Medetomidine Analogs as α_2-Adrenergic Ligands. 3. Synthesis and Biological Evaluation of a New Series of Medetomidine Analogs and Their Potential Binding Interactions with α_2-Adrenoceptors Involving a "Methyl Pocket"

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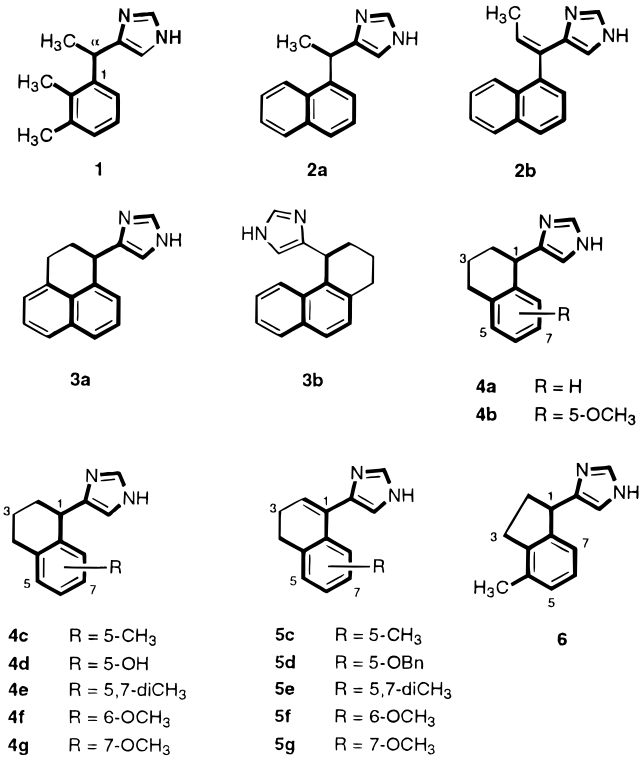
The synthesis and the biological evaluation of a new series of medetomidine analogs are reported. The substitution pattern at the phenyl ring of the tetralin analogs had a distinct influence on the α_2-adrenoceptor binding affinity. 4-Methylindan analog **6** was the most potent α_2-adrenoceptor binding ligand among these 4-substituted imidazoles, and its α_2-adrenoceptor selectivity was greater than the 5-methyl tetralin analog **4c**. Ligand-pharmacophore and receptor modeling were combined to rationalize α_2-adrenoceptor binding data of the imidazole analogs in terms of ligand−receptor interactions. The structure−activity relationships that were apparent from this and previous studies were qualitatively rationalized by the binding site models of the α_2-adrenoceptor. The benzylic methyl group of medetomidine or the naphthyl analog **2a** was superimposable with the α-methyl group of (−)-α-methylnorepinephrine and fit into the proposed "methyl pocket" of the α_2-adrenoceptor defined by the residues Leu110, Leu169, Phe391, and Thr395.

Introduction

Medetomidine (**1**) is the prototype of a class of α-adrenoceptor agents.[1] We previously described the synthesis, biological evaluation, and computer modeling studies of the 4-substituted imidazoles as α-adrenoceptor agents.[2,3] Naphthyl analog **2a** exhibited equal potency and higher selectivity at α_2-adrenoceptors than medetomidine. Conformationally restricted analog **3a** of the naphthyl series retained high binding affinity but low selectivity at α_2-adrenoceptors. In a subsequent study, we found that an unsubstituted tetralin analog of medetomidine **4a** showed moderate binding affinity at α_2-adrenoceptors,[4] whereas the 5-methoxytetralin analog **4b** was very potent on α_2-adrenoceptors.[5] In this paper, we have further explored the structure−activity relationships of a tetralin series (**4c**−**g**) by placing various substituents at the different positions of the phenyl ring. The synthetic intermediates of the tetralin series, 3,4-dihydronaphthalene analogs **5c**−**g**, were also examined for their α-adrenoceptor binding affinities. These two series are conformationally restricted analogs of medetomidine, as the connection of the benzylic methyl substituent with the *o*-methyl group on the phenyl ring decreases the rotational flexibility of C_1-C_α bond in medetomidine. We also synthesized a 4-methylindan analog **6** as a comparison with the 5-methyltetralin analog **4c**.



During the course of our synthetic research, we conducted molecular modeling studies on the medetomidine-like analogs and found a common binding mode of the phenethylamines and the imidazoles with α_2-adrenoceptors by superimposition of the imidazole analogs with (−)-α-methylnorepinephrine (α-MeNE).[3] Recently acquired knowledge regarding the amino acid sequence of the α_2-adrenoceptor and the availability of a high-resolution three-dimensional structure of bacteriorhodopsin makes it attractive to construct an α_2-

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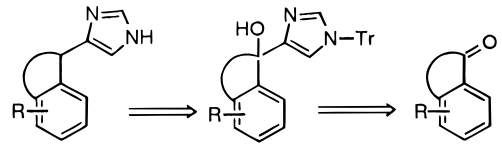
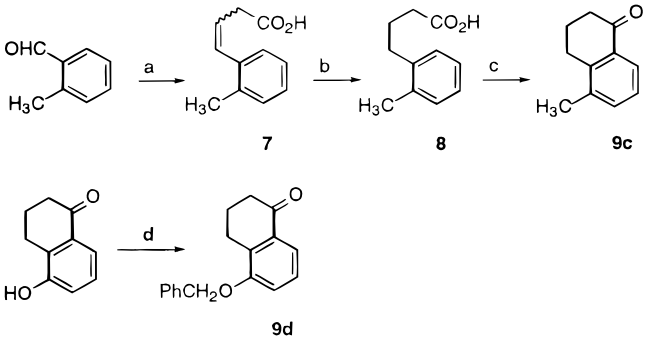


Figure 1. Retrosynthesis of 4-substituted imidazoles.

Scheme 1[a]



[a] (a) Triphenyl(2-carboxyethyl)phosphonium chloride, NaH, THF/DMSO (1:1), 0 °C → rt, (b) H_2 (30 psi), Pd/C (10%), EtOH; (c) (i) PCl_5, benzene, (ii) $SnCl_4$. (d) $PhCH_2Br$, K_2CO_3, $CHCl_3/CH_3OH$, reflux.

adrenoceptor model. In fact, a number of such models have been reported.[6,7] Herein we used an approach in which ligand−pharmacophore and receptor modeling were combined to rationalize α_2-adrenoceptor binding data of the imidazole analogs in terms of ligand−receptor interactions. The biological data reported in this paper and in the preceding papers[2,3] appear to accommodate the deduced α_2-adrenoceptor binding site models in a qualitative sense. Consequently, this proposed model may be useful in the design of novel α_2-adrenoceptor drugs.

Chemistry

Racemic analogs **4b**−**g** and analogs **5b**−**g** were synthesized by a straightforward method utilizing direct introduction of an intact imidazole, as we have previously reported.[3] The final compounds were derived from the appropriately substituted carbonyl precursors, **9b**−**g**, as illustrated in Figure 1. The preparation of the non-commercially available tetralones (**9c** and **9d**) is depicted in Scheme 1. Treatment of 2-methylbenzaldehyde with triphenyl(2-carboxyethyl)phosphonium chloride provided a mixture of alkenes **7** with both cis and trans configurations. Without further isolation, this mixture was hydrogenated to the saturated carboxylic acid **8**, which was then cyclized to the corresponding 1-tetralone **9c**. The synthesis of 5-hydroxytetralin analog was initiated from 5-hydroxy-1-tetralone, in which the hydroxy group was protected as a benzyl ether (**9d**) before subjecting it to the Grignard reaction.

Ketones **9b**−**g** were converted to the corresponding alcohols **10b**−**g** using Turner's approach (Scheme 2).[8] Deprotection of the imidazole ring afforded a series of 3,4-dihydronaphthalene analogs (**5b**−**g**), which were individually hydrogenated to give a series of 1,2,3,4-tetrahydronaphthalene analogs (**4b**−**g**).

4-Methyl-1-indanone (**13**, Scheme 3) was prepared following a similar route for the synthesis of perinaphthanone, as we reported earlier.[3] Difficulties were encountered in the cyclization step using $SnCl_4$ or $AlCl_3$ as the Friedel−Crafts catalyst. However, this step was carried out by using $TiCl_4$ as a Lewis acid. The synthesis of target compound **6** was accomplished successfully from alcohol **14** by using $Me_3SiCl-NaI-CH_3CN$.[9]

Biological Results

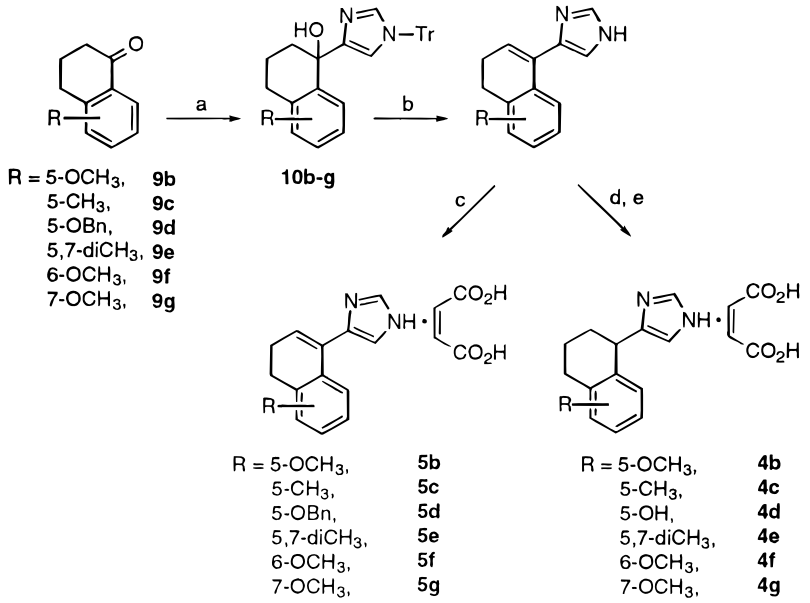
The α_1- and α_2-adrenoceptor binding affinities of the newly synthesized 4-substituted imidazoles were determined using membrane fractions of rat brain, as summarized in Table 1. The substitution pattern at the phenyl ring of tetralin analogs had a distinct influence on the α_2-adrenoceptor binding affinities. All 5-substituted tetralin analogs (**4b**−**e**) were about equipotent, displaying α_2-adrenoceptor binding affinities ranging from 63−103 nM. Compounds lacking the 5-substituent (**4f**−**g**) were less potent in binding to α_2-adrenoceptors. We previously reported that the unsubstituted tetralin analog **4a** exhibited moderate activity at the α_2-adrenoceptor.[4] Taken together, these findings suggest that the presence of a substituent at the 5-position of tetralin analogs is critical to obtain optimal α_2-adrenoceptor binding. Based on K_i values, the rank order of α_1-adrenoceptor affinities for the tetralin analogs is as follows: 5-OH (**4d**) ≈ 5,7-diCH_3 (**4e**) > 5-CH_3 (**4c**) ≈ 6-OCH_3 (**4f**) > 5-OCH_3 (**4b**) ≫ 7-OCH_3 (**4g**). In general, compounds in this series did not exhibit high selectivity for α_2- vs α_1-adrenoceptors. Although 3,4-dihydronaphthalene analogs **5b**−**g** were generally less potent than their corresponding tetralin analogs **4b**−**g**, the 5-methyl-substituted analog **5c** was 3-fold more potent at the α_2-adrenoceptor and showed much higher selectivity at the α_2-adrenoceptor than the corresponding 5-methyl tetralin analog **4c**. Similarly, the 5,7-dimethyl analog **5e** also exhibited higher selectivity for α_2- vs α_1-adrenoceptors than its corresponding tetralin analog **4e**. 4-Methylindan analog **6** was the most potent α_2-adrenoceptor binding ligand among these 4-substituted imidazoles, and its α_2-adrenoceptor selectivity was greater than the 5-methyltetralin analog **4c**.

Molecular Modeling

α_2-Adrenoceptors (α_{2A-D}) belong to a family of G-protein-coupled receptors (GPCR) that transmit information into the interior of cells through coupling to guanine nucleotide regulatory proteins (G-protein).[10] The α_2-adrenoceptors have been cloned and proposed to consist of seven transmembrane-spanning domains that are connected by three extracellular and three intracellular loops, with the amino terminus being extracellular and the carboxy terminus intracellular. The 3D structure of the transmembrane-spanning α-helices of the α_2-adrenoceptor might resemble the folding of bacteriorhodopsin, a membrane protein whose 3D structure has recently been obtained by cryomicroscopy.[11]

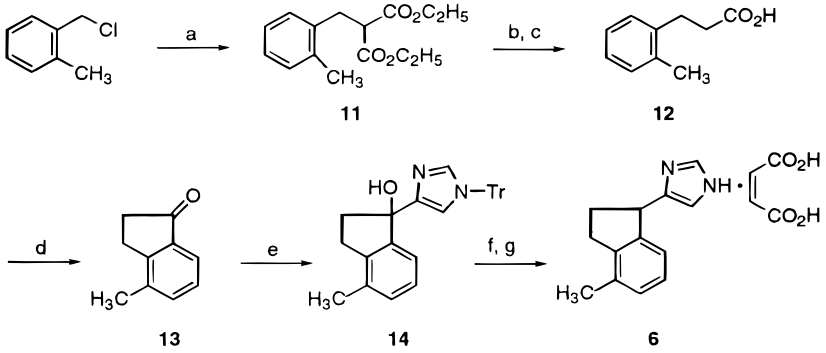
The α_2-adrenoceptor-ligand interactions have been studied by site-directed mutagenesis.[12,13] Several conclusions can be drawn from these studies. (1) The carboxy group of Asp113 in transmembrane domain III (TM3) interacts with the protonated amino group of phenethylamines, such as norepinephrine. (2) The *m*- and *p*-hydroxy groups of phenethylamines are postulated to form hydrogen bonds to Cys201 and Ser204, respectively, which are located in the fifth transmembrane spanning helix (TM5). (3) The hydroxy group of

Scheme 2[a]



[a] (a) 4-Iodo-*N*-tritylimidazole, EtMgBr, CH_2Cl_2; (b) TFA/H_2O (60%); (c) maleic acid, CH_3OH; (d) H_2 (30 psi), Pd/C (10%), EtOH; (e) maleic acid, CH_3OH.

Scheme 3[a]



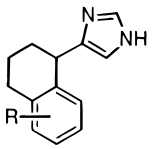
[a] (a) $CH_2(CO_2C_2H_5)_2$, $NaOC_2H_5$, HOC_2H_5, reflux; (b) KOH/H_2O, reflux, (c) 160 °C; (d) (i) $SOCl_2$, (ii) $TiCl_4$, CH_2Cl_2; (e) 4-iodo-*N*-tritylimidazole, EtMgBr, CH_2Cl_2; (f) TMSCl–NaI–CH_3CN, CH_2Cl_2; (g) maleic acid, CH_3OH.

Ser90 in TM2 could be the potential binding site for the β-hydroxy group of phenethylamines.[13] In our studies, the model of the human α_2-adrenoceptor was constructed using SYBYL and a strategy similar to that previously described by Hibert *et al.*[6] The template molecule of the phenethylamine, α-MeNE, and the more active *S*-isomers of medetomidine analogs were docked into the model individually. When trying to locate the binding site of α-MeNE with the α_2-adrenoceptor, we considered the interactions between the ligand and the important amino acid residues discussed above.

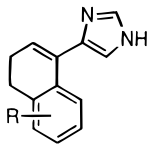
In the binding site model for the α-MeNE α_2-adrenoceptor complex (Figure 2), the protonated nitrogen of the ligand interacted with Aps113 in TM3 through a reinforced ionic bond. Hydrogen bonds were formed from the meta- and para- phenolic hydrogens of the ligand to Cys201 and Ser204 (in TM5), respectively. Aromatic edge-to-face interactions occurred between the aromatic moiety of the ligand and Phe205 (in TM4) and Phe391 (in TM6). The β-hydroxy group of Ser90 in TM2, a potential binding site for the β-hydroxy group of phenethylamines as indicated in the site-directed mutagenesis experiments,[13] was too far removed from the binding pocket in our proposed model. However, we found another Ser residue, Ser165 in TM4, occupied the ideal position in the recognition site to form a hydrogen bond with the β-hydroxy group of α-MeNE. Such an interaction was also suggested in the Trumpp–Kallmeyer's model.[7] The α-methyl group of α-MeNE was surrounded by the side chain of Leu110 (in TM3), Leu169 (in TM4), Phe391 and Thr395 (in TM6). This lipophilic cavity (the "methyl pocket") formed by the above four amino acid residues could be the additional recognition binding site at the α_2-adrenoceptor for the α-methyl group of α-methylphenethylamines, as proposed in 1970s by Ruffolo *et al.*[14]

In a recent meeting on α_2-adrenoceptors, Heible and co-workers reported that Ser165 may not be involved in the hydrogen bonding interactions with the β-hydroxyl group of catecholamines based on their site-directed mutagenesis studies.[15] Instead, their data indicated that Ser90 (TM2) and/or Ser419 (TM7) are the likely sites of hydrogen bonding interactions for the β-hydroxyl group. Mutation of either Ser90 or Ser419 to Ala resulted in 50–70 fold reduction in K_i values for (−)-epinephrine and (−)-norepinephrine but little if any change in the binding affinity of the less active (+) enantiomers and dopamine which lacks the β-hydroxyl group. These results do not appear to be consistent with our bacteriorhodopsin derived model of the α_2-adreno-

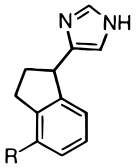
Table 1. α_1- and α_2-Adrenergic Binding Affinities of Conformationally Restricted Analogs of Medetomidine in Membrane Preparations of Rat Brain



4b-g



5b-g



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compound	R	K_i (nM)[a] α_1	K_i (nM)[a] α_2	α_2-selectivity ratio[b]
medetomidine		1110 ± 36	25 ± 13	44.4
4b	5-OCH_3	243 ± 30	98 ± 6	2.48
5b	5-OCH_3	2970 ± 75	1420 ± 812	2.10
4c	5-CH_3	191 ± 20	95 ± 12	2.01
5c	5-CH_3	992 ± 21	31 ± 11	32.0
4d	5-OH	126 ± 16	63 ± 10	2.01
5d	5-OBn	8250 ± 1414	2670 ± 637	3.09
4e	5,7-diCH_3	131 ± 49	103 ± 34	1.27
5e	5,7-diCH_3	2960 ± 603	232 ± 67	12.8
4f	6-OCH_3	198 ± 80	169 ± 26	1.17
5f	6-OCH_3	1630 ± 440	580 ± 74	2.81
4g	7-OCH_3	1770 ± 494	201 ± 98	8.81
5g	7-OCH_3	14200 ± 4378	1570 ± 159	9.03
6	4-CH_3	73 ± 28	8.8 ± 1.5	8.29

[a] Rat brain membrane preparations were incubated with 0.1 nM of [^{3}H]prazosin and 0.2 nM of [^{3}H]rauwolscine for α_1- and α_2-adrenoceptors, respectively. Phentolamine (10 μM) was used to determine the fraction of nonspecific binding in both assays. K_i values were determined using the equation as follows: K_i (nM) = IC_{50} (1 + [L]/K_d), where IC_{50} = concentration (nM) of analog which reduces binding by 50%; [L] = concentration of radioligand; and K_d = equilibrium dissociation constant of the radioligand. Values are average ± standard deviation (n = 3−9). [b] α_2-Selectivity ratio = K_i (α_1)/K_i (α_2).

ceptor. In our hypothetical model, the ligand binding site is formed by TM3, TM4, TM5, and TM6, and interaction of the β-hydroxyl group with either Ser90 or Ser419 would preclude important interactions with Asp113 (TM3), Cys201 (TM5), and Ser204 (TM5). Thus, if Ser90 and/or Ser419 do in fact form a hydrogen bond with the β-hydroxyl group of catecholamines, these recent mutational studies appear to be incompatible with our receptor model. A receptor model that can account for these recent and previous mutation studies would require a helical arrangement different from our model and bacteriorhodopsin. However, site-directed mutagenesis and chimeric receptor studies provide strong evidence that the transmembrane domains of G-protein-coupled receptors such as α_2- and β_2-adrenoceptors have a helical arrangement similar to bacteriorhodopsin.[16] In addition, the length of the extracellular and intracellular loops would seem to prevent helical arrangements that can accommodate these new findings.[15] Furthermore, one cannot dismiss the possibility of multiple binding modes or mutation-induced perturbations of the receptor binding site that may account for the observed binding of catecholamines to the Ala90 and Ala419 α_2-adrenoceptor mutants. The lack of change in catecholamine binding to Ala165 mutants is not unusual as some mutations of important serine residues in various GPCRs may have little if any effect on binding affinities but have significant effect on G-protein coupling or functional activity.[12,17−19] Thus, the hypothetical 3D model of the α_2-adrenoceptor presented here may be valid and can provide at least a qualitative assessment of ligand binding interactions.

In the preceding paper, we reported that medetomidine has much higher binding affinity at the α_2-adrenoceptor than α-MeNE with equal selectivity at α_2-vs α_1-adrenoceptors. We proposed that the benzylic methyl group of medetomidine interacts with the same site as the α-methyl group of α-MeNE.[3] Since the *S*-isomer of medetomidine and (*S*)-**2a** is the active isomer for α_2-adrenoceptors, we assumed that the *S*-isomer of other imidazole analogs is the more potent optical isomer for α_2-adrenoceptors if the racemate is active. As illustrated in Figure 3, one of the attractive features of the model reported herein is that it allowed for superimposition of the pharmacophoric elements (the nitrogen atom, the methyl group, and the aromatic moiety) of the two molecules without a significant change in the docking energies (−46 cal/mol for α-MeNE and −50 cal/mol for (*S*)-medetomidine). Interestingly, the other nitrogen of the imidazole ring, N^1, was postulated to form a hydrogen bond with the backbone carbonyl of Leu110 (TM3), instead of Ser165 in TM4.

Effects of the Benzylic Substituents in Naphthyl Derivatives. The binding site model of the α_2-adrenoceptor provided insight into the molecular basis for the observed binding differences of (*S*)-**2a** and **2b** at the α_2-adrenoceptor.[3] In the docking model of α-MeNE, (S)-medetomidine and (*S*)-**2a** (Figure 4a−c), the methyl group (illustrated by van de Waals surface) fit nicely into the "methyl pocket" as described above. However, the ethylene side chain of **2b** was obviously too large to fit into the "methyl pocket" (Figure 4d). Such a binding pattern was also observed when molecule **3a** and **3b** were docked into the α_2-adrenoceptor model, respectively. These observations appear to rationalize the fact that medetomidine, **2a**, and **3a** exhibited high affinity for the α_2-adrenoceptors, while **2b** and **3b** did not.

Effects of the Phenyl Substituents in Tetralin Series. In the present series, substituents on the

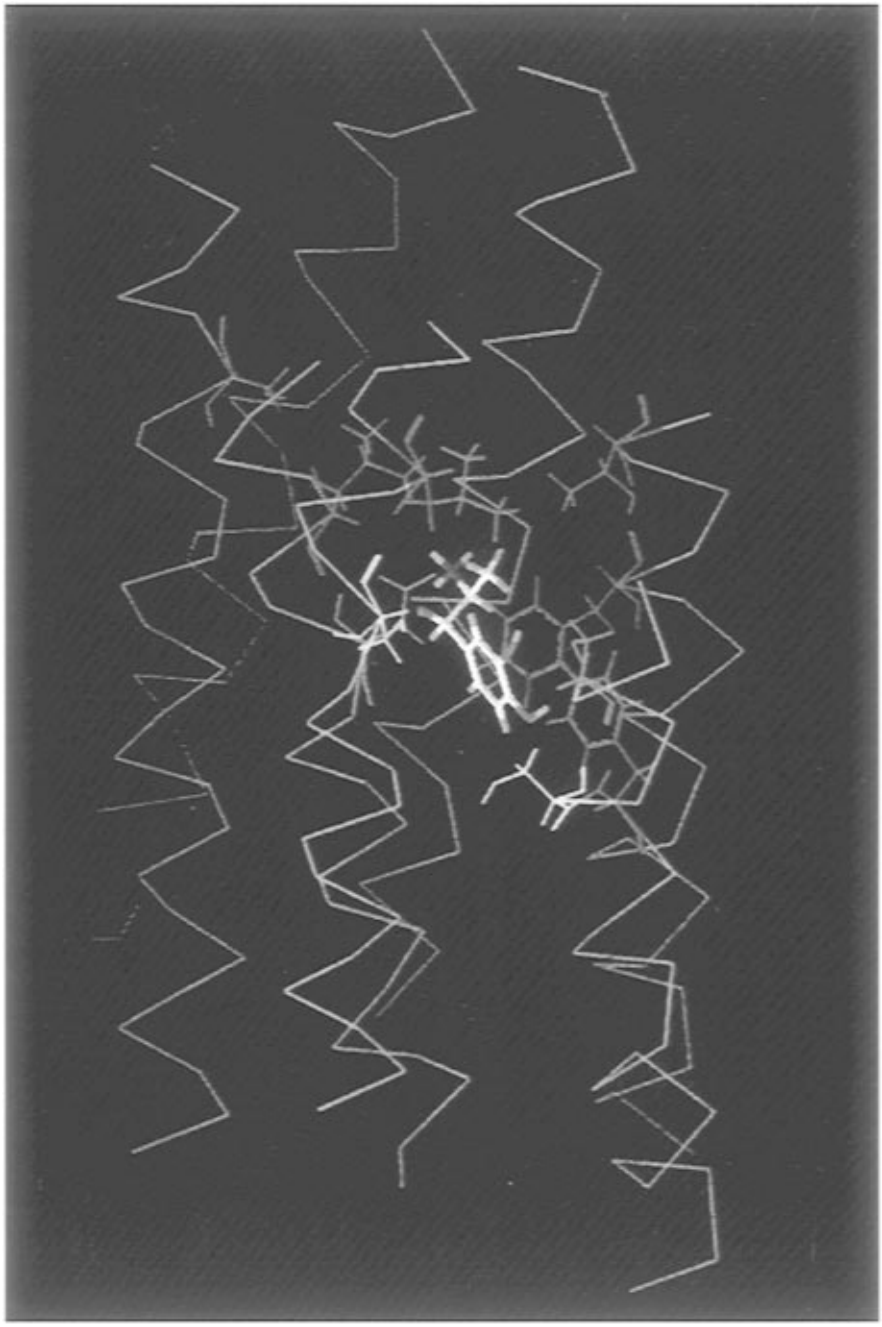

Figure 2. View of the seven transmembrane regions of the α_2-adrenoceptor and α-MeNE complex. The seven helices are indicated by the c_α-carbon trace. Only the residues around the binding site are displayed. Serine residues are yellow. Cys201 is green. Asp 113 is orange and the hydrophobic residues are red.

phenyl ring of the tetralin series have an important influence on α_2-adrenoceptor binding affinity. Superimposition of α-MeNE and the 5-methoxytetralin analog **4b** resulted in the overlap of the *m*-OH of α-MeNE and the 5-OCH_3 group of **4b**, suggesting that the 5-OCH_3 of **4b** may interact with Cys201 in TM5. Interestingly, when **4b** was docked into the α_2-adrenoceptor model, the distance of oxygen atom of 5-OCH_3 in **4b** to the oxygen atom of Ser165 and the sulfur atom of Cys201 was 3.6 and 3.4 Å, respectively. When 5-OH analog **4d** was docked into the α_2-adrenoceptor model, the 5-OH group formed a hydrogen bond with Ser165 in TM4, instead of with Cys201. The docking energies of **4b** and **4d** in α_2-model were −42 and −34 cal/mol, respectively. Moving the methoxy to the sixth or seventh positions (analogs **4f**,**g**) resulted in an increase in the docking energy to 453 and 128 cal/mol, respectively, indicating less favorable interactions between **4f** or **4g** and the α_2-adrenoceptor. A schematic representation of the interaction of **4d** with the binding site of the α_2-adrenoceptor is presented in Figure 5. The experimental evidence and observations from the model suggested that the cavity surrounded by Ser165 (in TM4) and Cys201 (in TM5) was important to obtain high α_2-adrenoceptor binding affinity. It also provided a rationale for the design of affinity labeling ligands based on the tetralin structure. In addition, the benzylic bridge formed between the C_1 and the C_2 of the 5-substituted tetralin analogs or the indan analog **6** fit perfectly into the "methyl pocket".

Conclusions

Remarkably, the α_2-adrenoceptor binding site model accommodates the binding data of these medetomidine

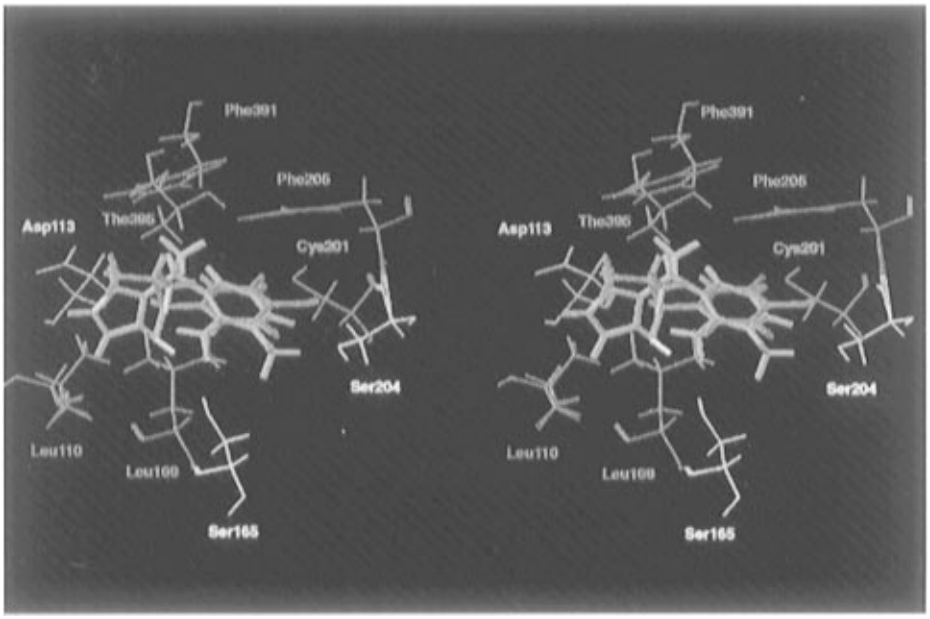

Figure 3. Stereo representation of the superimposition of α-MeNE (pink) and medetomidine (blue) in the binding site of α_2-adrenoceptor model.

analogs. In fact, the structure−activity relationships of medetomidine analogs at the α_2-adrenoceptor described herein and the preceding papers[2,3] can be partially rationalized by the α_2-adrenoceptor model. The presence of the "methyl pocket" and the cavity surrounded by Ser165 (in TM4) and Cys201 (in TM5) in the binding site model are particularly interesting, because these structural features of the α_2-adrenoceptor have been predicted on the basis of ligand−pharmacophore modeling and, thus, are supported by a wealth of experimental evidence. Thus, it may be possible to use the α_2-adrenoceptor binding site model in the design of affinity labeling ligands for the α_2-adrenoceptors.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR (^{1}H and ^{13}C) spectra were obtained on Bruker 300 spectrometer, and chemical shift values were reported as parts per million (δ) relative to tetramethylsilane (TMS) as an internal reference. IR spectra were obtained on System 2000-FTIR. Elemental analyses were performed by Atlantic Microlab, Inc., and the obtained analytical results were within ±0.4% of the theoretical values. Routine thin-layer chromatography (TLC) was performed on silica gel UNIPLATE (250 μm, 2.5 × 10 cm; Analtech Inc. Newark, DE). Flash chromatography was performed on silica gel (Merck, Grade 9385, 230−400 mesh, 60 Å). Acetonitrile (CH_3CN), benzene, ethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were dried by distillation from CaH_2. Tetrahydrofuran (THF) was dried by distillation from sodium metal with benzophenone as an indicator. Unless specifically indicated otherwise amine maleate salts were obtained and purified by the dropwise addition of a molar equivalent solution of maleic acid in anhydrous Et_2O to a solution of the amine in absolute methanol.

4-(2-Methylphenyl)butanoic Acid (8). To a solution of 2-methylbenzaldehyde (2 mL, 17.3 mmol) and triphenyl(2-carboxyethyl)phosphonium chloride (6.60 g, 17.8 mmol) in a 1:1 mixture of dry THF/DMSO (50 mL) was added dry sodium hydride powder (95%, 0.90 g, 35.6 mmol) in one portion at 0 °C under an atmosphere of argon. The resulting suspension was allowed to stir overnight at room temperature. After cooling to 0 °C, the dark-red mixture was diluted with 100 mL of water. The aqueous portion was washed with Et_2O (3 × 100 mL), acidified to pH 1−2 with concentrated HCl solution, and extracted with Et_2O (2 × 100 mL). The combined ether extracts were washed with water (5 × 200 mL), dried over $MgSO_4$, and evaporated to yield a mixture of *trans*- and *cis*-alkene isomers (**7**) in a 52% yield. This mixture (1.80 g, 10.2 mmol) was reduced by catalytic hydrogenation with 10% Pd/C (0.20 g) as a catalyst in absolute EtOH (100 mL) to afford 1.71 g (94%) of acid **8** as a white fluffy solid: mp 57−58 °C (lit.[20] 52−57 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90−1.98 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.41−2.46 (m, 2H, CH_2CO), 2.64−2.69 (m, 2H, $ArCH_2$), 7.11−7.14 (m, 4H, Ar-H); IR (KBr) 1718 cm^{-1}; MS *m/e* calcd for $C_{11}H_{14}O_2$: 178, found 178. Anal. ($C_{11}H_{14}O_2$): C, H.

5-Methyl-1-tetralone (9c). 4-(2-Methylphenyl)butanoic acid (**8**, 0.54 g, 3 mmol) was mixed with PCl_5 (0.75 g, 3.6 mmol) in dry benzene (5 mL). After stirring for 1 h, $SnCl_4$ (0.6 mL, 5.1 mmol) was added dropwise at 0 °C. The mixture was maintained at 0 °C for further 15 min and then quenched with aqueous HCl solution (10%). The benzene layer was washed successively with dilute acid, water, dilute alkali, water, and brine. The organic solution was dried over $MgSO_4$ and concentrated. The crude product was recrystallized in hexane to afford 0.44 g (92%) of **9c** as white crystals: mp 49−50 °C (lit.[21] 48−50 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13−2.21 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.62−2.66 (m, 2H, CH_2CO), 2.86 (t, J = 6.08 Hz, 2H, $ArCH_2$), 7.19−7.26 (m, 1H, ArH), 7.35 (d, J = 7.42 Hz, 1H, ArH), 7.93 (d, J = 7.76 Hz, 1H, ArH); IR (KBr) 1673 cm^{-1}; MS *m/e* calcd for $C_{11}H_{12}O$: 160, found 160. Anal. ($C_{11}H_{12}O_2$): C, H.

4-[1-(1-Hydroxy-5-methyl-1,2,3,4-tetrahydronaphthyl)]-*N*-(triphenylmethyl)imidazole (10c). A 3.0 M solution of EtMgBr (1.5 mL, 4.5 mmol) in Et_2O was added to a 0.25 M solution of 4-iodo-*N*-(triphenylmethyl)imidazole[22] (1.89 g, 4.3 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of 5-methyl-1-tetralone (**9c**, 0.46 g, 2.9 mmol) in 2 mL of dry CH_2Cl_2 was added and stirring was continued overnight. Saturated NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with an equal amount of CH_2Cl_2 (2×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was crystallized in CH_2Cl_2/hexane to yield 1.01 g (75%) of the title compound as a white solid: mp 122-123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72−1.82 (m, 1H), 2.04−2.12 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.30−2.34 (m, 1H), 2.59−2.61 (m, 1H), 2.66−2.68 (m, 1H), 3.18 (bs, 1H, OH), 6.46 (d, J = 1.47 Hz, 1H, Im-H), 6.99−7.02 (m, 2H), 7.08−7.14 (m, 7H), 7.28−7.34 (m, 9H), 7.37 (d, J = 1.46 Hz, 1H, Im-H); IR (KBr) 3368, 1493, 1446 cm^{-1}; MS *m/e* calcd for $C_{33}H_{30}N_2O$: 471, found 471. Anal. ($C_{33}H_{30}N_2O\cdot{}^1/_2H_2O\cdot CH_2Cl_2$): C, H, N.

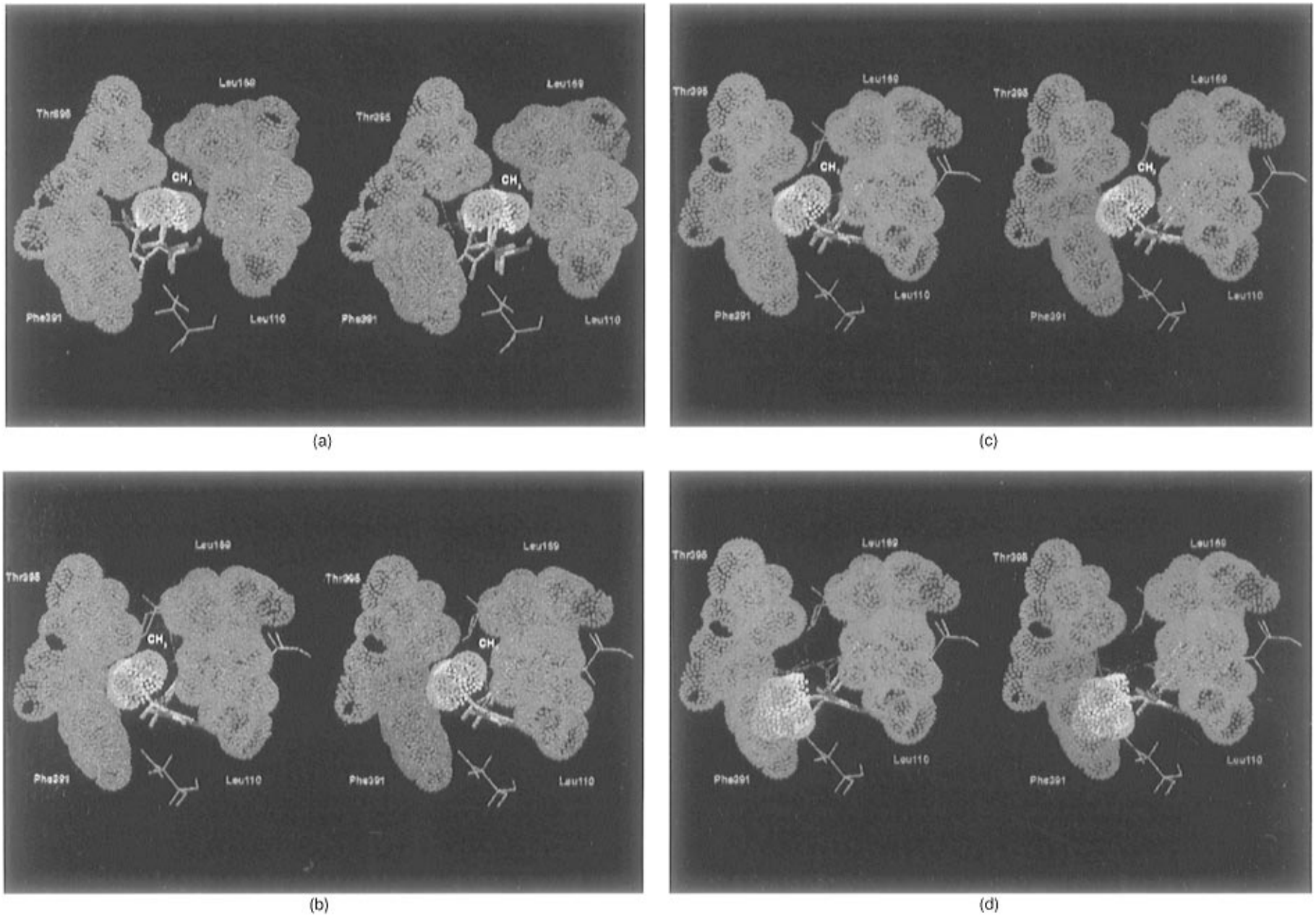

Figure 4. Stereo representation of the interactions between (a) α-MeNE, (b) medetomidine, (c) **2a**, or (d) **2b** and the binding site of α_2-adrenoceptor model. The methyl group of α-MeNE, medetomidine, and **2a** fit into the "methyl pocket" of the receptor defined by the residues Leu110, Leu169, Phe391, and Thr395. The ethylene side chain of **2b** does not fit into the "methyl pocket".

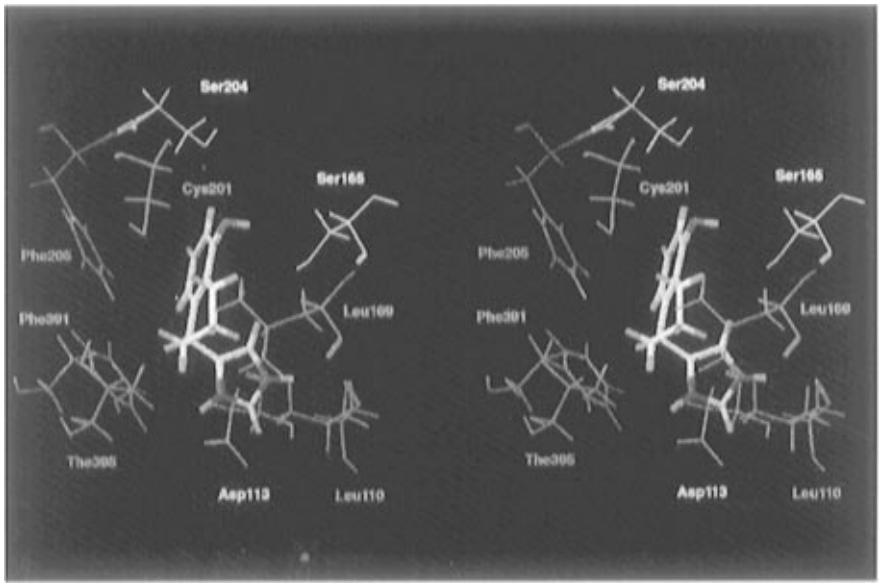

Figure 5. Stereo representation of the interaction of **4d** and the binding site of α_2-adrenoceptor model.

4-(3,4-Dihydro-5-methyl-1-naphthyl)-1*H*-imidazolium Maleate (5c). A solution of **10c** (0.56 g, 1.2 mmol) in 10 mL of TFA aqueous solution (60%) was stirred overnight. The solvents were evaporated, and the residue was partitioned between 15 mL of CH_2Cl_2 and 15 mL of HCl solution (10%). The organic portion was washed with HCl solution (10%, 3 × 15 mL). The combined acidic solutions were made basic (pH ~10) and then extracted with CH_2Cl_2 (4 × 75 mL). The organics were dried over Na_2SO_4 and concentrated to yield 0.20 g (79%) of **5c** as a free base, which was converted immediately to the maleate to afford the title compound as white crystals: mp 149−150 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.32 (s, 3H, CH_3), 2.39−2.46 (m, 2H, CH_2), 2.81 (t, J = 7.79 Hz, 2H, Ar-CH_2), 6.24 (s, 2H, HC=CH), 6.45 (t, J = 4.77 Hz, 1H, HC=C), 6.89 (d, J = 7.56 Hz, 1H), 7.06−7.14 (m, 2H), 7.53 (s, 1H, Im-H), 8.82 (d, J = 1.04 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 19.69 (CH_3), 23.95 (CH_2), 24.20 (CH_2), 170.71 (C=O); IR (KBr) 3448, 1572, 1455 cm^{-1}; MS (chemical ionization-NH_3) m/e calcd for $C_{14}H_{14}N_2$ (MH^+): 211, found 211. Anal. ($C_{18}H_{18}N_2O_4$): C, H, N.

4-(5-Methyl-1,2,3,4-tetrahydro-1-naphthyl)-1*H*-imidazolium Maleate (4c). To a solution of **5c** (free base, 0.24 g, 1.1 mmol) in absolute EtOH (10 mL) was added 10% Pd/C (0.02 g). The mixture was subjected to 40 psi of H_2 for 5 h. The mixture was filtered through Celite, and the solvent was evaporated to give 0.23 g (98%) of **5c** as a free base. The free base was converted immediately to the maleate to afford the title compound as white crystals: mp 144−145 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.84−1.90 (m, 2H, CH_2), 2.00−2.03 (m, 1H), 2.09−2.14 (m, 1H), 2.25 (s, 3H, CH_3), 2.70−2.76 (m, 2H, Ar-CH_2), 4.35 (t, J = 6.08 Hz, 1H, CH), 6.24 (s, 2H, HC=CH), 6.78 (d, J = 7.20 Hz, 1H), 6.98−7.07 (m, 3H), 8.75 (d, J = 1.42 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 19.70 (CH_3), 21.38, 27.41, 30.78, 37.48, 170.77 (C=O); IR (KBr) 1571, 1507, 1458 cm^{-1}; MS m/e calcd for $C_{14}H_{16}N_2$ (free base): 212, found 212. Anal. ($C_{18}H_{20}N_2O_4$): C, H, N.

4-[1-(5,7-Dimethyl-1-hydroxy-1,2,3,4-tetrahydronaphthyl)]-*N*-(triphenylmethyl)imidazole (10e). A 3.0 M solution of EtMgBr (1.4 mL, 4.2 mmol) in Et_2O was added to a 0.25 M solution of 4-iodo-*N*-(triphenylmethyl)imidazole (1.69 g, 3.9 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of 5,7-dimethyl-1-tetralone (**9e**, 0.45 g, 2.6 mmol) in 2 mL of dry CH_2Cl_2 was added, and stirring was continued overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **9c**. The crude product was recrystallized from CH_2Cl_2/hexane to provide 1.17 g (94%) of the title compound as a white solid: mp 140−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74−1.78 (m, 1H), 1.99−2.10 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.26−2.32 (m, 1H), 2.56−2.66 (m, 2H, CH_2), 3.20 (bs, 1H, OH), 6.44 (d, J = 1.45 Hz, 1H, Im-H), 6.83 (s, 1H), 6.96 (s, 1H), 7.10−7.15 (m, 6H, Tr-H), 7.30-7.35 (m, 9H, Tr-H), 7.38 (d, J = 1.45 Hz, 1H, Im-H); IR (KBr) 3233, 1492, 1445 cm^{-1}; MS m/e calcd for $C_{34}H_{32}N_2O$: 484, found 484. Anal. ($C_{34}H_{32}N_2O\cdot{}^3/_4CH_2Cl_2$): C, H, N.

4-(3,4-Dihydro-5,7-dimethyl-1-naphthyl)-1*H*-imidazolium Maleate (5e). A solution of **10e** (1.10 g, 2.3 mmol) in 30 mL of TFA aqueous solution (60%) was stirred overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **5c**. Removal of the solvent gave 0.40 g (79%) of **5e** as a free base, which was converted to the maleate to afford the title compound as white crystals: mp 149−150 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.22 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.37−2.44 (m, 2H), 2.71−2.78 (m, 2H), 6.24 (s, 2H, HC=CH), 6.43 (t, J = 4.81 Hz, 1H, HC=C), 6.71 (s, 1H), 6.96 (s, 1H), 7.53 (d, J = 1.35 Hz, 1H, Im-H), 8.83 (d, J = 1.35 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 19.62 (CH_3), 21.11 (CH_3), 23.91 (CH_2), 24.12 (CH_2), 170.71 (C=O); MS m/e calcd for $C_{15}H_{16}N_2$ (free base): 224, found 224. Anal. ($C_{19}H_{20}N_2O_4\cdot{}^1/_2H_2O$): C, H, N.

4-(5,7-Dimethyl-1,2,3,4-tetrahydro-1-naphthyl)-1*H*-imidazolium Maleate (4e). A solution of **5e** (free base, 0.25 g, 1.1 mmol) in absolute EtOH (10 mL) was shaken with 10% palladium on charcoal (0.02 g) for 8 h under 40 psi of H_2 on a Parr hydrogenator. The solution was filtered through Celite and the filtrate was evaporated to give 0.24 g (95%) of **4e** as a free base. The free base was converted to the maleate to afford the title compound as white crystals: mp 138−139 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.81−1.87 (m, 2H, CH_2), 1.97−2.00 (m, 1H), 2.06−2.11 (m, 1H), 2.17 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.65−2.70 (m, 2H, Ar-CH_2), 4.30 (t, J = 6.02 Hz, 1H, CH), 6.24 (s, 2H, HC=CH), 6.60 (s, 1H), 6.89 (s, 1H), 7.03−7.04 (m, 1H), 8.73 (d, J = 1.36 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 19.62 (CH_3), 20.91 (CH_3), 21.42, 27.09, 30.87, 37.44, 170.78 (C=O); IR (KBr) 1570, 1516, 1481 cm^{-1}; MS m/e calcd for $C_{15}H_{18}N_2$ (free base): 226, found 226. Anal. ($C_{19}H_{22}N_2O_4$): C, H, N.

5-(Benzyloxy)-1-tetralone (9d). A mixture of 70 mL of $CHCl_3$/MeOH (2:1) and anhydrous K_2CO_3 (3.01 g, 21.8 mmol) was heated to reflux for 15 min under argon. Benzyl bromide (0.65 mL, 5.5 mmol) and a solution of 5-hydroxy-1-tetralone (0.81 g, 5 mmol) in 20 mL of $CHCl_3$/MeOH (2:1) were added, and the mixture was heated at reflux for an additional 3 h. After filtration, the filtrate was evaporated, and the residue was dissolved in $CHCl_3$, washed with HCl (1 N), dried, and concentrated. Flash chromatography of the crude product, eluting with EtOAc/hexane (1:6), gave 1.12 g (89%) of **9d** as white crystals: mp 50−51.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08−2.16 (m, 2H, CH_2), 2.62−2.66 (m, 2H, $COCH_2$), 2.97 (t, J = 6.14 Hz, 2H, $ArCH_2$), 5.11 (s, 2H, OCH_2), 7.08 (dd, J = 1.11, 8.09 Hz, 1H, *o*-(OBn)), 7.23−7.28 (m, 1H, *m*-(OBn)), 7.32−7.46 (m, 5H), 7.68 (dd, J = 1.04, 7.88 Hz, 1H, *p*-(OBn)); IR

(KBr) 1684 cm^{-1}; MS *m/e* calcd for $C_{17}H_{16}O_2$: 252, found 252. Anal. ($C_{17}H_{16}O_2$): C, H.

4-[1-[5-(Benzyloxy)-1-hydroxy-1,2,3,4-tetrahydronaphthyl]-*N*-(triphenylmethyl)imidazole (10d). A 3.0 M solution of EtMgBr (2 mL, 6 mmol) in Et_2O was added to a 0.25 M solution of 4-iodo-*N*-(triphenylmethyl)imidazole (2.40 g, 5.5 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of 5-(benzyloxy)-1-tetralone (**9d**, 0.89 g, 3.5 mmol) in 2 mL of dry CH_2Cl_2 was added, and stirring was continued overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **9c**. The crude product was recrystallized from CH_2Cl_2/hexane to provide 1.66 g (84%) of the title compound as a white solid: mp 147−148 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70−1.75 (m, 1H), 1.95−2.00 (m, 1H), 2.05−2.13 (m, 1H), 2.29−2.37 (m, 1H), 2.66−2.74 (m, 1H), 2.81−2.91 (m, 1H), 3.22 (bs, 1H, OH), 5.03 (s, 2H, OCH_2), 6.45 (d, J = 1.45 Hz, 1H, Im-H), 6.74 (dd, J = 2.04, 1.07 Hz, 1H), 6.96−6.99 (m, 1H), 7.05−7.14 (m, 6H), 7.29−7.34 (m, 10H), 7.37−7.44 (m, 5H); IR (KBr) 3233, 1493, 1473, 1450 cm^{-1}; MS *m/e*: 243(Tr^+). Anal. ($C_{39}H_{34}N_2O_2 \cdot {}^1/_2H_2O$): C, H, N.

4-[3,4-Dihydro-5-(benzyloxy)-1-naphthyl]-1*H*-imidazolium Maleate (5d). A solution of **10d** (1.0 g, 1.8 mmol) in 20 mL of TFA aqueous solution (60%) was stirred overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **5c**. Removal of the solvent gave 0.50 g (92%) of **5d** as a free base, which was converted to the maleate to afford the title compound as white crystals: mp 168−169 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.39−2.42 (m, 2H, CH_2), 2.89 (t, J = 7.84 Hz, 2H, Ar-CH_2), 5.14 (s, 2H, OCH_2), 6.25 (s, 2H, HC=CH), 6.47 (t, J = 4.77 Hz, 1H, HC=C), 6.70 (d, J = 7.20 Hz, 1H), 7.03 (d, J = 7.51 Hz, 1H), 7.15 (t, J = 7.77 Hz, 1H), 7.30−7.40 (m, 3H), 7.43−7.46 (m, 2H), 7.53 (d, J = 1.35 Hz, 1H, Im-H), 8.81 (d, J = 1.36 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 20.54 (CH_2), 23.72 (CH_2), 71.46 (OCH_2), 170.69 (C=O); IR (KBr) 1569, 1508, 1467 cm^{-1}; MS *m/e* calcd for $C_{20}H_{18}N_2O$ (free base): 302, found 302. Anal. ($C_{24}H_{22}N_2O_5$): C, H, N.

4-(5-Hydroxy-1,2,3,4-tetrahydro-1-naphthyl)-1*H*-imidazolium Maleate (4d). A solution of **5d** (free base, 0.40 g, 1.3 mmol) in absolute EtOH (10 mL) was shaken with 10% palladium on charcoal (0.02 g) for 32 h under 40 psi of H_2 on a Parr hydrogenator. The solution was filtered through Celite, and the filtrate was evaporated to give 0.20 g (71%) of the free base, which was converted to the maleate to afford the title compound as white crystals: mp 138−140 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.76−1.86 (m, 2H, CH_2), 1.91−2.04 (m, 1H), 2.05−2.17 (m, 1H), 2.73 (t, J = 6.55 Hz, 2H, Ar-CH_2), 4.31 (t, J = 13.12 Hz, 1H, CH), 6.25 (s, 2H, HC=CH), 6.41 (d, J = 7.71 Hz, 1H), 6.66 (d, J = 7.87 Hz, 1H), 6.93 (t, J = 7.88 Hz, 1H), 7.09 (d, J = 0.68 Hz, 1H, Im-H), 8.75 (d, J = 1.33 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 21.11, 23.95, 31.03, 37.16, 170.72 (C=O); MS *m/e* calcd for $C_{13}H_{14}N_2O$ (free base): 214, found 214; Anal. ($C_{17}H_{18}N_2O_5 \cdot {}^1/_4H_2O$): C, H, N.

4-[1-(1-Hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthyl)]-*N*-(triphenylmethyl)imidazole (10b). A 3.0 M solution of EtMgBr (1.6 mL, 4.8 mmol) in Et_2O was added to a 0.25 M solution of 4-iodo-*N*-(triphenylmethyl)imidazole (2.1 g, 4.8 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of 5-methoxy-1-tetralone (**9b**, 0.56 g, 3.2 mmol) in 2 mL of dry CH_2Cl_2 was added, and stirring was continued overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **9c**. The crude product was recrystallized from CH_2Cl_2/hexane to provide 1.33 g (91%) of the title compound as a white solid: mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70−1.77 (m, 1H), 1.93−1.98 (m, 1H), 2.03−2.11 (m, 1H), 2.29−2.35 (m, 1H), 2.54−2.64 (m, 1H), 2.71−2.79 (m, 1H), 3.24 (bs, 1H, OH), 3.78 (s, OCH_3), 6.44 (d, J = 1.48 Hz, 1H, Im-H), 6.67 (dd, J = 8.03, 1.03 Hz, 1H, *o*-(OCH_3)), 6.95 (dd, J = 7.92, 1.04 Hz, 1H, *p*-(OCH_3)), 7.06 (d, J = 7.98 Hz, 1H, *m*-(OCH_3)), 7.09−7.13 (m, 6H, Tr-H), 7.28−7.33 (m, 9H, Tr-H), 7.37 (d, J = 1.46 Hz, 1H, Im-H). The product was used in the synthesis of **4b** without further characterization.

4-(5-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)-1*H*-imidazolium Maleate (4b). A solution of **10b** (1.2 g, 2.5 mmol) in 25 mL of TFA aqueous solution (60%) was stirred overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **5c**. Removal of the solvent gave 0.51 g (90%) of 4-(3,4-dihydro-5-methoxy-1-naphthyl)-1*H*-imidazole (**5b**) as white crystals: ^{1}H NMR (300 MHz, CD_3OD) δ 2.26−2.33 (m, 2H, CH_2), 2.77 (t, J = 7.75 Hz, 2H, $ArCH_2$), 3.83 (s, 3H, OCH_3), 6.28 (t, J = 4.72 Hz, 1H, HC=C), 6.86 (d, J = 7.95 Hz, 2H), 7.01 (s, 1H, Im-H), 7.10 (t, J = 7.92 Hz, 1H), 7.66 (s, 1H, Im-H). The product was used in the following step without further characterization.

A solution of **5b** (free base, 0.51 g, 2.3 mmol) in absolute EtOH (10 mL) was shaken with 10% palladium on charcoal (0.05 g) for 12 h under 30 psi of H_2 on a Parr hydrogenator. The solution was filtered through Celite, and the filtrate was evaporated to give 0.51 g (99%) of **4b** as a free base. The free base was converted to the maleate to afford the title compound as white crystals: mp 149−150 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.78−1.84 (m, 2H, CH_2), 1.97−2.01 (m, 1H), 2.07−2.14 (m, 1H), 2.72 (t, J = 6.54 Hz, 2H, $ArCH_2$), 3.82 (s, 3H, OCH_3), 4.33 (t, J = 6.21 Hz, 1H, CH), 6.24 (s, 2H, HC=CH), 6.53 (d, J = 7.78 Hz, 1H), 6.81 (d, J = 8.10 Hz, 1H), 7.07−7.12 (m, 2H), 8.73 (d, J = 1.39 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 20.94, 23.87, 30.85, 37.13, 55.83 (OCH_3), 170.77 (C=O); MS *m/e* calcd for $C_{14}H_{16}N_2O$ (free base): 228, found 228. Anal. ($C_{18}H_{20}N_2O_5$): C, H, N.

4-[1-(1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthyl)]-*N*-(triphenylmethyl)imidazole (10f). A 3.0 M solution of EtMgBr (1.6 mL, 4.8 mmol) in Et_2O was added to a 0.25 M solution of 4-iodo-*N*-(triphenylmethyl)imidazole (2.1 g, 4.8 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of 6-methoxy-1-tetralone (**9f**, 0.56 g, 3.2 mmol) in 2 mL of dry CH_2Cl_2 was added, and stirring was continued overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **9c**. The crude product was recrystallized from CH_2Cl_2/hexane to provide 1.29 g (84%) of the title compound as a white solid: mp 93−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62−1.73 (m, 1H), 1.91−2.03 (m, 1H), 2.04−2.15 (m, 1H), 2.26−2.38 (m, 1H), 2.77−2.79 (m, 2H, Ar CH_2), 3.16 (bs, 1H, OH), 3.75 (s, 3H, OCH_3), 6.46 (d, J = 1.44 Hz, 1H, Im-H), 6.56 (d, J = 2.63 Hz, 1H, *o*-(OCH_3)), 6.65 (dd, J = 2.70, 8.65 Hz, 1H, *o*-(OCH_3)), 7.10−7.15 (m, 6H, Tr-H), 7.21 (d, J = 8.65 Hz, 1H, *m*-(OCH_3)), 7.29−7.34 (m, 9H, Tr-H), 7.37 (d, J = 1.43 Hz, 1H, Im-H); IR (KBr) 3214, 1500, 1445 cm^{-1}; MS *m/e* calcd for $C_{33}H_{30}N_2O_2$: 487, found 487. Anal. ($C_{33}H_{30}N_2O_2 \cdot {}^1/_4H_2O \cdot {}^1/_2CH_2Cl_2$): C, H, N.

4-(6-Methoxy-3,4-dihydro-1-naphthyl)-1*H*-imidazolium Maleate (5f). A solution of **10f** (1.15 g, 2.4 mmol) in 20 mL of TFA aqueous solution (60%) was stirred overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **5c**. Removal of the solvent gave 0.33 g (61%) of **5f** (free base). The free base was converted to the maleate to afford the title compound as white crystals: mp 152−153 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.40−2.42 (m, 2H, CH_2), 2.82 (t, J = 7.67 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 6.25 (s, 2H, HC=CH), 6.31 (t, J = 4.80 Hz, 1H, HC=C), 6.74− 6.77 (m, 1H), 6.83 (d, J = 2.59 Hz, 1H), 7.02 (d, J = 8.50 Hz, 1H), 7.52 (d, J = 1.34 Hz, 1H), 8.78 (d, J = 1.36 Hz, 1H); ^{13}C NMR (300 MHz, CD_3OD) δ 26.66 (CH_2), 31.43 (CH_2), 58.21 (OCH_3), 170.75 (C=O); IR (KBr) 1566, 1508, 1459 cm^{-1}; MS *m/e* calcd for $C_{14}H_{14}N_2O$ (free base): 226, found 226. Anal. ($C_{18}H_{18}N_2O_5$): C, H, N.

4-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)-1*H*-imidazolium Maleate (4f). A solution of **5f** (free base, 0.24 g, 1.1 mmol) in absolute EtOH (10 mL) was shaken with 10% palladium on charcoal (0.02 g) for 12 h under 30 psi of H_2 on a Parr hydrogenator. The solution was filtered through Celite, and the filtrate was evaporated to give 0.23 g (96%) of **4f** as a free base. The free base was converted to the maleate to afford the title compound as white crystals: mp 138−139 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.78−1.84 (m, 2H, CH_2), 1.96−2.00 (m, 1H), 2.11−2.15 (m, 1H), 2.81−2.88 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.28 (t, J = 6.33 Hz, 1H, CH), 6.24 (s, 2H, HC=CH), 6.68−6.71 (m, 2H), 6.84 (d, J = 8.25 Hz, 1H), 7.07 (dd, J = 1.35, 0.63 Hz, 1H), 8.75 (d, J = 1.42 Hz, 1H); ^{13}C NMR (300 MHz, CD_3OD) δ 21.60, 30.45, 31.58, 36.42, 55.61 (OCH_3),

170.78 (C═O); MS *m/e* calcd for $C_{14}H_{16}N_2O$ (free base): 228, found 228. Anal. ($C_{18}H_{18}N_2O_5$): C, H, N.

4-[1-(1-Hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthyl)]-*N*-(triphenylmethyl)imidazole (10g). A solution of 4-iodo-*N*-(triphenylmethyl)imidazole (2.3 g, 5.3 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of 7-methoxy-1-tetralone (**9g**, 0.61 g, 3.5 mmol) in 2 mL of dry CH_2Cl_2 was added, and stirring was continued overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **9c**. The crude product was recrystallized from CH_2Cl_2/hexane to provide 1.35 g (80%) of the title compound as a white solid: mp 180−181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66−1.76 (m, 1H), 1.87−2.03 (m, 1H), 2.05−2.16 (m, 1H), 2.27−2.40 (m, 1H), 2.62−2.84 (m, 2H, CH_2), 3.24 (bs, 1H, OH), 3.67 (s, 3H, OCH_3), 6.42 (d, J = 1.48 Hz, 1H, Im-H), 6.70 (dd, J = 2.78, 8.40 Hz, 1H, *o*-(OCH_3)), 6.86 (d, J = 2.75 Hz, 1H, *o*-(OCH_3)), 6.95 (d, J = 8.45 Hz, 1H, *m*-(OCH_3)), 7.10−7.14 (m, 6H, Tr-H), 7.29−7.33 (m, 9H, Tr-H), 7.40 (d, J = 1.47 Hz, 1H, Im-H); IR (KBr) 3197, 1500, 1445 cm^{-1}; MS *m/e* calcd for $C_{33}H_{30}N_2O_2$: 487, found 487. Anal. ($C_{33}H_{30}N_2O_2 \cdot {}^1/_2H_2O$): C, H, N.

4-(3,4-Dihydro-7-methoxy-1-naphthyl)-1*H*-imidazolium Maleate (5g). A solution of **10g** (0.5 g, 2.1 mmol) in 10 mL of TFA aqueous solution (60%) was stirred overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **5c**. Removal of the solvent gave 0.17 g (74%) of **5g** (free base). The free base was converted to the maleate to afford the title compound as white crystals: mp 154−155 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.43−2.46 (m, 2H, CH_2), 2.80 (t, J = 7.64 Hz, 2H, Ar-CH_2), 3.75 (s, 3H, OCH_3), 6.27 (s, 2H, HC═CH), 6.51 (t, J = 4.80 Hz, 1H, HC═C), 6.65 (d, J = 2.56 Hz, 1H, *o*-(OCH_3)), 6.83 (dd, J = 8.25, 2.59 Hz, 1H, *o*-(OCH_3)), 7.19 (d, J = 8.24 Hz, 1H, *m*-(OCH_3)), 7.59 (d, J = 1.27 Hz, 1H, Im-H), 8.85 (d, J = 1.31 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 24.63 (CH_2), 27.52 (CH_2), 55.76 (OCH_3), 170.68 (C═O); MS *m/e* calcd for $C_{14}H_{16}N_2O$ (free base, MH^+): 227, found 227. Anal. ($C_{18}H_{18}N_2O_5$): C, H, N.

4-(7-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)-1*H*-imidazolium Maleate (4g). A solution of **5g** (free base, 0.25 g, 1.1 mmol) in absolute EtOH (10 mL) was shaken with 10% palladium on charcoal (0.02 g) for 5 h under 30 psi of H_2 on a Parr hydrogenator. The solution was filtered through Celite, and the filtrate was evaporated to give 0.25 g (99%) of the product (free base). The free base was converted to the maleate to afford the title compound as white crystals: mp 121−122 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.80−1.83 (m, 2H, CH_2), 1.96−2.00 (m, 1H), 2.12−2.16 (m, 1H), 2.77−2.83 (m, 2H, Ar-CH_2), 3.67 (s, 3H, OCH_3), 4.33 (t, J = 6.27 Hz, 1H, CH), 6.24 (s, 2H, HC═CH), 6.46 (d, J = 2.56 Hz, 1H), 6.78 (dd, J = 8.45, 2.65 Hz, 1H), 7.07−7.11 (m, 2H), 8.75 (d, J = 1.35 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 21.85, 29.30, 31.38, 37.32, 55.64 (OCH_3), 170.77 (C═O); IR (KBr) 1565, 1494 cm^{-1}; MS *m/e* calcd for $C_{14}H_{16}N_2O$ (free base): 228, found 228. Anal. ($C_{18}H_{20}N_2O_5$): C, H, N.

Diethyl (2-Methylbenzyl)malonate (11). A concentrated sodium ethoxide solution (21% in EtOH, 51 mmol) was diluted with 14 mL of absolute EtOH under argon. Freshly distilled diethyl malonate (7.8 mL, 51 mmol) was added dropwise at 70 °C to the above solution. After 10 min, 2-methylbenzyl chloride (6.6 mL, 51 mmol) was added while refluxing over a period of 15 min. The reaction mixture was stirred at refluxing condition for another 2 h and quenched with water at room temperature. The mixture was neutralized with aqueous HCl (6 N) and concentrated to remove EtOH. The residue was partitioned between 50 mL of H_2O and 100 mL of Et_2O. The water layer was extracted with Et_2O (3 × 50 mL), and the combined organics were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was distilled to yield 7.49 g (57%) of the product as a colorless oil: bp 155−160 °C at 3 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.14 Hz, 6H, $2CH_3$), 2.34 (s, 3H, Ar-CH_3), 3.22 (d, J = 7.79 Hz, 2H, Ar-CH_2), 3.64 (t, J = 7.82 Hz, 1H, CH), 4.11−4.19 (m, 4H, $2OCH_2$), 7.08−7.14 (m, 4H, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.97 (CH_3), 19.29 (CH_3), 31.89 (CH_2), 52.26 (CH), 61.44 (OCH_2), 168.99 (C═O); IR (neat) 1734 cm^{-1}; MS *m/e* calcd for $C_{15}H_{20}O_4$: 264, found 264. Anal. ($C_{15}H_{20}O_4$): C, H.

3-(2-Methylphenyl)propionic Acid (12). To a potassium hydroxide aqueous solution (18 M, 10 mL) was added diethyl (2-methylbenzyl)malonate (**11**, 7.0 g, 26.5 mmol). The solution was heated to reflux for 1.5 h and then diluted with 20 mL of water and evaporated to remove the ethanol formed in the hydrolysis. To the cold solution was added slowly a H_2SO_4 aqueous solution (7.0 M, 35 mL), and the mixture was heated to reflux for 5 h. After cooling, the aqueous solution was extracted with Et_2O (3 × 100 mL). The combined organics were washed with water, dried over Na_2SO_4, and concentrated. The crude product was a mixture of diacid and monoacid, which was placed in a flask and heated to 160 °C under argon. Evolution of CO_2 was observed at 140 °C and became vigorous as the material melted. The reaction was maintained at 160 °C for 30 min and cooled to room temperature with stirring to yield a light-yellow solid, which was then crystallized in Et_2O/hexane to give 3.55 g (82%) of the product as white needles: mp 99−100 °C (lit.[23] 102−104 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, CH_3), 2.62−2.68 (m, 2H, CH_2), 2.93−2.99 (m, 2H, CH_2), 7.15 (s, 4H, Ar-H); IR (KBr) 1700 cm^{-1}; MS *m/e* calcd for $C_{10}H_{12}O_2$: 164, found 164. Anal. ($C_{10}H_{12}O_2$): C, H.

4-Methyl-1-indanone (13). A solution of 3-(2-methylphenyl)propionic acid (**12**, 0.84, 5.1 mmol) in 10 mL of $SOCl_2$ was heated at reflux for 1 h. Excess $SOCl_2$ was evaporated under the reduced pressure to give 3-(2-methylphenyl)propionic acid chloride as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (d, J = 2.18 Hz, 3H, CH_3), 2.99−3.04 (m, 2H, CH_2), 3.14−3.19 (m, 2H, CH_2), 7.13−7.17 (m, Ar-H). This product was dissolved in 65 mL of dry CH_2Cl_2 and used immediately in the following step.

Titanium tetrachloride (1.2 mL, 11 mmol) was added dropwise to the above solution at −30 °C under argon. The mixture was stirred at −30 °C for an additional 30 min and then was warmed to room temperature. Stirring was continued for 2 days. The resulting brown mixture was carefully poured into 150 mL of crushed ice and stirred until the dark color disappeared. The layers were separated, and the aqueous portion was extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were washed successively with H_2O, HCl solution (10%), H_2O, saturated aqueous $NaHCO_3$ solution, and brine. After drying over Na_2SO_4, the solution was concentrated under the reduced pressure to give 0.63 g (86%) of **13** as a white solid: mp 93−94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H, CH_3), 2.69−2.73 (m, 2H, CH_2), 3.03 (t, J = 5.46 Hz, 2H, CH_2), 7.30 (t, J = 7.50 Hz, 1H, *m*-(CH_3)), 7.41 (d, J = 7.20 Hz, 1H, *o*-(CH_3)), 7.61 (d, J = 7.57 Hz, 1H, *p*-(CH_3)); IR (KBr) 1702 cm^{-1}; MS *m/e* calcd for $C_{10}H_{10}O$: 146, found 146. This compound was used in the synthesis of **14** without further characterization.

4-[1-(1-Hydroxy-4-methylindanyl)]-*N*-(triphenylmethyl)imidazole (14). A 3.0 M solution of EtMgBr (2.7 mL, 8.1 mmol) in Et_2O was added to a 0.25 M solution of 4-iodo-*N*-(triphenylmethyl)imidazole (3.48 g, 8.0 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of 4-methyl-1-indanone (**13**, 0.60 g, 4.1 mmol) in 2 mL of dry CH_2Cl_2 was added, and stirring was continued overnight. The reaction was worked up in a manner similar to that previously described for the synthesis of **9c**. The crude product was recrystallized from CH_2Cl_2/hexane to provide 1.15 g (61%) of the title compound as a white solid: mp 126−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 2.42−2.49 (m, 1H), 2.59−2.69 (m, 1H), 2.83−2.84 (m, 1H), 3.02−3.10 (m, 1H), 6.69 (d, J = 1.41 Hz, 1H, Im-H), 7.02−7.08 (m, 3H), 7.11−7.14 (m, 6H), 7.30−7.34 (m, 9H), 7.40 (d, J = 1.38 Hz, 1H, Im-H); IR (KBr) 3282, 1494, 1444 cm^{-1}; MS *m/e*: 438 ($M - H_2O$). Anal. ($C_{32}H_{28}N_2O \cdot {}^1/_4H_2O$): C, H, N.

4-[1-(4-Methylindanyl)]-1*H*-imidazolium Maleate (6). To a mixture of Me_3SiCl (1.68 mL, 13.2 mmol), NaI (2.0 g 13.2 mmol), and dry CH_3CN (0.5 mL, 13.2 mmol) was added a solution of **14** (1.0 g, 2.2 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred for 24 h at room temperature. Dilution with H_2O, extraction with CH_2Cl_2, and subsequent flash chromatography, eluting with CH_2Cl_2/CH_3OH (20:1), gave 0.33 g (76%) of **6** (free base) as a white solid. The free base was

converted to the maleate and the salt was recrystallized in CH_3OH/Et_2O: mp 127−129 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.10−2.18 (m, 1H), 2.29 (s, 3H, CH_3), 2.60−2.65 (m, 1H), 2.91−2.96 (m, 1H), 3.00−3.05 (m, 1H), 4.58 (t, J = 8.12 Hz, 1H, CH), 6.24 (s, 2H, HC=CH), 6.88 (d, J = 6.98 Hz, 1H), 7.04−7.12 (m, 2H), 7.27 (d, J = 1.29 Hz, 1H, Im-H), 8.77 (d, J = 1.35 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 19.07 (CH_3), 30.81, 34.16, 42.78, 170.77 (C=O); MS *m/e* calcd for $C_{13}H_{14}N_2$ (free base, MH^+): 199, found 199. Anal. ($C_{17}H_{18}N_2O_4 \cdot {}^1/_4H_2O$): C, H, N.

Radioligand Binding Studies. All of the newly synthetic imidazoles were determined on α_1- and α_2-adrenoceptor systems using membrane fractions of rat brain, as described previously.[3]

Receptor Modeling. The receptor model was constructed using SYBYL 5.5 (TRIPOS associates Inc.). The coordinates for bacteriorhodopsin were obtained from Brookhaven Protein Data Bank. The amino acid sequence for the human α_2-adrenoceptor was obtained from Hibert *et al*.[6] The receptor model of the human α_2-adrenoceptor was constructed in a similar way according to a strategy previously described by Hibert *et al*.[6] In short, the model was based on a presumed similarity in three-dimensional structure between bacteriorhodopsin and the GPC receptors. α-Helices were constructed from the primary structure of the human α_2-adrenoceptor with ϕ and ψ values of −59° and −44°, and the proline kinks were fixed. Each helices were energy minimized using Kollmann all-atom force field in SYBYL. Fitting of the backbone of these helices onto the backbone of bacteriorhodopsin in such a way that the conserved residues were oriented toward the inside of the receptor, as were the charged amino acids. The loop regions of the receptor were not included in the modeling. Finally, the resulting bundle of the receptor was energy minimized by Kollmann all-atom force field for 2000 steps using conjugate gradient minimizer. A cutoff of 8 Å was used.

Binding Site Modeling. The conformational analysis of α-MeNE and the medetomidine-like analogs have been described previously.[3] The low-energy conformation of α-MeNE was docked into the receptor model manually. The potential interactions of α-MeNE with α_2-adrenoceptor derived by site-directed mutagenesis was considered during the docking procedure. The complex of receptor−ligand was optimized by Tripos force field. The low-energy conformations of (*S*)-medetomidine and its analogs were aligned with the one of α-MeNE by fitting the aromatic ring and the nitrogen atom and then used in the docking.

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