.0 mmol) in 2-PrOH was heated at reflux for 2 h at which point the starting material had been consumed. The reaction was quenched by the cautious addition of cold 3 N HCl. Most of the 2-PrOH was evaporated from the reaction. The residue was diluted with water, basified with solid Na_2CO_3 and extracted with $CHCl_3$ (2×). The extracts were combined and dried over Na_2SO_4, and then filtered and the solvent was evaporated in vacuo. The residue was triturated with Et_2O to give an off-white solid. The solid was dissolved in MeOH and combined with Pearlman's catalyst (2 g) and hydrogenated at 50 °C, 50 psi for 48 h. The catalyst was removed by filtration and the filtrate was evaporated in vacuo. The reisdue was dissolved in dilute HCl, washed with Et_2O (2×), and then basified with Na_2CO_3 and extracted with EtOAc. The extracts were combined and dried over K_2CO_3, filtered and the solvent evaporated in vacuo. The residue was converted to the HCl salt (Et_2O·HCl) and recrystallized from acetone to give the title compound as a white solid: mp 131−133 °C; ^{1}H NMR (DMSO-d_6) δ 2.4 (s, 3H), 4.2 (s, 2H), 6.65 (s, 1H), 6.8 (d, 1H, J = 3 Hz), 7.5 (s, 1H), 9.05 (s, 1H), 14.6 (br s, 1H). Anal. ($C_9H_{10}N_2S$·HCl) C,H,N.

4-[(3-Bromothiophene-2-yl)methyl]-1*H*-imidazole Hydrochloride (11e). **Method G**. To a solution of TFA (12.2 mL, 0.16 mol) in CH_2Cl_2 cooled in an ice bath was added BH_3·Me_2S (90 mL, 0.90 mol) dropwise. After the addition was complete, **10e** (2.0 g, 0.004 mol) was added as a solid in one portion. The reaction mixture was allowed to warm to room temperature, stirred an additional 1 h at room temperature and then quenched with water and 3 N HCl. The solution was basified with solid Na_2CO_3 and extracted with CH_2Cl_2 (2×). The extracts were combined and dried over K_2CO_3, filtered and the solvent evaporated in vacuo. The residue was dissolved in MeOH (25 mL) containing 3 N HCl (5 mL) and the mixture heated at reflux 2−3 h. The solvent was evaporated in vacuo. The residue was dissolved in water and washed with Et_2O (2×), then basifed and extracted with EtOAc (2×). The extracts were combined and dried over Na_2SO_4, filtered and the solvent evaporated in vacuo. The residue was dissolved in Et_2O, charcoaled and filtered through Dicalite. The filtrate was treated with Et_2O·HCl and the product was collected and then recrystallized from MeOH/MeCN to give the title compound as a white crystalline solid (0.49 g, 44%): mp 211.5−213.5 °C; ^{1}H NMR (DMSO-d_6) δ 4.2 (s, 2H), 7.1 (d, 1H, J = 5 Hz), 7.45 (s, 1H), 7.6 (d, 1H, J = 5 Hz), 9.0 (s, 1H) 14.5 (br s, 1H). Anal. ($C_8H_7BrN_2S$·HCl) C,H,N.

4-[(4-Bromothiophene-2-yl)methyl]-1*H*-imidazole Hydrochloride (11f). **Method H**. TFA (50 mL) was cooled in an ice bath under Ar and $NaBH_4$ 5/16" pellets (3 pellets, 0.5

g, 75 mmol) was added and the mixture was stirred 20 min at 0 °C. When pellets were almost gone, **10f** (3.5 g, 7.0 mmol) and 2 additional $NaBH_4$ pellets were added. After 30 min, the starting material had not been completely consumed and 2 more pellets were added and the mixture was allowed to stir and slowly warm to room temperature overnight. The reaction mixture was diluted with water and neutralized with solid Na_2CO_3 and then extracted with $CHCl_3$ (2×). The combined extracts were dried over K_2CO_3 and then filtered and the solvent was evaporated in vacuo. The residue was chromatographed on silica (97/3 $CHCl_3$/10% NH_4OH in MeOH) to give an oil which crystallized on standing. This material was dissolved in acetone and treated with Et_2O·HCl. The product was collected by filtration and recrystallized from MeCN to give the title compound as a white solid (0.6 g, 30%): mp 186−189.5 °C; ^{1}H NMR (DMSO-d_6) δ 4.3 (s, 2H), 7.05 (d, 1H, J = 1 Hz), 7.5 (d, 1H, J = 1 Hz), 7.6 (d, 1H, J = 1 Hz), 9.05 (d, 1H, J = 1 Hz), 14.7 (br s, 1H). Anal. ($C_8H_7BrN_2S$·HCl) C,H,N.

4-[(Benzo[*b*]thiophene-2-yl)methyl]-1*H*-imidazole Hydrochloride (11i). Method I. To a solution of **10i** (4.7 g, 10 mmol) in CH_2Cl_2 (50 mL) was added TFA (24.6 mL, 320 mmol). To this was added Et_3SiH (12.7 mL, 80 mmol) dropwise from a syringe and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water and the aqueous layer was basified with solid Na_2CO_3. The organic layer was separated washed with brine and dried over K_2CO_3. The solution was filtered and the solvent was evaporated in vacuo. The residue was chromatographed on silica (50% to 90% EtOAc/hexane) to afford a colorless oil. This was treated with Et_2O·HCl to give the title compound (2.3 g, 93%) as a pale yellow solid: ^{1}H NMR (CD_3OD) δ 4.3 (s, 2H), 7.1 (s, 1H), 7.2 (s, 1H), 7.35 (m, 2H), 7.65 (d, 1H), 7.75 (d, 1H), 8.2 (s, 1H). Anal. ($C_{12}H_{10}N_2S$·HCl) C,H,N.

4-[(3-Methylthiophene-2-yl)ethyl]-1*H*-imidazole Hydrochloride (12b). Method J. To a solution of **8b** (10.1 g, 24.0 mmol) in THF (100 mL) under Ar was added MeMgBr (10.5 mL, 31.5 mmol), and the reaction was stirred at room temperature for 2 h. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (2×). The combined organic layers were washed with water and brine and then dried over Na_2SO_4. After filtering, the solvent was evaporated in vacuo. The residue was triturated with acetone to give the carbinol as an off-white solid. To a solution of TFA (58.5 mL, 0.76 mol) in CH_2Cl_2 (100 mL) cooled in an ice bath, was added BH_3·THF (380 mL, 0,38 mol) maintaining a temperature <10 °C. The mixture was stirred an additional 1 h after the addition was complete and then the carbinol was added in one portion. The reaction was stirred in an ice bath for 90 min and then quenched with water. The aqueous layer was basified with solid Na_2CO_3 and extracted with an additional portion of CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4. The mixture was filtered and the solvent evaporated in vacuo. The residue was dissolved in MeOH (100 mL) and 3 N HCl (25 mL) was added and the mixture was heated at reflux for 3 h. The solvent was evaporated in vacuo and the residue partitioned between water and Et_2O. The aqueous layer was washed with a second portion of Et_2O, and then basified and extracted with EtOAc. The extracts were dried over K_2CO_3, filtered and the solvent evaporated in vacuo. The residue was dissolved in Et_2O and treated with Et_2O·HCl to give a white solid which was recrystallized from acetone to give the product as a white crystalline solid (2.2 g, 40%): mp 164−166 °C; ^{1}H NMR (DMSO-d_6) δ 1.6 (d, 3H, J = 7 Hz), 2.2 (s, 3H), 4.6 (q, 1H, J = 7 Hz), 6.9 (d, 1H, J = 5 Hz), 7.3 (d, 1H, J = 5 Hz), 7.45 (s, 1H), 9.1 (s, 1H), 14.7 (s, 1H). Anal. ($C_{10}H_{12}N_2S$·HCl) C,H,N.

4-[(3,4-Dimethylthiophene-2-yl)ethyl]-1*H*-imidazole Fumarate (12d). Method K. To a solution of **8d** (2.0 g, 4.5 mmol) in THF (20 mL) was added MeMgBr in Et_2O(1.5 mL, 4.5 mmol) and the reaction was stirred overnight at room temperature. The reaction was quenched with aqueous NH_4Cl and the aqueous layer was extracted with an additional portion of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo and the residue triturated with EtOAc to give an off-white solid. The solid was combined with 1 N HCl (3.8 mL) and $Pd(OH)_2$ in EtOH and the mixture was hydrogenated at 50 °C, 50 psi for 24−48 h. The catalyst was removed by filtration and the solvent was evaporated in vacuo. The residue was chromatographed on silica (97.5/2.5 $CHCl_3$/10% NH_4OH in MeOH) to give the crude product. This was dissolved in 2-PrOH and treated with fumaric acid (1 equiv). The solvent was evaporated in vacuo and the residue was recrystallized from acetone to give the desired product (0.36 g, 25%) as a white solid: mp 127−129 °C; ^{1}H NMR (DMSO-d_6) δ 1.5 (d, 3H, J = 7 Hz), 2.05 (2s, 6H), 4.35 (q, 1H, J = 7 Hz), 6.65 (s, 2H), 6.8 (s, 1H), 6.9 (s, 1H), 7.6 (s, 1H). Anal. ($C_{11}H_{14}N_2S$·$C_4H_4O_4$) C,H,N.

4-[(3-Bromothiophene-2-yl)ethyl]-1*H*-imidazole Hydrochloride (12e). Method L. This was essentially the same procedure as method J except BH_3·Me_2S was used in place of BH_3·THF and the reaction was allowed to go overnight before quenching. The crude product was purified by chromatography (98:1:1 EtOAc:MeOH:NH_4OH). The appropriate fractions were combined and the solvent was evaporated in vacuo. The residue converted to the HCl salt (Et_2O·HCl) and recrystallized from MeCN to give a pale yellow solid: mp 185−188 °C; ^{1}H NMR (DMSO-d_6) δ 1.65 (d, 3H, J = 7 Hz), 4.6 (q, 1H, J = 7 Hz), 7.0 (d, 1H, J = 5 Hz), 7.5 (s, 1H), 7.6 (d, 1H, J = 5 Hz), 9.1 (s, 1H), 14.8 (br s, 1H). Anal. ($C_9H_9BrN_2S$·HCl) C,H,N.

4-[(4-Bromothiophene-3-yl)ethyl]-1*H*-imidazole Fumarate (21e). Method M. To a solution of **17e** (10.3 g, 20.0 mmol) in THF (150 mL) was added MeMgBr (3.0 M, 8 mL) and the reaction mixture was stirred at room temperature overnight. An additional 1.0 mL of MeMgBr was added and the reaction was stirred an additional 1 h and then quenched with aqueous NH_4Cl and extracted with EtOAc (2×). The combined extracts were washed with water and then brine and then dried over Na_2SO_4. The solution was filtered and the solvent was evaporated in vacuo and the residue was recrystallized from EtOAc to give a beige solid. To this solid (7.2 g, 14.0 mmol) was added Et_3SiH (45 mL, 280 mmol) and the reaction mixture was cooled to −10 °C (ice/MeOH). To this was added TFA (43 mL) and the reaction mixture was allowed to warm to room temperature overnight. The mixture was poured into 10% Na_2CO_3 and extracted with EtOAc (2×). The combined extracts were dried over K_2CO_3 and then filtered, and the solvent was evaporated in vacuo. The residue was chromatographed on silica starting with 60:39:1 and increasing to 50:49:1 CH_2Cl_2/EtOAc/10% NH_4OH in MeOH. The appropriate fractions were combined and the solvent was evaporated in vacuo. The residue was combined with 1 equiv of fumaric acid in 2-PrOH, the solvent was evaporated in vacuo and the residue was recrystallized from acetone to give a white solid (2.1 g, 40%): mp 137−139 °C; ^{1}H NMR (DMSO-d_6) δ 1.49 (d, 3H, J = 7.1 Hz), 4.1 (q, 1H, J = 7.1 Hz), 6.6 (s, 2H), 6.75 (s, 1H), 7.25 (d, 1H, J = 3.2 Hz), 7.65 (d, 1H, J = 3.2 Hz). Anal. ($C_9H_9BrN_2S$·$C_4H_4O_4$) C,H,N.

4-[(3-Bromothiophene-2-yl)methoxymethyl]-1*H*-imidazole Fumarate (14e). Method N. To a solution of **10e** (1.1 g, 2.2 mmol) in MeOH (25 mL) was added 5−6 drops of concentrated HCl and the mixture was heated at reflux overnight. The solvent was evaporated in vacuo. The residue was partitioned between water and Et_2O. The aqueous layer was washed with an additional portion of Et_2O and then basified with Na_2CO_3 and extracted with EtOAc. The extracts were dried over Na_2SO_4 and then filtered and the solvent was evaporated in vacuo. The residue was dissolved in 2-PrOH and treated with 1 equiv of fumaric acid. The solvent was evaporated in vacuo and the residue was recrystallized from acetone to give the title compound (0.30 g, 35%) as a white solid: mp 127.5−129.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.25 (s, 3H), 5.55 (s, 1H), 6.65 (s, 2H), 7.05 (m, 2H), 7.65 (m, 2H). Anal. ($C_9H_9N_2OS$·$C_4H_4O_4$) C, H, N.

***N*-Triphenylmethyl-4-[(3-methylthiophene-2-yl)ethylene]-1*H*-imidazole (24)**. To a solution of **8b** (4.2 g, 9.7 mmol) in THF (40 mL) under Ar was added MeMgBr (6.0 mL, 18 mmol), and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (2×). The combined organic layers

were washed with water and brine and then dried over Na_2SO_4. After filtering, the solvent was evaporated in vacuo. The residue was dissolved in toluene and TsOH (250 mg) was added and the mixture heated at reflux overnight. The solution was allowed to cool and then washed with water and brine and dried over Na_2SO_4. The solution was filtered and the filtrate was evaporated in vacuo. The residue was recrystallized from Et_2O to give the title compound as an off white solid (2.0 g, 48%): ^{1}H NMR ($CDCl_3$) δ 2.0 (s, 3H), 5.2 (d, 1H, $J = 2$ Hz), 6.1 (d, 1H, $J = 2$ Hz), 6.6 (s, 1H), 6.75 (d, 1H, $J = 5$ Hz), 7.1 (d, 1H, $J = 5$ Hz), 7.15 (m, 6H), 7.3 (m, 9H), 7.45 (s, 1H). Anal. ($C_{29}H_{24}N_2S\cdot 0.5H_2O$) C,H,N.

1-(*N*-Triphenylmethyl-1*H*-imidazol-4-yl)-1-(3-methylthiophene-2-yl)cyclopropane (25). To a solution of **24** (0.85 g, 2.0 mmol) in toluene (10 mL) were added CH_2I_2 (1.6 g, 6.0 mmol) and 1.1 M Et_2Zn (6.0 mL, 6.0 mmol) and the mixture was heated at 90 °C overnight. An additional 1.6 g of CH_2I_2 and 6.0 mL of Et_2Zn were added and the mixture again heated at 90 °C overnight. The reaction was quenched with saturated NH_4Cl and filtered. The aqueous layer was extracted with EtOAc (2×). The organic extracts were combined and dried over Na_2SO_4. The solution was filtered and the solvent was evaporated in vacuo to give the crude product. The residue was chromatographed on silica ($CHCl_3$) to give the title compound (0.3 g, 33%): ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 2H, $J = 2.5$ Hz), 1.5 (m, 2H), 2.0 (s, 3H), 6.2 (s, 1H), 6.65 (d, 1H, $J = 5$ Hz), 6.95 (d, 1H, $J = 5$ Hz), 7.1 (m, 6H), 7.22 (m, 9H). Anal. ($C_{30}H_{26}N_2S$) H,N; C: calcd, 80.68; found, 79.77.

1-(1*H*-Imidazolyl)-1-(3-methylthiophene-2-yl)cyclopropane (26). To a solution of **25** (0.55 g, 1.23 mmol) in MeOH (40 mL) was added 1 N HCl (3 mL) and the mixture was stirred at room temperature until the starting material had been consumed as judged by TLC. The solvent was evaporated in vacuo. The residue was dissolved in water and washed with Et_2O. The aqueous layer was basified with Na_2CO_3 and extracted with EtOAc. The combined extracts were dried over K_2CO_3 and then filtered and the filtrate was evaporated in vacuo. The residue was dissolved in 2-PrOH and combined with 1 equiv of fumaric acid. The solvent was evaporated and the residue was recrystallized from acetone to give the desired compound (0.17 g, 44%) as a tan soli: mp 151−155 °C; ^{1}H NMR (DMSO-d_6) δ 1.1 (d, 2H, $J = 3$ Hz), 1.35 (d, 2H, $J = 3$ Hz), 2.1 (s, 3H), 6.35 (s, 1H), 6.6 (s, 2H), 6.8 (d, 1H, $J = 5$ Hz), 7.2 (d, 1H, $J = 5$ Hz), 7.5 (s, 1H). Anal. ($C_{11}H_{12}N_2S\cdot C_4H_4O_4$) C,H,N.

(+)-4-[(3-Methylthiophene-2-yl)ethyl]-1*H*-imidazole Hydrochloride ((+)12b). To a solution of **(±)12b** (0.98 g, 5.1 mmol) in 2-PrOH was added a solution of dibenzoyl-L-tartaric acid (1 equiv) in 2-PrOH and the final volume was brought to 75 mL. After stirring overnight at room temperature the product was collected by filtration and then recrystallized from 2-PrOH (2×). The enantiomeric excess (ee) was measured by ^{1}H NMR in $CDCl_3$ to be >98% (the other enantiomer could not be detected) using 1 equiv of Mosher's acid. The salt was converted back to free base and the treated with $Et_2O\cdot$HCl to give the title compound (0.21 g) as a white solid: mp 167−169 °C; $[\alpha] = +45.8$ ($c = 1.0$, MeOH).

(+)-4-[(3-Bromothiophene-2-yl)ethyl]-1*H*-imidazole Hydrochloride ((+)12e). Same procedure as described above except started with racemic **12e**: $[\alpha] = +52.6$ ($c = 1.0$, MeOH). Anal. ($C_9H_9BrN_2S\cdot$HCl) C,H,N.

(−)-4-[(4-Bromothiophene-3-yl)ethyl]-1*H*-imidazole Fumarate ((−)21e). Racemic material was separated on a Chiracel AD column. Free base was combined with 1 equiv of fumaric acid in 2-PrOH and the solvent was evaporated in vacuo. The residue was recrystallized from acetone to give the title compound as a white solid: mp 132−134 °C; $[\alpha] = -3.6$ ($c = 1.0$, MeOH). Anal. ($C_9H_9BrN_2S\cdot C_4H_4O_4$) C,H,N.

Biological Methods. 1. In Vitro α_{2D} Adrenoceptor Binding Assay. Male Wistar rats (150−250 g, VAF; Charles River, Kingston, NY) were sacrificed by cervical dislocation and their brains removed and placed immediately in ice-cold HEPES-sucrose (10 mM HEPES, 300 mM sucrose, pH 7.4, 23 °C). Tissue from the cerebral cortex was dissected out and homogenized in 20 volumes of HEPES-sucrose in a Teflon-glass homogenizer. The homogenate was centrifuged at 1000*g* for 10 min, and the resulting supernatant centrifuged at 42000*g* for 10 min. The pellet was resuspended in 30 volumes of 3 mM potassium phosphate buffer, pH 7.5, preincubated at 25 °C for 30 min and recentrifuged. The pellet was resuspended as described above and used for the receptor binding assay. Incubation (20 min at 25 °C) was performed in test tubes containing phosphate buffer, 0.1 mL of the synaptic membrane fraction, tritiated *p*-aminoclonidine (0.1 nM) and test drug. The incubation was terminated by filtration of the tube contents through Whatman GF/B filter sheets on a Brandel cell harvester. Following washing of the sheets with 2 × 2 mL of cold 10 mM HEPES buffer (pH 7.5), the adhering radioactivity was quantified by liquid scintillation spectrometry.

Data Analysis. Data were analyzed using LIGAND, a nonlinear curve-fitting program designed specifically for the analysis of ligand binding data.[15] Nonspecific binding was computed by LIGAND as a fitted parameter. The K_i values were derived from single-site models of the data, which in each case provided the best fit. Each concentration curve included 8−10 concentrations of the investigational compound, each concentration run in triplicate. Replicate determinations of the inhibition constants usually differed from each other by less than 10%.

2. In Vivo Studies: Animals. Male 18−24 g pathogen-free albino CD-1 mice (Charles River Laboratories, Kingston Facility, Stone Ridge, NY) were maintained in a climate-controlled room on a 12-h light/dark cycle (lights on at 06:00 h) with food and water available ad libitum up to the time of the test. All tests were performed in accordance with the recommendations and policies of the International Association for the Study of Pain (IASP), the National Institutes of Health (NIH), and Johnson & Johnson guidelines for the use of laboratory animals.

3. Acetylcholine-Induced MAIT. The procedure with minor modifications was that described by Collier.[16] Test compounds or appropriate vehicle was administered po by gavage, and at specified intervals later, the animals received an ip injection of 5.5 mg/kg of acetylcholine bromide. The mice were then placed into large glass bell jars and observed for the occurrence a response to the noxious stimulus such a writhing. The percent inhibition of this response (equal to percent antinociception) was calculated for each dose as follows: % antinociception = 100 × (no. of responders)/(no. of mice in group). The ED_{50} value (dose of agonists that produced 50% antinociception) and the corresponding 95% confidence intervals were determined using the probit anaylsis of Litchfield and Wilcoxon,[17] including a χ-square test for linearity.

4. Rat Cardiovascular EKG (ΔQT). Pathogen-free, normotensive male albino Long-Evans rats (350−450 g at time of testing) were purchased from Charles River Laboratories (Raleigh, NC) and were maintained on a 12-h light/dark cycle (lights on at 06:00 h) in climate-controlled room with food and water available ad libitum until the time of the testing. All housing, treatment, and testing were in accordance with the recommendations and policies of the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals.

5. Cardiovascular Tests. The rats were anesthetized using sodium pentobarbital injection (50 mg/kg ip) and were allowed to respire spontaneously. Body temperature was monitored by rectal thermometer and maintained constant under a heat lamp equipped with feedback control. A midline incision was made in the upper abdominal area and a thread was placed under the duodenum for the convenience of drug administration. The carotid artery was isolated and cannulated for measurement of arterial blood pressure. The surface electrocardiogram was recorded using standard limb leads II. Mean arterial pressure, pulse pressure, heart rate and EKG parameters (including QT interval) were measured using an MI^2 (Malvern, PA) data acquisition system and Biowindows software. The rats were allowed to acclimate for 5−20 min after being instrumented and then α_2 agonist or vehicle was directly

injected into the duodenum by 1-mL syringe with 26th gauge needle. The total volume of solution injected was around 0.5 mL. The α_2 adrenoceptor agonist doses were 1-, 3-, or 10-fold the ED_{50} in the analgesic test described above. Three doses were injected intraduodenum at 0, 20, and 40 min separately. The cardiovascular parameters were then monitored from drug-treated rats ($n = 3-5$) and vehicle-treated rats ($n = 3-5$) continuously for 60 min.

Supporting Information Available: Analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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