Articles

α_2 Adrenoceptor Agonists as Potential Analgesic Agents. 1. (Imidazolylmethyl)oxazoles and -thiazoles

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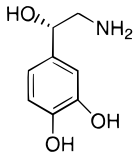
A series of (imidazolylmethyl)oxazoles and -thiazoles were prepared and evaluated as α_2 adrenoceptor agonists. These compounds were also tested in in vivo paradigms that are predictive of analgesic activity. Variations in both the imidazole and thiazole portions of the molecule were investigated. Some of the more potent compounds such as **22**, **26**, **45**, and **53** displayed α_2 receptor binding in the 10−20 nM range and also had significant antinociceptive activity in the mouse abdominal irritant test (MAIT).

Introduction

Unrelieved pain continues to be a medical problem and, hence, research on new analgesic agents occupies a prominent position in the pharmaceutical industry. The design of compounds that interact with receptors that mediate the effects of opioids (morphine-like compounds) represents one approach. Another is the design of compounds directed at nonopioid receptor mechanisms. Compounds that act as agonists at α_2-adrenoceptors for which norepinephrine (**1**) is the endogenous ligand produce antinociception in animals (and analgesia in humans[1]) with reduced risk of the abuse liability or side effects typically associated with opioids.[2] Recently developed compounds such as medetomidine (**2**) and the more potent (+)-enantiomer dexmedetomidine (**3**) have been shown to have analgesic effects.[3] These compounds bind with high affinity to the α_2-adrenergic receptor and are very potent in a number of in vivo analgesic paradigms. However, a number of unwanted side effects such as sedation, have limited the usefulness of these compounds.



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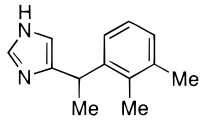

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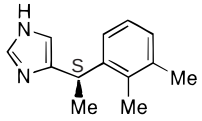

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There has recently been some indication that adrenergic receptor subtype selectivity may be key in the separation of side effects from analgesia.[4] Adrenoceptors were first recognized by Ahlquist as divided into two types (designated as α and β), based on different rank orders of potency for a series of adrenergic compounds in different physiological functions.[5] The β-adrenoceptor category subsequently has been subdivided further and subtype-selective agents became clinically useful as antihypertensives (β_1 blockers, such as metoprolol) and in asthma therapy (β_2 agonists, such as terbutaline).[6] Subtypes of α-adrenoceptors were identified in 1974 and were designated α_1 and α_2.[7] Further subdivision has been prompted by the results of in vivo and in vitro studies.[8] All of the adrenoceptors are members of the seven-transmembrane G protein-coupled superfamily and mediate their effects, including antinociception, through a variety of second messenger systems, including adenylate cyclase and phosphatidyl inositide pathways.[9] Pertussis toxin, which ADP-ribosylates a Cys residue in the α subunit of G_i proteins, attenuates α_2-adrenoceptor-induced antinociception.[10] In addition, α_2-adrenoceptor agonists increase membrane conductance of K^+ (a mechanism that might result in inhibition of neurotransmitter release), and in vivo studies have demonstrated that glibenclamide (a blocker of ATP-dependent K^+ channels) antagonizes the antinociception induced by α_2-adrenoceptor agonists.[11] It has been proposed that α_2-adrenoceptor-mediated antinociception might result from the inhibition of release of primary afferent neurotransmitters (e.g., substance P and glutamate) at synapses within the spinal cord. The association of antinociception with α_2-adrenoceptors has been demonstrated in vivo by Takano and Yaksh,[12] who reported that clonidine- and dexmedetomidine-induced antinociception in rats was antagonized by the α_2-adrenoceptor antagonists idazoxan, yohimbine, and

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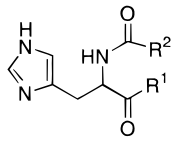
Table 1. Chemical Data for Amidoketones



entry	R^1	R^2	recrys. sol.[a]	% yield	formula	mp (°C)
5	Me	Me	Acn	27[b]	$C_9H_{13}N_3O_2$	141−144
6	Et	Et	Ac	53[b]	$C_{11}H_{17}N_3O_2$	112.5−113.5
7	*n*-Pr	*n*-Pr	Ac	53[b,c]	$C_{13}H_{21}N_3O_2 \cdot HNO_3$	99.5−100.5
8	*i*-Pr	*i*-Pr	EA	38	$C_{13}H_{21}N_3O_2$	135.5−137.5
9	*n*-Bu	*n*-Bu	Acn	53[b]	$C_{15}H_{25}N_3O_2$	107−109.5
11	Et	Me		71	$C_{10}H_{15}N_3O_2$[d]	
12	Et	*n*-Pr	Ac/EA	53	$C_{12}H_{19}N_3O_2$	107−108
13	Et	*i*-Pr	Ac	67	$C_{12}H_{19}N_3O_2$	146−147
14	Et	CF_3	Ac/Et	13	$C_{10}H_{12}F_3N_3O_2$	122.5−123.5
15	Me	Et		57	$C_{10}H_{15}N_3O_2$[d]	
16	*n*-Pr	Et	Ac/Et	25	$C_{12}H_{19}N_3O_2$	120−122
17	*i*-Pr	Et	Ac	48	$C_{12}H_{19}N_3O_2 \cdot HNO_3$	117−118

[a] Solvents: Ac = acetone; Acn = acetonitrile; EA = ethyl acetate; Et = diethyl ether. [b] No DMAP used in reaction. [c] Product isolated as HNO_3 salt. [d] Products were difficult to purify and were therefore carried on directly to the next step.

atipamezole but not by the α_1-adrenoceptor antagonist prazosin. The α_2-adrenoceptors are further subdivided into α_{2A} (gene/chromosome ADRA2A/10q2325; also designated α_2-C-10), α_{2B} (ADRA2A/2; α_2-C-2) and α_{2C} (ADRA2A/4; α_2-C-4). The α_{2A} subtype has relatively low affinity for prazosin and for ARC-239 2-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-4,4-dimethyl-1,3(2*H*,4*H*)-isoquinolinedione, whereas α_{2B} and α_{2C} subtypes have relatively high affinity for prazosin and ARC-239. Species variation gives rise to α_{2A} subtype orthologues. The α_{2D} receptor is a rat orthologue of the human α_{2A} adrenoceptor. Millan and colleagues[13] have further suggested that the $\alpha_{2A/D}$ subtype is primarily responsible for the antinociceptive effect, and genetically modified mice lacking functional $\alpha_{2A/D}$ receptor are not responsive to α_2-agonist-mediated analgesia. A "hit and run" gene targeting model also suggests that the relevant subtype that mediates the antinociceptive response is the $\alpha_{2A/D}$-adrenoceptor subtype.[14]

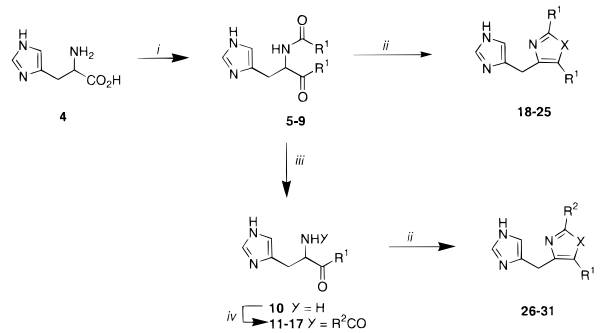
In this paper we describe the synthesis of a number of imidazole compounds and the evaluation of selected compounds for analgesic activity. A number of dialkyl thiazole analogues were effective in a broad range of antinociceptive paradigms and far less sedating in dogs than the other compounds tested.

Chemistry

The initial targets in this series were prepared as shown in Scheme 1.[15] Reaction of histidine (**4**) with an acid anhydride in the presence of a base[16] afforded the desired amidoketones (**5**−**9**; Table 1). Cyclization of these intermediates was carried out with the appropriate anhydride to give the symmetrically substituted oxazoles **18**−**20**. Compound **20** was isolated directly from the Dakin-West reaction mixture. The corresponding thiazoles **21**−**25** were obtained by cyclization of the amidoketone with Lawesson's reagent in refluxing $CHCl_3$ or toluene.

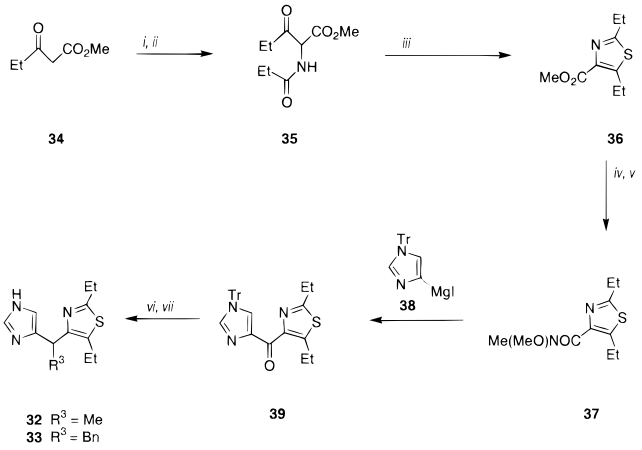
Targets with unsymmetrical alkyl substitution were prepared by acid hydrolysis of the amidoketone to give aminoketone **10**. These compounds were often difficult to isolate and purify and therefore were taken without purification and treated with an acid anhydride in the presence of NEt_3 to afford unsymmetrical amidoketones **11**−**17**. These amidoketones were cyclized with Lawesson's reagent to afford thiazoles **26**−**31**.

Scheme 1[a]



[a] Reagents: (i) $(R^1CO)_2O$, R^1CO_2H, DMAP. (ii) $(R^1CO)_2O$ or $POCl_3$ (X = O); Lawesson's reagent: (X = S). (iii) 6 N HCl. (iv) $(R^2CO)_2O$, NEt_3.

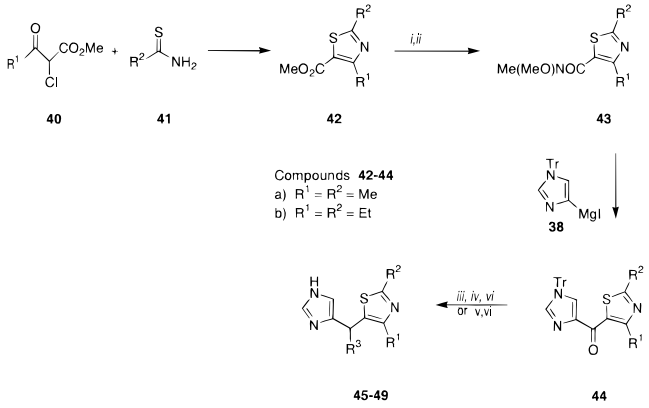
Scheme 2[a]



[a] Reagents: (i) $NaNO_2$, HCl. (ii) H_2, $(R^2CO)_2O$. (iii) P_4S_{10}. (iv) 6N HCl. (v) $SOCl_2$, HNMe(OMe). (vi) MeMgBr or BnMgBr. (vii) $Pd(OH)_2$, H_2.

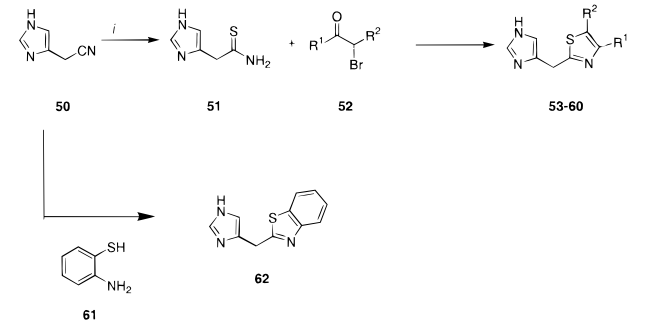
An alternate route that allowed for the incorporation of alkyl substitution at the methylene bridge is shown in Scheme 2. Nitrosation of *β*-ketoester **34** followed by catalytic reduction of the oxime in the presence of an acid anhydride gave amidoketoester **35**. This was cy-

Scheme 3[a]



[a] Reagents (i) 3N NaOH; H^+. (ii) CDI, HNMe(OMe) or $(COCl)_2$, HNMe(OMe). (iii) MeOH/HCl. (iv) $NaBH_4$. (v) R^3MgBr. (vi) HCl, $Pd(OH)_2$, H_2.

Scheme 4[a]

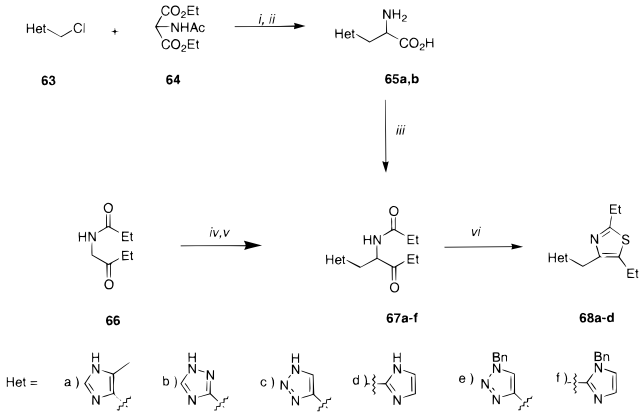


[a] Reagents: (i) HCl, $MeCSNH_2$.

clized with P_4S_{10} to give thiazole ester **36** in good yield. Hydrolysis of **36** afforded the carboxylic acid, which was quite insoluble in organic solvents. Consequently the reaction with carbonyldiimidazole (CDI) and *N*,*O*-dimethylhydroxylamine gave only a modest yield of Weinreb amide **37**. Addition of **37** to the Grignard reagent prepared from *N*-trityl-4-iodoimidazole[17] (**38**) afforded a good yield of **39**. Branched compounds such as **32** and **33** were obtained by addition of a Grignard reagent to give the tertiary carbinol, followed by hydrogenation with Pearlman's catalyst [$Pd(OH)_2$].

To further explore the SAR of these compounds, the 5-thiazole and 2-thiazole isomers were prepared as shown in Schemes 3 and 4, respectively. The synthesis of 5-thiazolecarboxylates has been documented in the literature.[18] Accordingly, 2-chloroketoester **40** and thioamide **41** were reacted in EtOH to give thiazole ester **42**. Conversion to the Weinreb amide **43** and addition of the imidazole Grignard reagent **38** afforded the tritylated imidazole ketone **44**. After removal of the trityl protecting group with HCl/MeOH, these ketones were reduced in a two-step process of $NaBH_4$ in refluxing 2-PrOH, followed by catalytic hydrogenation to give the unsubstituted methylene compounds. Alternatively, the addition of a Grignard reagent to **44**, followed by reduction and deprotection, afforded targets that were substituted on the methylene bridge. The 2-thiazole targets were prepared from imidazolylacetonitrile **50**[19] that was converted to thioamide **51** by reaction with HCl and thioacetamide in DMF.[20] Cyclization of this thioamide with an α-bromoketone **52** gave the 2-thiazolyl targets **53**−**60**, although the yields were quite variable.

Scheme 5[a]



[a] Reagents: (i) NaH, DMF. (ii) 6 N HCl. (iii) $(EtCO)_2O$, $EtCO_2H$, pyridine, DMAP. (iv) NaH, **63e** or **63f**. (v) $H_2/Pd(OH)_2$. (vi) P_4S_{10}.

The synthesis of the requisite regiospecific α-bromoketones has recently been reported from this laboratory.[21] Benzothiazole **62** was prepared, albeit in low yield, from imidazolylacetonitrile and 2-aminothiophenol.

Finally, we wanted to explore variations in the imidazole portion of the molecule. The synthesis of these compounds is shown in Scheme 5. The first approach was to prepare the appropriate histidine analogue such as **65a**,[22] followed by a Dakin-West reaction to provide the requisite amidoketone. Yields of these intermediates, however, were quite poor and an alternative route was explored. The anion of ketoamide **66** was alkylated with a benzyl-protected heteroarylmethyl chloride to furnish the protected amidoketone. Debenzylation of these compounds was accomplished by catalytic hydrogenation with Pearlman's catalyst [$Pd(OH)_2$]. Finally, the target compounds were obtained by cyclization of these intermediates to thiazoles as previously described.

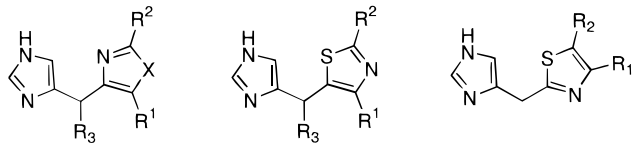
Biological Results and Discussion

Following the identification of the initial lead structure, diethyloxazole **19**, a number of other oxazole and thiazole analogues were prepared and evaluated in the rat $\alpha_{2A/D}$ radioligand binding assay (Table 2). Evaluation in vivo was based on the fact that α_2-adrenoceptor agonists are known to produce potent, dose-dependent analgesia in a variety of tests across species.[23] The mouse abdominal irritant test (MAIT) was selected for the present study because it is well established as a model sensitive to spinal, supraspinal,[24] and peripherally[25] mediated adrenergic antinociception. The results of this testing are also shown in Table 2. The antinociceptive activity of several of the novel compounds shown is blocked by preadministration of the α_2-adrenoceptor antagonist idazoxan (data not shown), supporting adrenergic mediation of the antinociception observed.

The data reveal that the thiazoles generally bind to the α_2-adrenoceptor with higher affinity than the corresponding oxazoles. For example, thiazoles **22** and **24** had 2−3-fold higher affinities than oxazoles **19** and **20**. For this reason, additional targets were designed to focus on the thiazole moiety.

Longer chain alkyl groups, such as in the di-*n*-Pr and di-*n*-Bu thiazoles (**23** and **25**, respectively), resulted in a modest reduction in $\alpha_{2A/D}$ binding. The di-*i*-Pr side chain compound **24** had a more dramatic effect on this

Table 2. Chemical and Biological Data for (Imidazolylmethyl)oxazoles and -thiazoles



18-33 **45-49** **53-61**

compd	R^1	R^2	R^3	X	% yield	recrys. sol.[a]	formula	mp	$\alpha_{2A/D}$ K_I[b] (nM)	MAIT (ED_{50})[c] mpk
18[d]	Me	Me	H	O					>1000	>30
19	Et	Et	H	O	60	Ac	$C_{11}H_{15}N_3O\cdot HCl\cdot H_2O$	79−81	58	2.8 (2.0, 3.8)
20	*i*-Pr	*i*-Pr	H	O	42[e]	Acn	$C_{13}H_{19}N_3O\cdot HNO_3$	130−131	714	6.9 (3.5, 14.7)
21	Me	Me	H	S	39	Ac	$C_9H_{11}N_3S\cdot 1.5C_4H_4O_4$[f]	163−164	38	>30
22	Et	Et	H	S	48	Ac	$C_{11}H_{15}N_3S\cdot HNO_3$	102−103	17	1.8 (1.3, 3.1)
23	*n*-Pr	*n*-Pr	H	S	57	EA/Ac	$C_{13}H_{19}N_3S\cdot HNO_3$	84−85	97	30.0 (15.3, 48.9)
24	*i*-Pr	*i*-Pr	H	S	46	Ac/Et	$C_{13}H_{19}N_3S\cdot HNO_3$	136−137	285	23.8 (23.8, 155.9)
25	*n*-Bu	*n*-Bu	H	S	53[c]	Ac/Et	$C_{15}H_{23}N_3S\cdot 2HNO_3$	88−89	35	>30
26	Et	Me	H	S	37	Ac	$C_{10}H_{13}N_3S$	145−146	10	2.3 (1.1, 4.1)
27	Et	*i*-Pr	H	S	52[d]	Ac/Et	$C_{12}H_{17}N_3O\cdot HNO_3$	118.5−119	28	7.5 (4.9, 10.4)
28	Me	Et	H	S	21	Et	$C_{10}H_{13}N_3S$	86−87	57	>30
29	*i*-Pr	Et	H	S	49	Ac/Et	$C_{12}H_{17}N_3O\cdot HNO_3$	112−114	235	25.3 (12.7, 46.4)
30	Et	CF_3	H	S	20[g]	Ac/Et	$C_{10}H_{10}F_3N_3S\cdot HNO_3$[h]	140.5−141	320	20.3 (9.8, 35.5)
31	Et	Ph	H	S	55[g]	Acn	$C_{15}H_{15}N_3S\cdot HCl$	202−204	13	15.0 (8.8, 25.2)
32	Et	Et	Me	S	42	Ac	$C_{12}H_{17}N_3S\cdot C_4H_4O_4$	139−141	407	16.0 (8.8, 40.0)
33	Et	Et	Bn	S	18	Acn	$C_{18}H_{21}N_3S\cdot HCl$	185−188	37	>30
45	Me	Me	H	S	76	Acn	$C_9H_{11}N_3S\cdot HCl$[i]	201−203	8	1.0 (0.6, 1.5)
46	Me	Me	Me	S	42	Acn	$C_{10}H_{13}N_3S\cdot HCl$	194−196	60	>30
47	Me	Me	Ph	S	5	Et	$C_{15}H_{15}N_3S$	169−171	269	>30
48	Et	Et	H	S	36	Ac	$C_{11}H_{15}N_3S\cdot HCl$	139−141	23	>30
49	Et	Et	Me	S	10	EA	$C_{12}H_{17}N_3S\cdot C_4H_4O_4\cdot 0.5H_2O$	94−97	97	>30
53	Me	Me	H	S	66	Acn	$C_9H_{11}N_3S\cdot 1.3HCl\cdot 0.3H_2O$	188−200	11	1.7 (1.1, 2.4)
54	Et	Me	H	S	23	Ac	$C_{10}H_{13}N_3S\cdot_{1.5}C_4H_4O_4$	154−157	18	>30
55	Me	Et	H	S	59	Ac	$C_{10}H_{13}N_3S\cdot HCl\cdot H_2O$	90−98	18	2.8 (1.8, 3.8)
55	Et	Et	H	S	33	Ac	$C_{11}H_{15}N_3S\cdot C_4H_4O_4$	109−111	86	>30
57	Et	H	H	S	44	Ac	$C_9H_{11}N_3S\cdot C_4H_4O_4$	133−134	36	>30
58	H	Et	H	S	3	Ac	$C_9H_{11}N_3S\cdot C_4H_4O_4\cdot 0.25H_2O$[j]	90−95	381	>30
59	-$(CH_2)_3$-		H	S	33	Ac	$C_{10}H_{11}N_3S\cdot 1.5C_4H_4O_4$[k]	168−170	28	>30
60	-$(CH_2)_4$-		H	S	10	IP	$C_{11}H_{13}N_3S\cdot 1.5C_4H_4O_4$	169−171	110	>30
62	-$(CH)_4$-		H	S	11	Ac	$C_{11}H_9N_3S\cdot 1.5C_4H_4O_4$	186−187	18	>30
3									0.015	0.09

[a] Solvents; see Table 1. IP is isopropanol. [b] K_i values are determined in duplicate and generally agree within 10%. [c] Values expressed are ED_{50} (95% confidence limit). Compounds with <50% inhibition at the screening dose of 30 mpk are recorded as >30. [d] Reference 15. [e] Isolated from Dakin-West reaction. [f] N, Calcd, 11.44; Found, 11.90. [g] Toluene used as solvent. [h] N, Calcd, 17.28; Found, 17.78. [i] H, Calcd, 4.83; Found, 5.25. [j] N, Calcd, 13.39; Found, 12.95. [k] N, Calcd, 4.52; Found, 4.10.

binding, and all three analogues had significantly less in vivo activity than the diethyl compound. It would also appear from these data that R^1 = Et is a key element of the α_2 pharmacophore. For example, when the R^1 group is Et, substitution of Me or *i*-Pr for R^2 (compounds **26** and **27**) has only minor effects on in vitro and in vivo activity. The reverse situation (compounds **28** and **29**), in which R^2 = Et and R^1 is Me or *i*-Pr, resulted in a more dramatic decrease in binding and biological activity. The substitution of an electron-withdrawing group such as CF_3 or a phenyl group at the R^2 position, such as in **30** and **31**, respectively, significantly diminishes MAIT activity. There is also a significant decrease in MAIT activity for compounds **32** and **33** in which the methylene bridge is substituted with Me or Bn.

The orientation of the thiazole ring appears to be moderately important for biological activity. In the 5-thiazole series, for example, the dimethyl analogue **45** has good in vivo activity, while the diethyl thiazole **48** has very little antinociceptive activity. This contrasts with the 4-thiazole series, in which the diethyl compound was the most potent analogue. Once again for this series, any substitution on the methylene bridge such as compounds **46**, **47**, and **49** results is a significant loss of biological activity. It is also noteworthy that most of the compounds in the 2-thiazole series had little or no antinociceptive activity despite their high affinity for the $\alpha_{2A/D}$ adrenoceptor. The MAIT activity of compounds **53** and **55** would seem to indicate that R^1 = Me is a necessary criterion for the pharmacophore, and any variation in R^1, such as either H or Et (**54, 57**, and **58**), resulted in a significant loss of activity, $\alpha_{2A/D}$ binding, or both. It is also noteworthy that incorporation of these alkyl groups into a five- or six-membered ring (**59**, **60**, and **62**) also results in loss of antinociceptive activity. Moreover, in vivo studies with several of these compounds (e.g., **57**, **59**, **60**, and **62**) revealed that they attenuate the antinociceptive action of the α_2-adrenergic agonist clonidine (data not shown), suggesting their antagonist function.

Finally, the importance of the imidazole portion of the molecule was investigated. The thiazole portion was held constant as the 2,5-diethylthiazol-4-yl and the methylene bridge was unsubstituted. These results are shown in Table 3. It can be seen from these data that any variation in this portion of the molecule results in

Table 3. Chemical and Biological Data for Imidazole Isosteres

entry	% yield	formula	mp (°C)	$\alpha_{2A/D}$ K_i (nM)	MAIT (ED_{50})
68a	14	$C_{12}H_{17}N_3S \cdot HNO_3$	125.5−127	53	
68b	12	$C_{10}H_{14}N_4S \cdot HNO_3$	102−104	>1000	>30
68c	24	$C_{10}H_{14}N_4S$	63.5−65	>1000	>30
68d	7	$C_{11}H_{15}N_3S \cdot C_4H_4O_4$	153−155	>1000	>30

a drastic reduction in receptor binding and antinociceptive activity.

Conclusion

We have prepared and evaluated a series of (imidazolylmethyl)oxazoles and -thiazoles. Several of these compounds possess significant $\alpha_{2A/D}$ adrenoceptor binding affinity and in vivo antinociceptive activity in mice. The importance of the 4-imidazole moiety has been clearly demonstrated and only small alkyl side chains are permitted in order to maintain biological activity. In particular, compounds **22**, **26**, **45**, and **53** were efficacious in an animal model predictive of analgesic activity. While some safety issues precluded the development of any of these compounds as a clinical candidate, we were encouraged to pursue other structural types in this general area and the results of these studies will be reported in due course.

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 analysis were within 0.4% of the calculated value, except where indicated. $Et_2O \cdot NHO_3$ is prepared by adding a few drops of concentrated nitric acid to diethyl ether.

General Procedures for the Synthesis of Amidoketones: *N*-[1-(1*H*-Imidazol-4-yl)-3-oxo-4-methyl-2-pentyl]-2-methylpropanamide (8). A mixture of histidine hydrochloride hydrate (10.5 g, 0.05 mol), anhydrous sodium isobutyrate (8.3 g, 0.075 mol), isobutyric anhydride (55.4 g, 0.35 mol), and 0.1 g of (dimethylamino)pyridine (DMAP) was heated at 115−120 °C for 4 h. The mixture was cooled in an ice bath and diluted with Et_2O (300 mL). The organic layer was extracted with 3 N HCl (3×) and then water. The combined aqueous layers were washed once with Et_2O and then made basic with cold NaOH and extracted with $CHCl_3$ (3×). The extracts were combined, dried over K_2CO_3, and filtered and the solvent was evaporated in vacuo. The residue was recrystallized from EtOAc to give the title compound as a free base (4.8 g. 38%). ^{1}H NMR (DMSO-d_6) δ 0.95 (m, 12H), 2.4 (m, 1H), 2.8 (m, 2H), 2.95 (m, 1H), 4.7 (m, 1H), 6.75 (s, 1H), 7.55 (s, 1H), 8.15 (d, 1H), 11.8 (br s, 1H). Anal. ($C_{13}H_{21}N_3O_2$) C, H, N.

***N*-[1-(5-Methyl-1*H*-imidazol-4-yl)-3-oxo-2-pentyl]propanamide (67a).** A mixture of 5-methylhistidine (15.0 g, 58 mmol), NEt_3 (30 mL), propionic anhydride (30 mL), and DMAP (0.15 g) was heated in an oil bath at 90−100 °C. After the vigorous reaction and CO_2 evolution had subsided, the mixture was heated for an additional 1 h at 100 °C and then cooled to room temperature. Propionic anhydride (50 mL) was added and the mixture was stirred at room temperature for 1 h and then was evaporated in vacuo. The residue was dissolved in 3 N NaOH and extracted with $CHCl_3$ (3×). The combined extracts were washed with dilute NaOH and water and then dried over Na_2SO_4. The solution was filtered, the solvent was evaporated in vacuo, and the residue was recrystallized from EtOAc to give the title compound (5.0 g, 36%) as a light yellow solid. ^{1}H NMR δ ($CDCl_3$) 0.85 (t, 3H), 0.95 (t, 3H), 2.0 (s, 3H), 2.1 (m, 2H), 2.3 (m, 2H), 2.75 (m, 2H), 4.4 (q, 1H), 7.4 (s, 1H), 8.15 (d, 1H), 11.7 (br s, 1H). Anal. ($C_{12}H_{19}N_3O_2$) C, H, N. C: Calcd, 60.74; Found, 59.73.

2-Amino-1-(1*H*-imidazol-4-yl)pentan-3-one Dihydrochloride (10). A solution of **6** (19.5 g, 0.1 mol) in 6 N HCl (35 mL) was heated at reflux for 90 min. The solvent was evaporated in vacuo and the residue was triturated with acetone and then 2-PrOH to give an off-white solid (R^1 = Et; 3.8 g, 79%), which was pure enough to be used without further purification. ^{1}H NMR (DMSO-d_6) δ 1.0 (t, 3H), 2.7 (m, 2H), 3.2 (m, 1H), 3.4 (m, 1H), 4.6 (m, 1H), 7.5 (s, 1H), 8.6 (br s, 2H), 9.1 (s, 1H), 14.5 (br s, 1H).

***N*-[1-(1*H*-Imidazol-4-yl)-3-oxo-2-pentyl]-2-methylpropanamide (13).** To a mixture of aminoketone **10** (R^1 = Et) (3.6 g, 15 mmol) and butyric anhydride (9.5 g, 60 mmol) in $CHCl_3$ (40 mL) was added NEt_3 (4.0 g, 40.0 mmol) in $CHCl_3$ (10 mL). The mixture was stirred for 2 h at room temperature and then poured into ice−water and stirred for 2 h to decompose the excess anhydride. The aqueous solution was basified with Na_2CO_3 and extracted with $CHCl_3$. The extracts were combined and dried over K_2CO_3. The solution was filtered and the solvent was evaporated in vacuo to give a crude solid, which was recrystallized from acetone to give the title compound (2.4 g, 67%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 0.9 (m, 3H), 1.0 (m, 6H), 2.45 (m, 3H), 2.8 (m, 1H), 2.9 (m, 1H), 4.45 (q, 1H), 6.8 (s, 1H), 7.55 (s, 1H), 8.2 (d, 1H), 11.85 (br s, 1H). Anal. ($C_{12}H_{19}N_3O_2$) C, H, N.

***N*-[1-[1-Benzyl-1,2,3-(1*H*)-triazol-5-yl]-3-oxo-2-pentyl]-propanamide (67e).** NaH (80% mineral oil, 6.75 g, 0.225 mol) was washed with hexane (2×) and then suspended in DMF (200 mL) and cooled to −20 °C in an ice/salt/water bath. To this was added ketoamide **66** (32.1 g, 0.225 mol) in portions, with the temperature maintained below 5 °C. The mixture was stirred for an additional 30 min, and then a solution of **63e** (22.3 g, 0.09 mol) in DMF (100 mL) was added dropwise and the reaction was allowed to stir and slowly warm to room temperature overnight. Most of the DMF was evaporated in vacuo (40−50 °C), and the residue was dissolved in dilute HCl and washed with Et_2O (2×). The solution was made basic and extracted with EtOAc (2×). The extracts were combined and dried over K_2CO_3. The solution was filtered and the solvent was evaporated in vacuo. The residue was chromatographed on silica ($CHCl_3$/MeOH/NH_4OH 98/1.8/0.2) and the residue was recrystallized from acetone/Et_2O to give the title compound (7.4 g, 26%) as a white solid, mp 95.5−97 °C. ^{1}H NMR (DMSO-d_6) δ 1.0 (t, 3H), 1.1 (t, 3H), 2.25 (m, 2H), 2.55 (m, 2H), 3.15 (m, 2H), 4.8 (q, 1H), 5.5 (s, 2H), 6.85 (d, 1H), 7.3 (m, 6H). Anal. ($C_{17}H_{22}N_4O_2$) C, H, N. N: Calcd, 17.82; Found, 18.26.

***N*-[1-(1*H*-1,2,3-Triazol-4-yl)-3-oxo-2-pentyl]propanamide (67c).** To a solution of **67e** (7.3 g, 23 mmol) in MeOH (50 mL) was added $Pd(OH)_2$ (1.5 g) and the mixture was hydrogenated at 50 °C and 55 psi until H_2 uptake had stopped. The solution was filtered through dicalite and the solvent was evaporated *in vacuo*. The residue was recrystallized from Et_2O to give the title compound (3.4 g, 67%) as a white solid, mp 82.5−84 °C. ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H), 1.15 (t, 3H), 2.25 (q, 2H), 2.6 (m, 2H), 3.2 (m, 2H), 4.95 (q, 1H), 6.75 (br s, 1H), 7.5 (s, 1H), 12.85 (br s, 1H). Anal. ($C_{10}H_{16}N_4O_2$) C, H, N. H: Calcd, 7.19; Found, 7.70.

General Procedures for the Synthesis of 4-Oxazoles and 4-Thiazoles: 4-[(2,5-Diethyloxazol-4-yl)methyl]-1*H*-imidazole Hydrochloride Hydrate (19). Amidoketone **9** (6.7 g, 30.0 mmol) was converted to the HCl salt and then heated at reflux in propionic anhydride (25 mL) for 90 min. The mixture was cooled and diluted with Et_2O and the crude product was collected by filtration. The residue was recrystallized from 1% aqueous acetone to give the title compound (4.7 g, 60%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.2 (m, 6H), 2.7 (m, 4H), 3.85 (s, 2H), 7.4 (s, 1H), 9.0 (s, 1H), 14.5 (br s, 1H). Anal. ($C_{11}H_{15}N_3O \cdot HCl \cdot H_2O$) C, H, N.

4-[[2,5-Di(1-methylethyl)thiazol-4-yl]methyl]-1*H*-imidazole Nitrate (24). A solution of **8** (3.77 g, 15.0 mmol) and Lawesson's reagent (9.1 g, 22.5 mmol) in $CHCl_3$ (100 mL) was

heated at reflux overnight. The reaction mixture was cooled and then extracted with dilute HCl (2×) and then water (1×), and the aqueous extracts were combined and washed with Et_2O. The solution was then basified and extracted with Et_2O (2×). The organic extracts were combined, dried over K_2CO_3, and filtered and the solvent was evaporated in vacuo. The residue was dissolved in EtOAc and treated with $Et_2O{\cdot}HNO_3$. The solid was collected and recrystallized from acetone to give the title compound (2.2 g, 46%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 1.2 (m, 6H),1.35 (d, 6H), 3.2 (m, 2H), 4.1 (s, 2H), 7.0 (s, 1H), 8.6 (s, 1H). Anal. ($C_{13}H_{19}N_3S{\cdot}HNO_3$) C, H, N.

4-[(2,5-Dimethylthiazol-4-yl)methyl]-5-methyl-1*H*-imidazole Nitrate (68a). A mixture of amidoketone **67a** (3.5 g, 15 mmol) and P_4S_{10} (6.5 g, 15 mmol) in $CHCl_3$ (50 mL) was heated at reflux for 3 h. The reaction mixture was diluted with Et_2O and dilute NaOH. The aqueous layer was extracted with two additional portions of Et_2O. The organic layers were combined, washed sequentially with dilute NaOH and brine, and then dried over K_2CO_3. The solution was filtered and the solvent was evaporated in vacuo. The residue was chromatographed on silica (EtOAc/MeOH/NH_4OH 98/2/2) to give the crude product. The residue was dissolved in EtOAc and treated with $Et_2O{\cdot}HNO_3$. A white solid was filtered and recrystallized from acetone to give the title compound (0.64 g, 14%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.15−1.3 (2t, 6H), 2.2 (s, 3H), 2.85 (m, 4H), 3.95 (s, 2H), 8.85 (s, 1H), 13.9 (br s, 2H). Anal. ($C_{12}H_{17}N_3S{\cdot}HNO_3$) C, H, N.

3-[(2,5-Diethylthiazol-4-yl)methyl]-1*H*-1,2,4-triazole Mononitrate (68b). A solution of **67b** (3.4 g, 15 mmol) and Lawesson's reagent (7.1 g, 17.5 mmol) in toluene (100 mL) was heated at reflux overnight (14 h). The reaction mixture was diluted with EtOAc and extracted with dilute HCl (3×). These extracts were basified with solid Na_2CO_3 and extracted with Et_2O (2×). The combined extracts were dried over K_2CO_3 and filtered, and the solvent was evaporated in vacuo. The residue was chromatographed on silica (98/1/1 EtOAc/MeOH/NH_4OH) to give a residue that was dissolved in MeCN and treated with $Et_2O{\cdot}HNO_3$. The solid was collected by filtration and recrystallized from MeCN to afford **42** (0.50 g, 12%) as fine white needles. ^{1}H NMR (DMSO-d_6) δ 1.25 (m, 6H), 2.85 (m, 4H), 4.3 (s, 2H), 8.95 (s, 1H). Anal. ($C_{10}H_{14}N_4S{\cdot}HNO_3$) C, H, N.

Ethyl 2,5-Dimethylthiazole-4-carboxylate (36). A mixture of **35** (31.5 g, 0.146 mol) and P_4S_{10} (16.3 g, 0.073 mol) in toluene (200 mL) was heated in an oil bath at 50−60 °C until the starting material had been consumed as judged by TLC. The reaction mixture was diluted with EtOAc and water. The aqueous layer was extracted with a second portion of EtOAc, and the combined organic extracts were dried over $MgSO_4$ and filtered and the solvent was evaporated in vacuo. Chromatography on silica (3/1 hexane/Et_2O) afforded the title compound (23.3 g, 75%) as an orange oil. ^{1}H NMR ($CDCl_3$) δ 1.4 (m, 9H), 3.05 (q, 2H), 3.25 (q, 2H), 4.45 (q, 2H). Anal. ($C_{10}H_{15}NO_2S$) C, H, N.

Ethyl 2,4-Diethylthiazole-5-carboxylate (42b). A solution of propionic thioamide (16.5 g, 0.185 mol) and ethyl-2-chloro-3-oxopentanoate (33.1 g, 0.185 mol) in absolute EtOH (200 mL) was stirred at room-temperature overnight. The solvent was evaporated in vacuo and the residue was dissolved in water and extracted with Et_2O (3×). The combined extracts were washed 2× with saturated $NaHCO_3$ and dried over $MgSO_4$. The solution was filtered and the solvent was evaporated in vacuo to give an oil. This material was distilled (0.75 mmHg/100−105 °C) to give the title compound (34.0 g, 86%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.35 (3t, 9H), 3.15 (2q, 4H), 4.3 (q, 2H). Anal. ($C_{10}H_{15}NO_2S$) C, H, N.

General Procedures for the Synthesis of Weinreb Amides: *N*-Methyl-*N*-methoxy-2,5-diethylthiazole-4-carboxamide (37). A mixture of **36** (22.9 g, 0.107 mol) and 150 mL of 1 N NaOH was stirred overnight at room temperature. The solution was acidified with concentrated HCl, and a white solid was filtered and dried. To a suspension of this solid (9.3 g, 50 mmol) in DMF (75 mL) was added carbonyldiimidazole (CDI) (12.2 g, 75 mmol). This mixture was stirred for 30 min and then added in one portion to a mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (24.4 g, 250 mmol) and NEt_3 (25.3 g, 250 mmol) in DMF (75 mL). The reaction was allowed to stir overnight at room temperature, and then diluted with water and extracted with Et_2O (4×). The combined extracts were washed with (3) small portions of water and then brine and then dried over $MgSO_4$. The solution was filtered and the solvent was evaporated to give a viscous oil, which was chromatographed on silica (4/1 hexane/Et_2O) to afford the title compound (4.7 g, 41%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.3 (2t, 6H), 3.0 (q, 4H), 3.35 (s, 3H), 3.8 (s, 3H). Anal. ($C_{10}H_{16}N_2O_2S$) C, H, N. C: Calcd, 52.61; Found, 53.30. N: Calcd, 12.27; Found, 11.70.

***N*-Methyl-*N*-methoxy-2,4-dimethylthiazole-5-carboxamide (43a).** A mixture of **42a** as the HCl salt (104.0 g, 0.47 mol) and 500 mL of 3 N NaOH was stirred overnight at room temperature. The solution was acidified with concentrated HCl and a white solid was filtered, air-dried, and then recrystallized from acetone. A portion of this material (15.7 g, 0.1 mol) was combined with CDI (24.3 g, 0.15 mol) in DMF (75 mL) and stirred 3 h at room temperature. In a separate flask, NEt_3 (84 mL, 0.6 mol) was added dropwise to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (48.8 g, 0.5 mol) in DMF (400 mL) cooled in an ice bath. To this cooled suspension was added the activated carboxylic acid reagent prepared above. The reaction was stirred at room temperature for 3 h. Most of the DMF was evaporated in vacuo and the residue was diluted with water and extracted with Et_2O (3×). The combined extracts were dried over $MgSO_4$ and then filtered, and the solvent was evaporated in vacuo. The residue was purified by chromatography on silica (2/1 hexane/Et_2O, then 1/1 hexane/Et_2O) to give the title compound as an orange oil. ^{1}H NMR ($CDCl_3$) δ 2.7 (2t, 6H), 3.35 (s, 3H), 3.7 (s, 3H). Anal. ($C_8H_{12}N_2O_2S$): C, H, N. C: Calcd, 47.98; Found, 47.52.

***N*-Methyl-*N*-methoxy-2,4-diethylthiazole-5-carboxamide (43b).** A mixture of **42b** (33.7 g, 0.158 mol) and 200 mL of 1 N NaOH was stirred overnight at room temperature. The solution was acidified with concentrated HCl and a white solid was filtered, air-dried, and then recrystallized from acetone. This material was then converted to the sodium salt with 1 N NaOH, the water was evaporated, and the salt was dried under vacuum. To this salt was added 250 mL of benzene, followed by oxalyl chloride (11.2 mL, 0.129 mol). The reaction mixture was stirred for 2 h and then filtered, and the solvent was evaporated in vacuo. The residue was dissolved in $CHCl_3$, and *N*,*O*-dimethylhydroxylamine hydrochloride was added, and the reaction mixture was cooled in an ice bath. To this was added NEt_3 (43 mL, 0.31 mol) in $CHCl_3$ (200 mL) from a dropping funnel. The reaction was allowed to warm to room temperature and stirred for 1 h. The mixture was transferred to a separatory funnel and washed with water and dilute HCl, and then dried over $NaSO_4$. The solution was filtered and the solvent was evaporated in vacuo, and the residue was distilled on a Kugelrohr to give the title compound (19.6 g, 64%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H), 1.4 (t, 3H), 3.0 (2q, 4H), 3.35 (s, 3H), 3.7 (s, 3H). Anal. ($C_{10}H_{16}N_2O_2S$) C, H, N.

General Procedure for the Reaction of Imidazole Grignard Reagents with Thiazole Esters: 1-(Triphenylmethyl)-1*H*-imidazol-4-yl-(2,5-diethylthiazol-4-yl)methanone (39). To a solution of 1-(triphenylmethyl)-4-iodoimidazole (10.9 g, 25 mmol) in CH_2Cl_2 (100 mL) under Ar was added 3.0 M EtMgBr in Et_2O (8.5 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 **37** (5.7 g, 25 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 (8.6 g, 67%). ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3H), 1.3 (t, 3H), 2.8 (q, 2H), 3.3 (q, 2H), 7.25 (m, 15H), 7.45 (s, 1H), 8.4 (s, 1H). Anal. ($C_{30}H_{27}N_3OS$) C, H, N.

General Procedure for the Addition of Grignard Reagents to Imidazole Ketones: 4-[1-(2,5-Diethylthiazol-4-yl)-2-phenylethyl]-1*H*-imidazole Hydrochloride (33). To a solution of **39** (2.3 g, 5.0 mmol) in dry THF (50 mL) was added 2.0 M BnMgCl in THF (3.75 mL), and the reaction was stirred at room temperature. After the starting material had been consumed as judged by TLC, the reaction was quenched with NH_4Cl and extracted with EtOAc (2×). The combined extracts were dried over Na_2SO_4 and filtered, and the solvent was evaporated in vacuo. The residue was dissolved in MeOH, 1.0 N HCl (5.0 mL) was added, and the mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo, and the residue was dissolved in water and washed with Et_2O (2×). The aqueous layer was basified with Na_2CO_3 and extracted with EtOAc. After drying over Na_2SO_4, the solution was filtered and the solvent was evaporated in vacuo. The residue was chromatographed on silica (96/3.6/0.4 $CHCl_3$/MeOH/NH_4OH) to give the carbinol intermediate (0.93 g, 57%). These compounds were often hydrates and difficult to fully characterize and were generally taken on directly to the next step. To a solution of the carbinol intermediate in EtOH was added 1−1.25 equiv of HCl and Pearlman's catalyst (1.0 g), and the mixture was hydrogenated at 50 °C and 50 psi. After the starting material had been consumed, the catalyst was removed by filtration and the filtrate was evaporated in vacuo. The residue was chromatographed on silica (97.5/2.25/0.25 $CHCl_3$/MeOH/NH_4OH). The appropriate fractions were combined and the solvent was evaporated in vacuo. The residue was dissolved in Et_2O and treated with Et_2O·HCl, and the crude salt was recrystallized from MeCN to give the title compound (0.17 g, 18%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 3H), 1.3 (t, 3H), 2.3 (m, 1H), 2.6 (m, 1H), 2.95 (q, 2H), 3.2 (m, 1H), 3.4 (m, 1H), 4.45 (q, 1H), 7.15 (m, 2H), 7.25 (m, 3H), 7.5 (s, 1H), 9.0 (s, 1H), 14.35 (br s, 1H). Anal. ($C_{18}H_{21}N_3S$·HCl) C, H, N.

4-[(2,4-Dimethylthiazol-5-yl)methyl]-1*H*-imidazole Hydrochloride (45). A mixture of $NaBH_4$ (0.75 g, 20 mmol) and **44a** (6.0 g, 13.3 mmol) in 2-PrOH (50 mL) was heated at reflux for 3 h and then left to cool overnight. The solvent was evaporated in vacuo, and 3 N HCl was added to the residue. When the remaining $NaBH_4$ had been consumed, the solution was basified and extracted with EtOAc (2×). The combined extracts were dried over Na_2SO_4 and filtered, and the solvent was evaporated in vacuo. The residue was recrystallized from acetone to give a white solid. This material was refluxed overnight in EtOH (100 mL) containing 3 N HCl (15 mL). The solvent was evaporated in vacuo and the residue was dissolved in water and extracted with Et_2O (2×). The aqueous layer was separated and evaporated to dryness, and the residue was dissolved in EtOH, combined with $Pd(OH)_2$, and hydrogenated at 50 °C and 50 psi overnight. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was chromatographed on silica (96/3.6/0.4 $CHCl_3$/MeOH/NH_4OH). The residue was converted to the hydrochloride salt with 1 N HCl. The solvent was evaporated in vacuo and the residue was recrystallized from MeCN to give the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3H), 2.3 (s, 3H), 4.4 (s, 2H), 4.7 (br s, 1H), 7.6 (s, 1H), 9.1 (s, 1H), 14.5−15.0 (br s, 1H). Anal. ($C_9H_{11}N_3S$·HCl) C, H, N.

General Procedures for the Synthesis of 2-Thiazole Compounds: (4-Imidazolyl)thioacetamide Hydrochloride (51). A solution of (4-imidazolyl)acetonitrile (12.8 g, 120 mmol) and thioacetamide (18.0 g, 40 mmol) in DMF (75 mL) was heated in an oil bath to 90−100 °C for about 2 h, while HCl(g) was being bubbled into the reaction mixture. The solvent was evaporated in vacuo, and the residue was triturated with acetone to give crude product. This material was recrystallized from 2-PrOH to give the title compound (16.2 g, 76%) as a tan solid, mp 199−201 °C. ^{1}H NMR (DMSO-d_6) δ 4.05 (s, 2H), 7.5 (s, 1H), 9.05 (s, 1H), 9.7 (d, 2H), 14.5 (br s, 2H). Anal. ($C_5H_7N_3S$·HCl) C, H, N.

4-[(4,5-Dimethylthiazol-2-yl)methyl]-1*H*-imidazole Hydrochloride (53). A solution of **51** (4.6 g, 26 mmol) and 3-bromo-2-butanone (6.9 g, 45.6 mmol) in 2-PrOH (25 mL) was heated at reflux. After the starting material had been consumed as judged by TLC, the reaction mixture was cooled and the crude product was collected by filtration. Flash chromatography on silica (90/9/1 $CHCl_3$/MeOH/NH_4OH) yielded a yellow oil (3.3 g, 66%), which was dissolved in MeCN and treated with Et_2O·HCl. A white solid was collected and recrystallized from MeCN to yield the title compound as a mixture of $C_9H_{11}N_3S$·HCl and $C_9H_{11}N_3S$·2HCl·H_2O (7:3), as judged by elemental analysis. ^{1}H NMR (DMSO-d_6) δ 2.3 (s, 3H), 2.35 (s, 3H), 4.4 (s, 2H), 4.8 (br s, 1H), 7.6 (s, 1H), 9.1 (s, 1H), 14.8 (br s, 1H). Anal. ($C_9H_{11}N_3S$·1.3 HCl·0.3 H_2O) C,H,N, Cl,H_2O(KF).

4-[(Benzothiazol-2-yl)methyl]-1*H*-imidazole Fumarate 2:3 (62). A solution of (imidazol-4-yl)acetonitrile (3.0 g, 28 mmol) and 2-aminobenzenethiol hydrochloride (5.0 g, 30 mmol) in EtOH (75 mL) was heated at reflux overnight. The solvent was evaporated in vacuo, and the residue was dissolved in 3 N HCl and washed with Et_2O (2×). The aqueous layer was basified with solid Na_2CO_3 and extracted with $CHCl_3$ (2×). The organic extracts were combined, dried over K_2CO_3, and filtered and the solvent was evaporated in vacuo. The residue was dissolved in acetone and treated with 1 equiv of fumaric acid, which was dissolved in a minimum amount of 2-PrOH. The solid was collected and recrystallized from acetone to give the title compound as an off-white solid (1.27 g, 11%). ^{1}H NMR (DMSO-d_6) δ 4.4 (s, 2H), 6.65 (s, 3H), 7.1 (s, 1H), 7.45 (2t, 2H), 7.7 (s, 1H), 8.0 (2d, 2H). Anal. ($C_{11}H_9N_3S$·1.5$C_4H_4O_4$) C, H, N.

Biological Methods: (1) In Vitro α_{2D}-Adrenoceptor Binding Assay. Male, Wistar rats (150−250 g, VAF, Charles River Laboratories, Kingston Facility, Stone Ridge, NY) were sacrificed by cervical dislocation, and their brains were removed and placed immediately in ice−cold HEPES−sucrose (10 mM HEPES and 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 was 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 nL of cold 10 mM HEPES buffer (pH 7.5), the adhering radioactivity was quantified by liquid scintillation spectrometry.

Data Analysis. Data were analyzed with LIGAND, a nonlinear curve-fitting program designed specifically for the analysis of ligand binding data.[26] 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, with 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) Mouse Acetylcholine-Induced Abdominal Irritant Test (MAIT). The procedure with minor modifications was that described by Collier.[27] Test compounds or appropriate vehicle were administered p.o. by gavage and at specified intervals later, the animals received an i.p. injection of 5.5 mg/

kg acetylcholine bromide. The mice were then placed into large glass bell jars and observed for the occurrence of a single response. The percent inhibition of this response (equated to percent antinociception) was calculated for each dose as follows: % antilnociception = 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 by the probit anaylsis of Litchfield and Wilcoxon,[28] including a χ^2 test for linearity.

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