Medetomidine Analogs as α_2-Adrenergic Ligands. 2. Design, Synthesis, and Biological Activity of Conformationally Restricted Naphthalene Derivatives of Medetomidine

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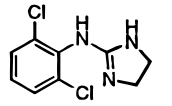
A new series of naphthalene analogs of medetomidine have been prepared and evaluated for their α-adrenergic activities. The methylnaphthyl analog **5a** showed significant selectivity for α_2-adrenoceptors and behaved as a partial α_1-agonist in rat aorta preparations. In contrast, the *Z*-ethylene analog **8c** was α_1-selective and behaved as a potent α_1-antagonist. Two rigid analogs (**6** and **7**) exhibited large differences in binding affinities at α_1- vs α_2-receptors, indicating that the conformational flexibility of **5a** is important for the fulfillment of the α-adrenergic activities. Molecular modeling studies began with conformational analysis of classical phenethylamines and medetomidine analogs. Superimposition of medetomidine conformations with those of phenethylamines provided a tentative explanation for the α_2-adrenergic activity of the new imidazoles. A common binding mode for phenethylamines and imidazoles with α_2-adrenoceptors is proposed. Knowledge of the biological properties of the 4-substituted imidazoles, integrated with the information derived from computer-assisted molecular modeling, has provided new insights for the structural and conformational requirements of this class as new adrenergic drugs.

Introduction

α_2-Adrenergic agonists have therapeutic applications in a variety of disease states.[1] Clonidine (**1**) is the most familiar antihypertensive drug which possesses agonist activity at α_2-adrenoceptors. However, the use of clonidine and other α_2-agonists in the treatment of hypertension has been limited by the presence of sedation. This side effect has been linked to the stimulation of the central α_2-adrenoceptors. Since the discovery of clonidine, separation of the centrally mediated antihypertension and sedation has been sought. On the other hand, rilmenidine (**2**)[2] and moxonidine (**3**)[3] have been used as new therapeutic agents for the treatment of hypertension which exhibit little sedation. On the other hand, the sedative effects of α_2-agonists have therapeutic application as adjuncts to general anesthesia.[4] Compared to barbiturates and benzodiazepines as preanesthetic medications, α_2-agonists provide an advantage in that their anesthetic action can be readily reversed by α_2-antagonist administration.

Medetomidine (**4**) is a new synthetic drug which shows a higher degree of the sedative-analgesic effect than clonidine.[5] It represents a new class of α-agonists that contains a 4-substituted imidazole ring and is highly selective at α_2-adrenoceptors. Dexmedetomidine, the *S*-(+)-enantiomer of medetomidine, was identified as the active component and has been used as an anesthetic in animals.[6] As such, medetomidine provides a unique template for the design of α_2-adrenoceptors ligands.



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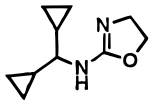

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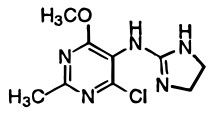

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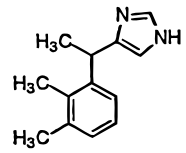

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We previously described the synthesis and pharmacological evaluation of a series of novel naphthyl analogs (**5a**−**e**) in selected α_1- and α_2-adrenoceptor systems.[7] Analog **5a** possessed an equal potency and higher selectivity for α_2-adrenoceptors than medetomidine. Moreover, the enantiomers of **5a** exhibit a stereoselective interaction [e.g., (*R*)-(−)-**5a** < (*S*)-(+)-**5a**] for the blockade of the α_{2A}-adrenergic-mediated responses in human platelets and qualitative differences in activity on α_2-adrenoceptors in electrically stimulated guinea pig ileum. Replacement of the benzylic methyl group with other functional groups resulted in decreased activities at both α_1- and α_2-adrenoceptors. From the structure−activity relationships (SAR) derived from this series, we concluded that the benzylic substituent of the naphthyl analogs plays a critical role in their potent and selective interactions with α_2-adrenergic binding sites.

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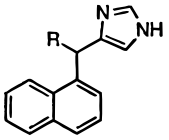
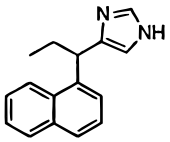
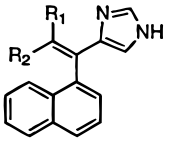


5a. R = C H_3
5b. R = C F_3
5c. R = H
5d. R = OH
5e. R = OCH_3

Further investigations are needed to determine conformational preferences of analog **5a** that can account for its high selectivity on α_2-adrenoceptors. A knowledge of the active conformation of medetomidine-like analogs, and therefore of the spatial relationship of their presumed pharmacophoric group (the aromatic moiety and the imidazole ring), is basic for the rational design of new molecules capable of interacting with α_2-adrenoceptors. Various studies have dealt with the pharmacophoric conformational requirements of adrenergic drugs.[8] One of the most frequently used methods is to design conformationally restricted analogs derived from a flexible molecule. Such a method has been successfully carried out to study the conformation−activity relationships of the phenethylamine class.[9−13] The present report includes two novel conformationally restricted analogs of **5a** which incorporate the benzylic methyl group at either the 8-position (compound **6**) or 2-position (compound **7**) of the naphthyl ring (Figure 1). The major drawback of this design is that in order to construct these rigid molecules, additional atoms and bonds have to be added to the parent compound (**5a**) which could potentially affect the chemical and physical properties of the drug, particularly its hydrophilic properties in this case. Thus, analogs **5f** and **8a**−**c** were proposed to further explore the SAR with regard to the benzylic modifications of the naphthyl series. We envisioned that this approach would provide compounds with higher potency and afford a better understanding of the spatial and steric requirements for drug activity and selectivity at α_2-adrenoceptors.



5f



8a. $R_1 = R_2 = H$
8b. $R_1 = H$, $R_2 = CH_3$
8c. $R_1 = CH_3$, $R_2 = H$

Chemistry

The 4-substituted imidazole analogs were synthesized in a straightforward manner by utilizing a direct introduction of an imidazole ring, as recently reported by Turner and Lindell.[14] In this approach, an imidazol-4-yl anion (**9b**) was generated at ambient temperature by addition of ethylmagnesium bromide to the N-protected 4-iodoimidazole **9a**. The imidazol-4-yl anion was then reacted with a variety of aldehydes and ketones using CH_2Cl_2 as a solvent to prevent formation of 2-alkylated products. Different strategies were applied in the last step of the synthesis to convert tertiary alcohols to the corresponding target compounds (Figure 2).

Following Turner's procedure, 1-naphthaldehyde was allowed to react with *N*-tritylimidazol-4-yl anion **9b** to give secondary alcohol **10a** in 85% yield (Scheme 1). This alcohol was easily oxidized by manganese dioxide to afford ketone **11**, which served as the common intermediate of analogs **5a**,**b**,**f** and **8a**−**c**. Ketone **11** was treated with methylmagnesium bromide in THF followed by simultaneous dehydroxylation and deprotonation to give analog **8a**.

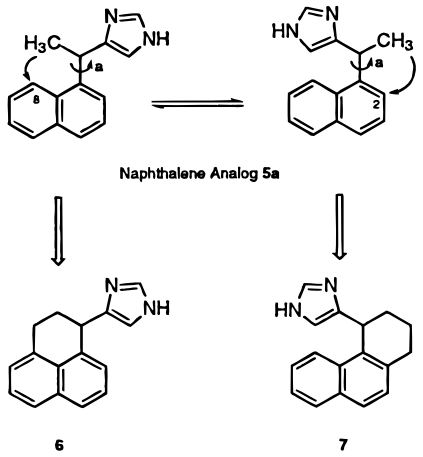


Figure 1.

The initial synthetic route employed for the preparation of analogs **5f** and **8b**,**c** is shown in Scheme 2. A Grignard reaction was applied to introduce an ethyl group to the benzylic position. Since Grignard additions are sensitive to steric effects, a competing process involving reduction of the carbonyl group of **11** was observed. This competing reduction was minimized by using benzene as a solvent. The two ethylene analogs **8b**,**c** were obtained by elimination of tertiary alcohol **10c** in 60% of trifluoroacetic aqueous solution. Flash chromatography of the crude product afforded the two geometric isomers (*E* and *Z*) which were distinguishable by their H-NMR spectra. The structure of the *Z*-isomer **8c** was further confirmed by the X-ray crystallography (Figure 3). These two isomers exhibited great differences in the hydrogenation reaction. The alkene group of **8c** was easily hydrogenated with Pd/C under moderate pressure, whereas compound **8b** was resistant to hydrogenation under various conditions, most likely due to steric effects. The overall yields of **8c** and **5f** were very low using this approach due to the *Z*-isomer **8c** being a minor product produced from alcohol **10c**. To circumvent this problem, ketone **11** was converted to the ethylene derivatives **12a**,**b** by the Wittig reaction (Scheme 3). The ratio of *Z*/*E*-isomers was dependent on the reaction temperature, with the *Z*-isomer **12b** as the major product when the reaction was carried out at 80 °C. N-Deprotection of **12b** followed by hydrogenation gave the saturated analog **5f**.

Enormous difficulties were encountered in the preparation of analog **6**. Initially, we attempted to synthesize analog **6** from the commercially available material perinaphthenone (**13a**) (Scheme 4). Grignard coupling with **13a** gave exclusively the 1,2-addition product **14a** in 49% yield. However, deoxygenation of **14a** using either hydrogenation or triethylsilane under acidic conditions or radical reduction was not successful.[15] Mixtures were usually obtained after the reactions. A plausible explanation for the failure of these reactions is due to the high symmetry of the perinaphthenyl cation (**14b**) or radical leading to a considerable amount of resonance stabilization of these entities.[16]

An alternate route to **6** included introduction of the imidazole ring to the saturated ketone **13b** (Scheme 5).

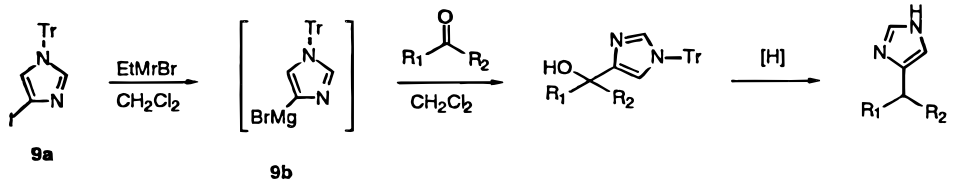
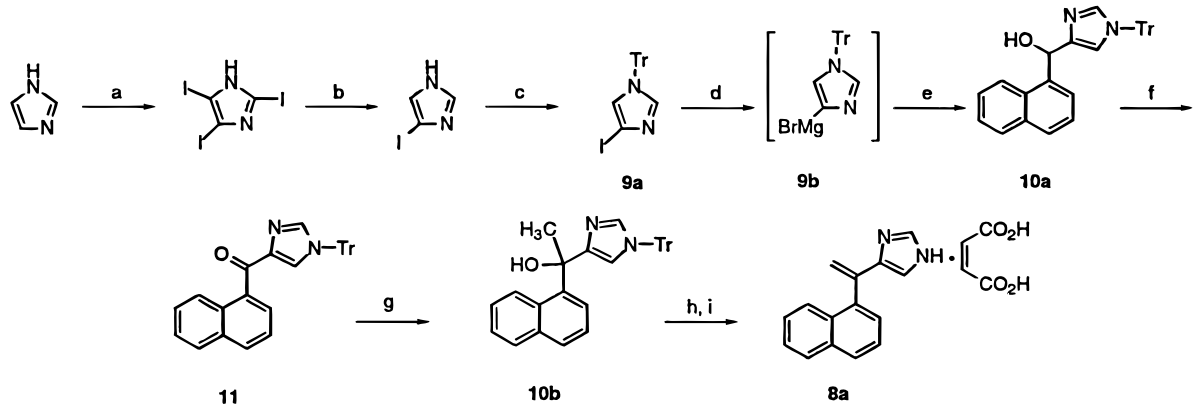


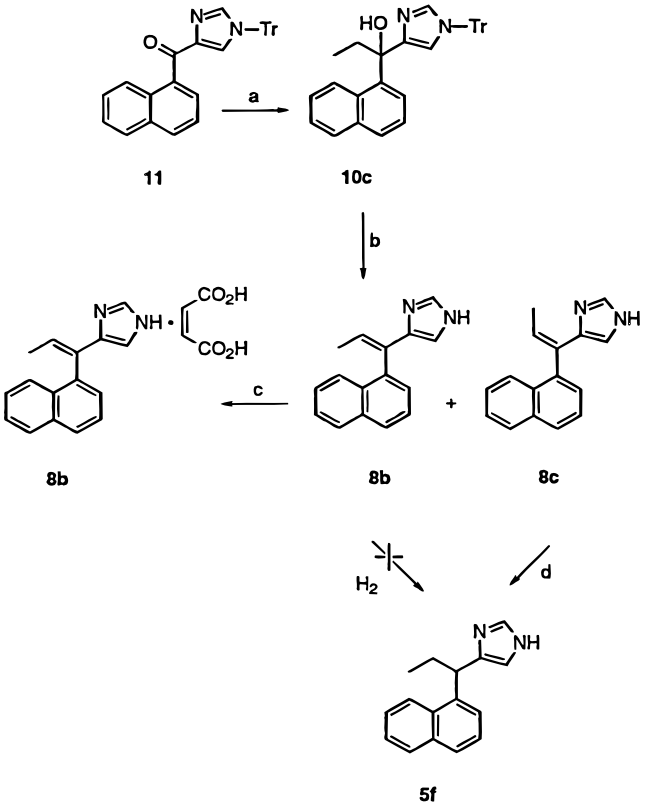
Figure 2. Retrosynthesis of 4-substituted imidazoles.

Scheme 1[a]



[a] (a) I_2, KI (20%), NaOH (2 N); (b) Na_2SO_3, EtOH/H_2O (3:7), reflux; (c) TrCl, Et_3N, THF; (d) EtMgBr, CH_2Cl_2; (e) 1-naphthaldehyde; (f) MnO_2, CH_2Cl_2, reflux; (g) CH_3MgBr, THF; (h) TFA, H_2O (60%); (i) maleic acid, CH_3OH.

Scheme 2[a]



[a] (a) EtMgBr, benzene; (b) (i) TFA/H_2O (60%); (ii) flash chromatography; (c) maleic acid, CH_3OH; (d) H_2 (40 psi), Pd/C (5%), EtOH.

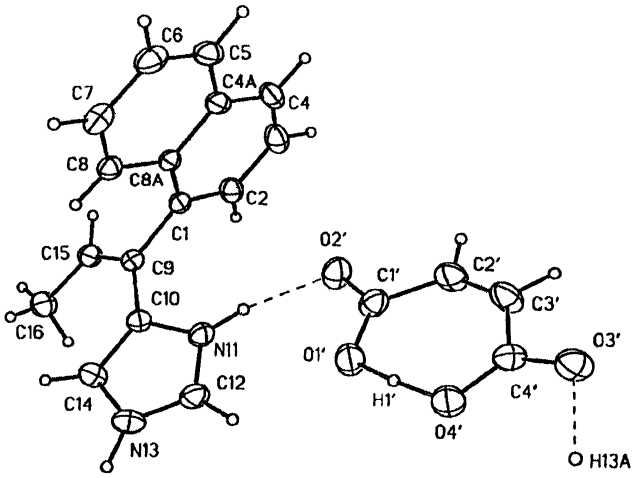
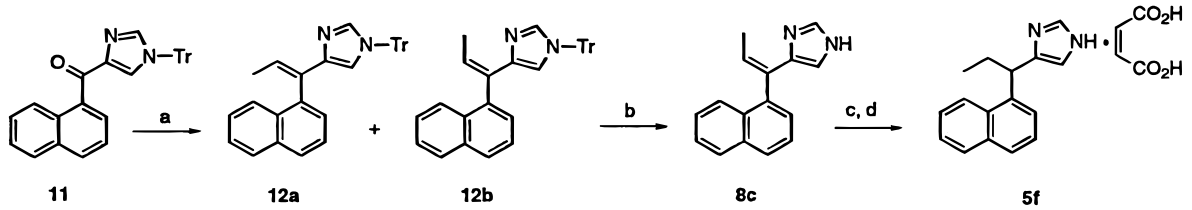


Figure 3. Thermal ellipsoid plot of **8c** (as a maleate salt). Dashed lines are intramolecular hydrogen bonds, and the open bonds are linear intramolecular hydrogen bonds. Atom labeled H13A is a symmetry-generated atom.

Conversion of perinaphthenone **13a** to perinaphthanone **13b** was described in the 1950s using lithium aluminum hydride (LAH) with a reported 65% yield.[17] However, we were unable to duplicate the yield, especially for a large reaction scale. In addition, isolation of the desired compound **13b** from the crude product was tedious, and the overall yield of the material was low. Other reducing agents, such as K-Selectride,[18] diimide,[19] or Wilkinson's hydrogenation,[20] were tried and either resulted in the isolation of unreacted **13a** or generated complex mixtures. An alternate route to **13b** was explored using a multistep synthesis. The synthesis of 3-(1-naphthyl)-propionic acid (**15**) was conveniently achieved by allowing α-(chloromethyl)naphthalene to react with a malonic ester and then subjecting the product to hydrolysis and facile decarboxylation.[21] Intramolecular Friedel–Crafts reaction of **15** gave ketone **13b** using stannic chloride as a Lewis acid. Although the yield of the cyclization step was not significantly higher than that of LAH reduction, the purification procedure was much easier. Isolation of ketone **13b** from the reaction mixture must be carried out quickly due to its instability, and **13b** had to be used in the Grignard addition immediately after preparation.

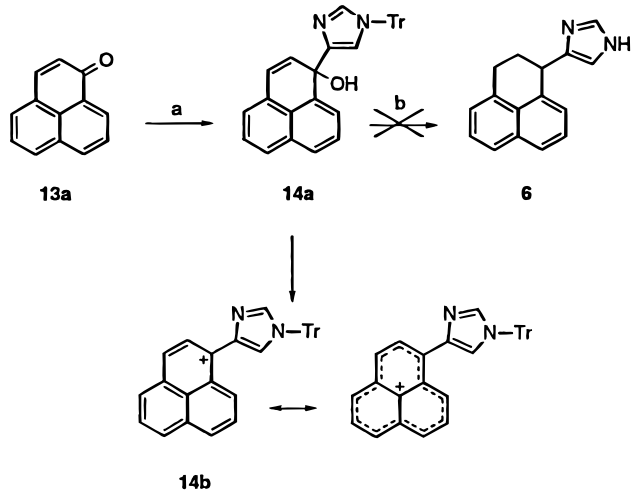
After the Grignard reaction, an attempt to eliminate the hydroxy group of **14c** was not successful by using

Scheme 3[a]



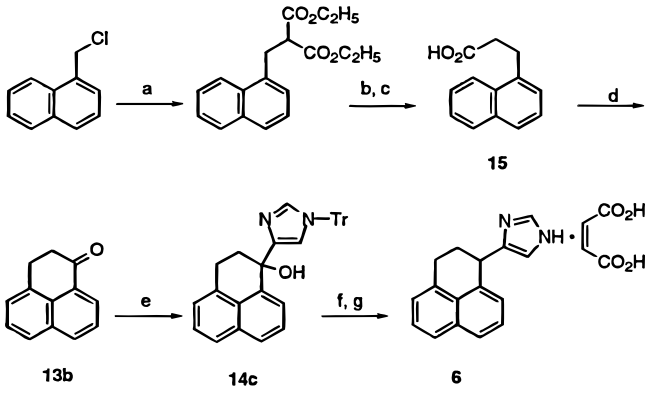
[a] (a) Ethyltriphenylphosphonium bromide, NaH, DMSO, 80 °C; (b) AcOH/H_2O (90%), 60 °C; (c) H_2 (40 psi), Pd/C (5%), EtOH; (d) maleic acid, CH_3OH.

Scheme 4[a]



[a] (a) **9b**, CH_2Cl_2; (b) hydrogenation of Et_3SiH, TFA or (i) PTC-Cl, pyridine, CH_2Cl_2, (ii) nBu_3SnH, AIBN, benzene, reflux.

Scheme 5[a]

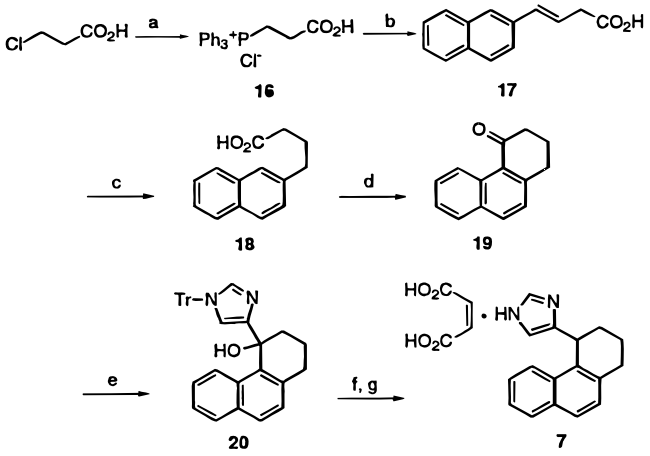


[a] (a) $CH_2(CO_2C_2H_5)_2$, $NaOC_2H_5$, HOC_2H_5, reflux; (b) NaOH/H_2O, reflux; (c) 180 °C; (d) (i) $SOCl_2$, (ii) $SnCl_4$; (e) **9b**, CH_2Cl_2; (f) $TMSCl-NaI-CH_3CN$, CH_2Cl_2; (g) maleic acid, CH_3OH.

triethylsilane in a large excess of hot TFA. Purification of the reaction mixture was complicated by the presence of unidentified byproducts. The synthesis of target compound **6** was eventually accomplished successfully by using $Me_3SiCl-NaI-CH_3CN$. This reagent has been recognized as a Me_3SiI equivalent and has been reported to be an efficient reduction agent of tertiary benzylic alcohols, although the mechanism of the reaction has not been elucidated.[22]

The preparation of analog **7** is outlined in Scheme 6. The Wittig reagent **16** was obtained from the reaction of β-chloropropionic acid and triphenylphosphine.[23] Treatment of 2-naphthylaldehyde and the Wittig reagent **16** with 2 equiv of base gave butenoic acid **17** with trans configuration.[24] Saturated acid **18** was then produced by hydrogenation. Intramolecular Friedel–

Scheme 6[a]



[a] (a) Triphenylphosphine, 150 °C; (b) 2-naphthaldehyde, NaH, THF/DMSO (1:1), 0 °C → room temperature; (c) H_2 (15 psi), Pd/C (10%), EtOH; (d) (i) PCl_5, (ii) $SnCl_4$; (e) **9b**, CH_2Cl_2; (f) Et_3SiH, TFA, 50–55 °C; (g) maleic acid, CH_3OH.

Crafts acylation of butanoic acid **18** into 2,3-dihydro-4(1*H*)-phenanthrone (**19**) produced the phenanthrene carbon skeleton exclusively.[25,26] This ketone was then reacted with **9b** to give tertiary alcohol **20** in 72% yield. Deoxygenation and N-deprotection was performed in triethylsilane–trifluoroacetic acid solution at 50–55 °C in 56% yield.

Biological Results

The α_1- and α_2-adrenoceptor binding affinities of the 4-substituted imidazoles were determined in membrane fractions of rat brain. Results for the newly synthesized 4-substituted imidazoles are summarized in Table 1. Extension of the side chain with one more carbon (**5f**) resulted in a 13-fold reduction in binding affinity on α_2-adrenoceptors but only a slight decrease (3-fold) at α_1-adrenoceptors as compared to the methyl derivative **5a**. The methylene analog **8a** retains good binding affinity as well as selectivity at α_2-adrenoceptors. In contrast, the ethylene analogs **8b**,**c** exhibited reversed selectivity on α-adrenoceptors. For example, the *Z*-ethylene analog **8c** was 33-fold more selective for α_1-adrenoceptors in the rat brain membrane, and it is the most potent and selective α_1-binding ligand that we have found in the 4-substituted imidazole series.

The two rigid molecules **6** and **7** exhibited significantly different binding affinities at both α_1- and α_2-adrenoceptors. Molecule **6** was nearly equipotent to the parent compound **5a** at α_2-adrenoceptors; however, it also displayed high affinity at α_1-receptors and thus a lost of selectivity. Molecule **7** showed a 111-fold reduction in binding affinity at α_2-adrenoceptors but was only 3-fold less potent at α_1-adrenoceptors, as compared to

Table 1. α_1- and α_2-Adrenergic Binding Affinity of 4-Substituted Imidazoles in Membrane Preparations of Rat Brain

	K_i (nM)[a]		
compd	α_1	α_2	α_2-selectivity ratio[b]
4	1109 ± 36	25 ± 13	44.36
5a	224 ± 20	13 ± 11	17.23
5f	574 ± 413	165 ± 52	3.48
8a	1734 ± 400	122 ± 27	14.21
8b	387 ± 87	1474 ± 586	0.26
8c	57 ± 19	1890 ± 923	0.03
6	55 ± 12	33 ± 5	1.67
7	655 ± 150	1449 ± 658	0.45
21	9221 ± 1196	205 ± 55	44.98

[a] Rat brain membrane preparations were incubated with 0.1 nM [^{3}H]prazosin and 0.2 nM [^{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 = $K_i(\alpha_1)/K_i(\alpha_2)$.

Table 2. Functional Studies of 4-Substituted Imidazoles for α_1- and α_2-Adrenoceptor Activities in Rat Aorta (α_1-Type) and Human Platelets (α_2-Type)

	α_1-agonist			α_2-antagonist	
compd	E_{max}[a]	EC_{50} (nM)[b]	α_1-antagonist K_B (nM)[c]	IC_{50} (μM)[d]	potency ratio[e]
4	33 ± 14	281 ± 43		2.9	1.00
5a	39 ± 12	153 ± 60		4.3	0.69
8c			3388	215.4	0.01
6	38 ± 11	156 ± 54		14.3	0.20
7			136	97.7	0.03

[a] Data are expressed as the percent maximal analog response relative to phenylephrine = 100%. [b] EC_{50} = molar 50% effective concentration. [c] K_B of the antagonist was calculated by the following equation: $K_B = [B]/(DR - 1)$, where [B] is in the presence and absence of the antagonist. [d] $pIC_{50} = -\log IC_{50}$, where IC_{50} = molar 50% inhibitory concentration. [e] Potency ratio = IC_{50}(medetomidine)/IC_{50}(analog).

Table 3. Computational Data for **21** from Conformational Analysis

conformations of **21**		energy[a] (kcal/mol)	torsion angle[b] (deg)	distance[c] (Å)	height[d] (Å)
anti$^-$	α-rotamer	0.01	178.8	5.175	1.385
	β-rotamer	0.01	179.0	5.174	1.388
gauche$^+$	α-rotamer	0	57.8	3.896	2.409
	β-rotamer	0	57.9	3.898	2.408
gauche$^-$	α-rotamer	0.12	−64.4	4.032	2.137
	β-rotamer	0.09	−64.4	4.030	2.147

[a] The lowest-energy conformation is set arbitrarily to 0 kcal/mol. [b] Torsion angle is defined as C−C_β−C_α−N. [c] The distance is measured from the center of the phenyl to the nitrogen (see Figure 5). [d] The height is measured from the nitrogen to the plane of the phenyl ring (see Figure 5).

5a. Therefore, similar to the two ethylene analogs **8b**,**c**, **7** is more selective at α_1-receptors. Results obtained with the two rigid molecules suggest that the conformational flexibility of **5a** is important for the fulfillment of the α-adrenergic activities.

Selected 4-substituted imidazoles were also evaluated for α-adrenergic functional activities on rat aorta (α_1) and human platelets (α_2), respectively, by methods that were previously reported.[7,27] Results are summarized in Table 2. On rat aorta, the α_1-adrenoceptor responses were expressed as a percentage of the maximum contraction to 1 μM of phenylephrine. Medetomidine is a partial agonist with a maximal response of 33% and EC_{50} value of 281 nM. The parent compound **5a** showed greater potency (EC_{50} = 153 nM) and exhibited a higher maximal contractile response (E_{max} = 39%) than medetomidine on rat aorta. The *Z*-isomer (**8c**) of the ethylene analogs, the most selective α_1-binding ligand, was an antagonist on α_1-receptors in this tissue with a K_B value of 3.4 μM. The two rigid analogs displayed opposite effects on rat aorta. Analog **6** was a partial agonist with potency and intrinsic activity equal to that of the parent compound **5a**, whereas analog **7** was a potent antagonist on α_1-receptors with a K_B value of 136 nM.

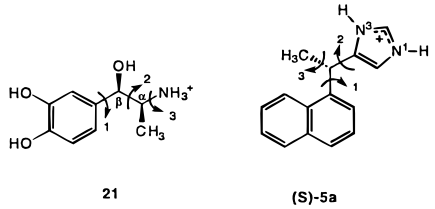


Figure 4. Rotatable bonds defined in the conformational search of **21** and (*S*)-**5a**.

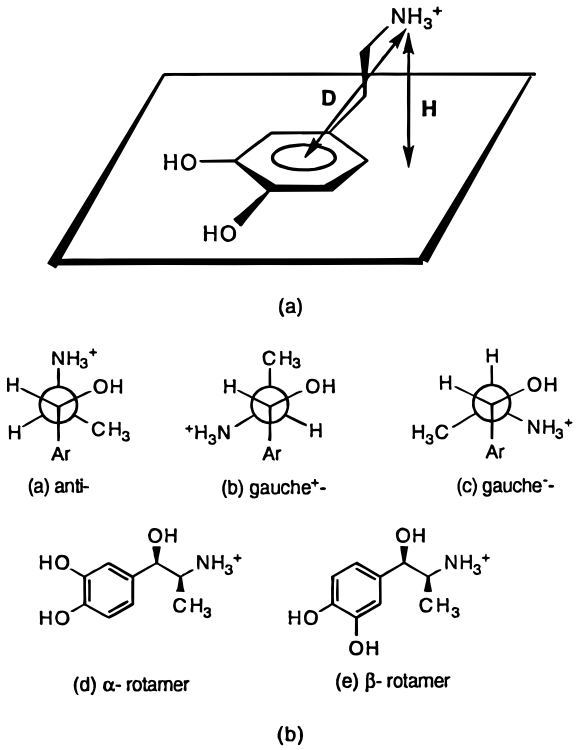


Figure 5. (a) Definition of *D* and *H* in phenethylamines. (b) Low-energy conformations of (−)-α-MeNE (**21**).

Selected 4-substituted imidazoles were incubated in human platelet-rich plasma in the presence of varying epinephrine concentrations (30−100 mM). All compounds were concentration-dependent inhibitors of human platelet aggregation induced by epinephrine. Compared to medetomidine, rigid molecule **6** showed moderate inhibitory activity at α_2-receptors, whereas **7** was a relatively poor inhibitor of platelet aggregation. These results are consistent with the binding studies on α_2-adrenoceptors in membrane fractions of rat brain.

Molecular Modeling Studies

In order to obtain a better understanding of our experimental findings and to support our efforts to optimize biological activity and α_2-receptor selectivity,

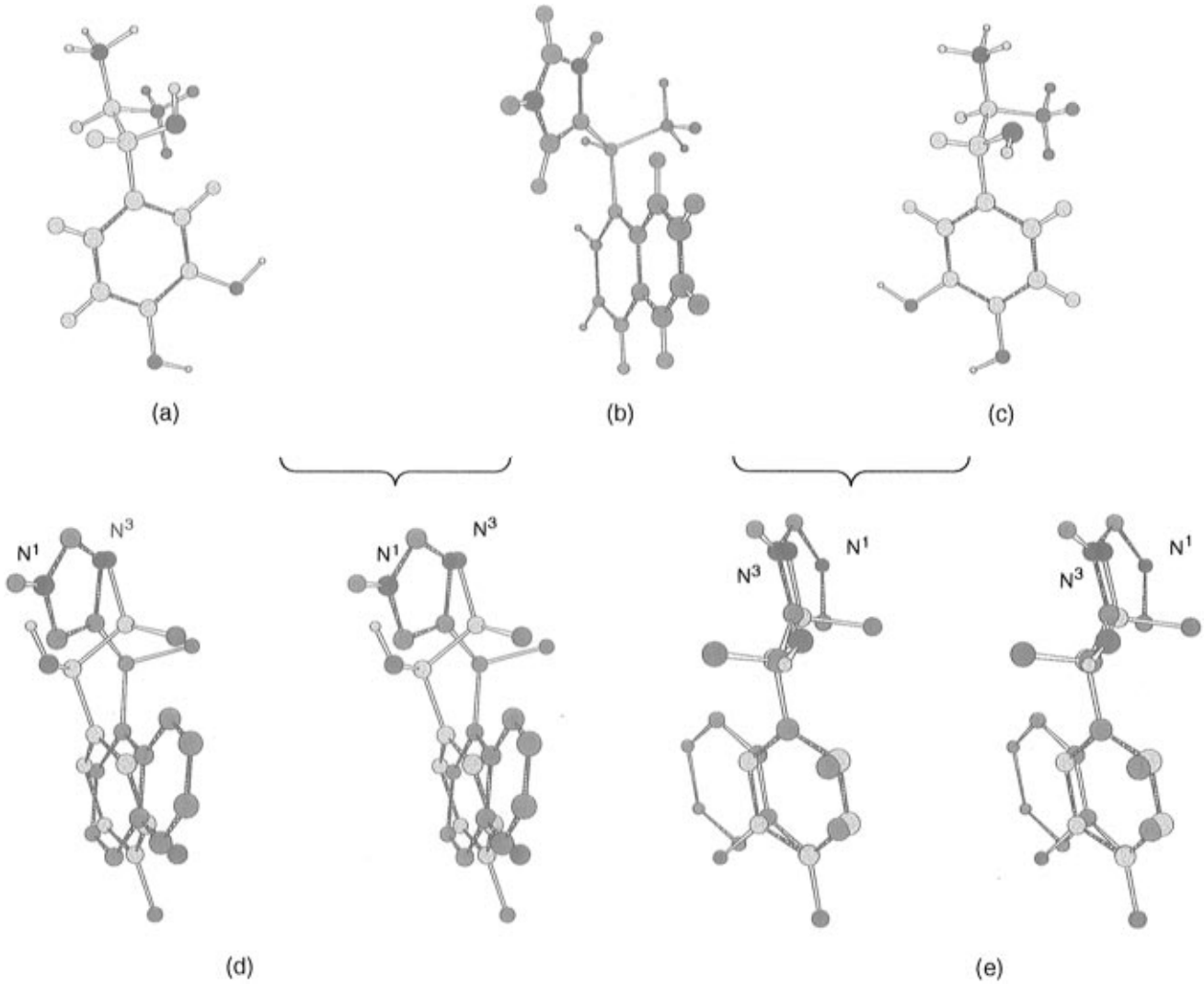


Figure 6. (a) α-Rotamer of **21** (yellow). (b) (*S*)-**5a** (green). (c) *β*-Rotamer of **21** (yellow). (d) Relaxed stereoview of superimposition of a and b. The rms value is 0.47. (e) Relaxed stereoview of superimposition of b and c. The rms value is 0.30. Nitrogen and oxygen atoms are blue and red, respectively. The α-methyl group of **21** and the benzylic methyl group of **5a** are pink. In d and e, all hydrogen atoms were hidden for better visualization except for the one of N^1 of the imidazole ring and the *β*-hydroxy group of **21**.

we concluded molecular modeling studies on the medetomidine-like analogs.

Phenethylamines, represented by norepinephrine (NE), are a well-known class of drugs that interact with α-adrenoceptors. Numerous studies on the structural and conformational requirements of phenethylamines binding at α-adrenoceptors have been published.[28,29] The "bioactive conformation" of phenethylamines interacting with α-adrenoceptors has been proposed based on the theoretical calculations, X-ray crystallography, NMR studies, and conformation−activity studies of conformationally restricted analogs.[28,30] Although NE and medetomidine are chemically different, both consist of an aromatic moiety some distance from a basic nitrogen atom and exhibit α-adrenergic activity. We hypothesized that these compounds present their presumed pharmacophores (aromatic moiety and basic amino group) situated in a similar spatial relationship, complementary to that of the active centers of the corresponding receptors. On the basis of this hypothesis, we examined the molecular superimposability of phenethylamines and imidazoles by using α-methylnorepinephrine (α-MeNE) as a model compound of phenethylamines.

(−)-α-MeNE (**21**) is the most active and selective isomer of α-MeNE at α_2-adrenoceptors.[31] Addition of a α-methyl group to NE in the correct configuration significantly enhances activity at α_2-adrenoceptors. Thus, α-methyl-substituted phenethylamines exhibit significant α_2- vs α_1-adrenoceptors selectivity. In the α-adrenergic binding assay, **21** was 8-fold less potent at the α_2-receptor than medetomidine, but its selectivity of α_2- vs α_1-subtypes was similar to that of medetomidine. Since our ultimate goal was to develop highly selective and potent α_2-agonists, we chose **21** as an α_2-agonist template for superimposition with the imidazole analogs.

(a) Conformational Analysis of (−)-α-MeNE. Using SYBYL software, (−)-α-MeNE was subjected to a full systematic search with three rotatable bonds as defined in Figure 4. Due to the flexibility of molecule **21**, many conformations were energetically possible. The conformational analysis reflected this by yielding numerous structures within a reasonable energy range. Concerning the aromatic ring to the amino group orientation, three different low-energy conformations, termed anti$^-$, gauche$^+$, and gauche$^-$, were obtained from the search (Figure 5). Rotation of the phenyl group

relative to the C_1-C_α side chain yielded two rotamers for each conformation, termed α- and *β*-rotamers. Thus, six conformational families were revealed from the computations. Valid conformations derived from the search were individually minimized, and their parameters are summarized in Table 3. The energy differences of these conformers are not significant (<0.2 kcal/mol); however, the distances *D* and *H* are remarkably different between the anti$^-$, gauche$^+$, and gauche$^-$ conformations. It has been proposed that phenethylamines adopt a fully extended trans conformation when interacting with α-adrenoceptors, and the distances *D* and *H* are in the range of 5.1−5.2 and 1.2−1.4 Å, respectively.[30] The anti$^-$ conformations of **21**, both α- and *β*-rotamers obtained from the computations, are in agreement with the published model. Therefore, both rotamers of the anti$^-$ conformation of **21** were considered as the template for the superimposition with imidazoles.

(b) Conformational Analysis of Imidazoles. (*S*)-Medetomidine (**4**), (*S*)-**5a**, and **8c** were constructed from their X-ray atomic coordinates. Since the *S*-isomer of medetomidine and **5a** are the active isomers for α_2-adrenoceptors, we assumed that the *S*-isomer of other imidazole analogs is the optically potent isomer for α_2-adrenoceptors if its racemate is active. The *S*-isomers of **5f**, **6**, and **7** were constructed based on the X-ray structure of (*S*)-**5a**. The structures were first energy minimized and then subjected to systematic searches with the rotatable bonds as exemplified in Figure 4. After the search, the conformations were sorted according to energy, and the low-energy conformations were examined for best fit with **21**.

(c) Superimposition of (−)-α-MeNE and Imidazole Analogs. The FIT ATOM function of SYBYL permitted least-squares fitting of two different molecules. Appropriate atoms (i.e., atoms that are part of the potential pharmacophore) were selected for fitting, and best fits were represented by low rms (root mean square) distance (typically <0.5 Å) between the fitted atoms.

More efficient overlaps (i.e., smaller rms value) were consistently observed when N^3, instead of N^1, of the imidazole ring was fitted with the nitrogen of **21**. This finding suggested that N^3 on the imidazole ring of medetomidine-like analogs may play the same important role as the amine function in phenethylamines. On the basis of site-directed mutagenesis experiments with α_{2A}-adrenoceptors, it has been proposed that the amine function in phenethylamines may interact with the carboxy group of Asp113 in the third transmembrane domain of α_{2A}-adrenoceptors.[32] This model suggests that a similar interaction may exist between the N^3 on the imidazole ring of medetomidine-like analogs and the carboxy group of Asp113 of α_{2A}-adrenoceptors.

A better fit (i.e., smaller rms values) was obtained when an imidazole analog was superimposed with the *β*-rotamer of **21** rather than the α-rotamer, as exemplified in Figure 6. In such a superimposition, the two benzylic carbons of the molecules are overlapped indicating that the benzylic substitution may mimic the *β*-hydroxy group of phenethylamines. However, this is not consistent with the experimental data which showed that replacement of the benzylic methyl group of **5a** with a hydroxy group did not increase, but significantly decreased, the affinity at α-adrenoceptors.[7] In addition, the stereochemical configuration of these two classes at the benzylic carbon does not match.[33] This result suggests that the *β*-rotamer of **21** may not be the appropriate conformation of phenethylamines, which is in agreement with hypotheses advanced by other authors.[12,13,34,35]

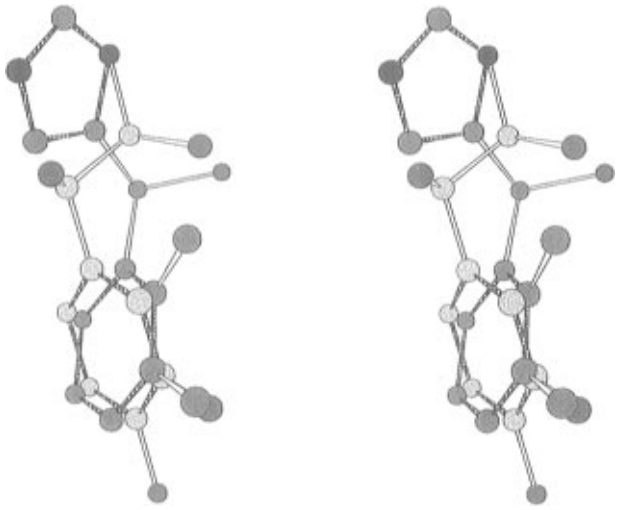


Figure 7. Relaxed stereoview of superimposition of α-rotamer of **21** (yellow) and (*S*)-medetomidine (green). The rms value is 0.45. Nitrogen and oxygen atoms are blue and red, respectively. The α-methyl group of **21** and the benzylic methyl group of medetomidine are pink. All hydrogen atoms were hidden for better visualization.

More examples of superimposition of the α-rotamer of **21** and imidazole analogs are shown in Figures 7−10 with rms values indicated for each fit. From these superimpositions, we observed the following interesting features about how the imidazole derivatives may interact with α_2-adrenoceptors. (1) N^1 of the imidazole ring projects to the same direction of the *β*-hydroxy group of **21**, although they do not overlap with each other (e.g., Figure 6d). A recent study of site-directed mutagenesis experiments with α_2-adrenoceptors revealed that Ser90 at the second transmembrane domain could be the potential binding site of the *β*-hydroxy group of NE.[36] If we assume that N^3 of the imidazole ring serves as the potential binding component with Asp113 of the receptor, the orientation of N^1 of the imidazole ring makes it possible to play a role like the *β*-hydroxy group of NE. (2) The benzylic methyl group of (*S*)-medetomidine and (*S*)-**5a**, which have high binding affinity at α_2-adrenoceptors, projects into the same region as the α-methyl group of **21** (Figures 6d and 7). However, the benzylic substituent of (*R*)-**5a** and **8c** does not overlap with the α-methyl group of **21** (Figure 8) and may account for the poor binding affinity at α_2-adrenoceptors. Such a pattern is also observed when the two rigid molecules **6** (high α_2-affinity) and **7** (low α_2-affinity) were superimposed with **21** (Figures 9 and 10). Therefore, this model provides an approach to explain the α_2-activity of imidazoles.

Due to their different steric characteristics, the benzylic substitution of **5a** and **8c** may have a profound influence on the conformation of the whole molecule and hence on the interaction with the receptor. Comparing the lowest-energy conformation of (*S*)-**5a** and **8c**, a significant difference was found in the dihedral angle $C_1-C_2-C_\alpha-C_\beta$ (Figure 11). This dihedral angle is

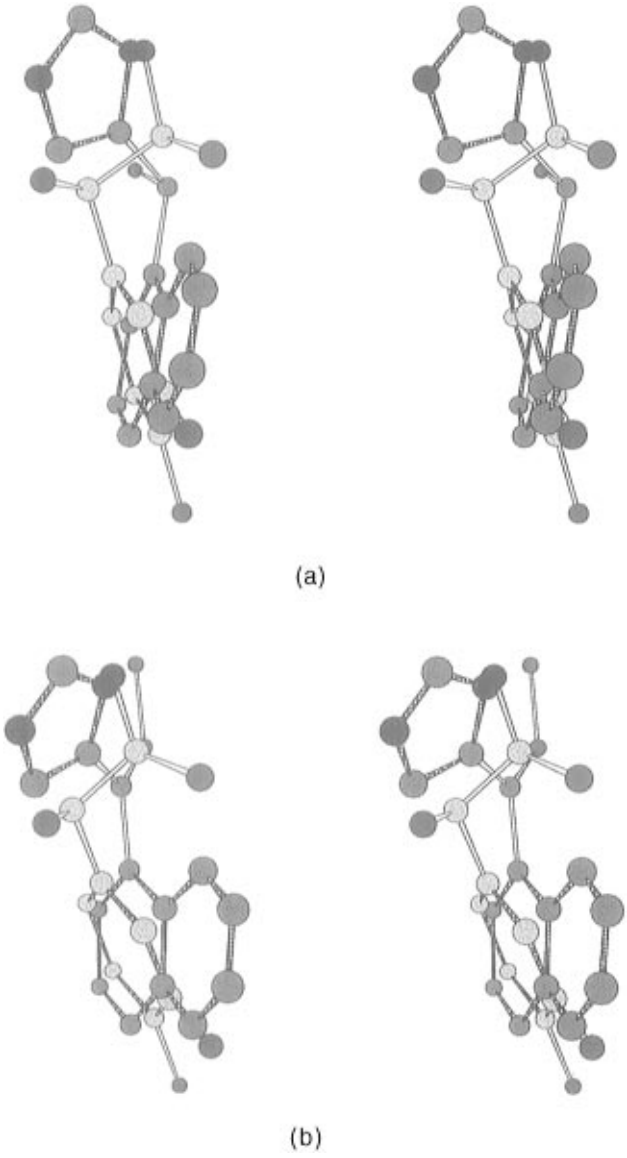


Figure 8. (a) Relaxed stereoview of superimposition of α-rotamer of **21** (yellow) and (*R*)-**5a** (green). The rms value is 0.40. (b) Relaxed stereoview of superimposition of α-rotamer of **21** and **8c**. The rms value is 0.49. Nitrogen and oxygen atoms are blue and red, respectively. The α-methyl group of **21** and the benzylic side chains of **5a** and **8c** are pink. All hydrogen atoms were hidden for better visualization.

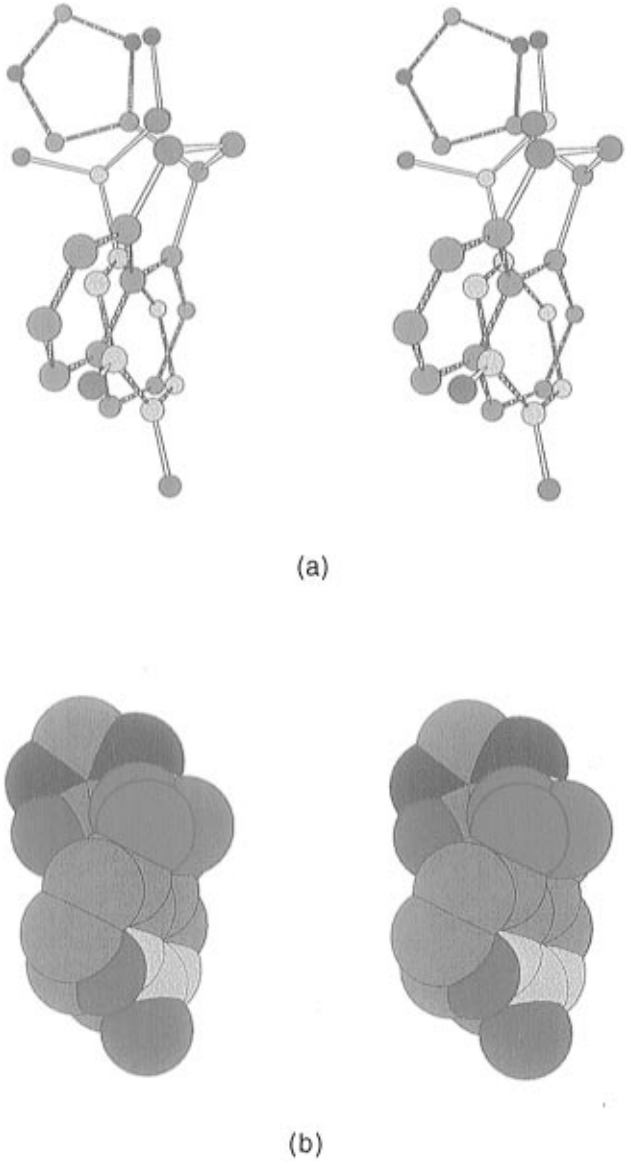


Figure 9. Relaxed stereoview of superimposition of α-rotamer of **21** (yellow) and **6** (green). The rms value is 0.53: (a) model with cylindrical bonds and (b) model of space filling. Nitrogen and oxygen atoms are blue and red, respectively. The α-methyl group of **21** and the benzylic bridge of **6** are pink. All hydrogen atoms were hidden for better visualization.

indicative of the twist out of plane of the benzylic side chain relative to the aromatic ring and is equal to 74.5° for (*S*)-**5a** and 127.3° for **8c**. The two rigid analogs **6** and **7** were designed in a way that forces the side chain into different orientations so that the dihedral angle of **6** (42.2°) is close to that of (*S*)-**5a**, while the angle of **7** (119.4°) is close to that of **8c**. This could account for the high α_2-affinities of (*S*)-**5a** and **6** and the low α_2-affinities of **8c** and **7**.

Ruffolo et al.[31] have proposed a four-point attachment for the interaction between α-MeNE (**21**) and α_2-adrenoceptors. In their model, the α-methyl group of **21** binds to an additional recognition site only at α_2-adrenoceptors, with the other three sites the same as described in Easson−Stedman hypotheses.[37] In this study, we were encouraged that the benzylic methyl group of medetomidine and the α-methyl group of **21** were superimposable, indicating that these two methyl groups may fit into the same binding pocket at α_2-adrenoceptors as Ruffolo proposed. Consequently, only imidazoles with an appropriate orientation of the benzylic substituent (e.g., **5a** and **6**) may exhibit high α_2-activity. Additional biological evidence to support this hypothesis is that demethylated analogs of medetomidine and **5a** were less potent at α_2-adrenoceptors than their parent compounds.[7]

In conclusion, from the results of this study, we have gained a new insight into the preferred conformation of imidazoles for interaction with α_2-receptors. We propose that the nitrogen N^3 on the imidazole ring binds with Asp113 of the receptor. The benzylic methyl group of (*S*)-medetomidine and its naphthyl analog (*S*)-**5a** is superimposable with the α-methyl group of **21**, indicating that both methyl groups of the two different classes of drugs may interact at the same site of α_2-adrenoceptors. By contrast, the activity of analog **8b**,**c** would appear to indicate that the steric hindrance created by the ethylene group and the limited freedom of rotation of the double bond ($C_\alpha-C_\beta$) are a hindrance to the

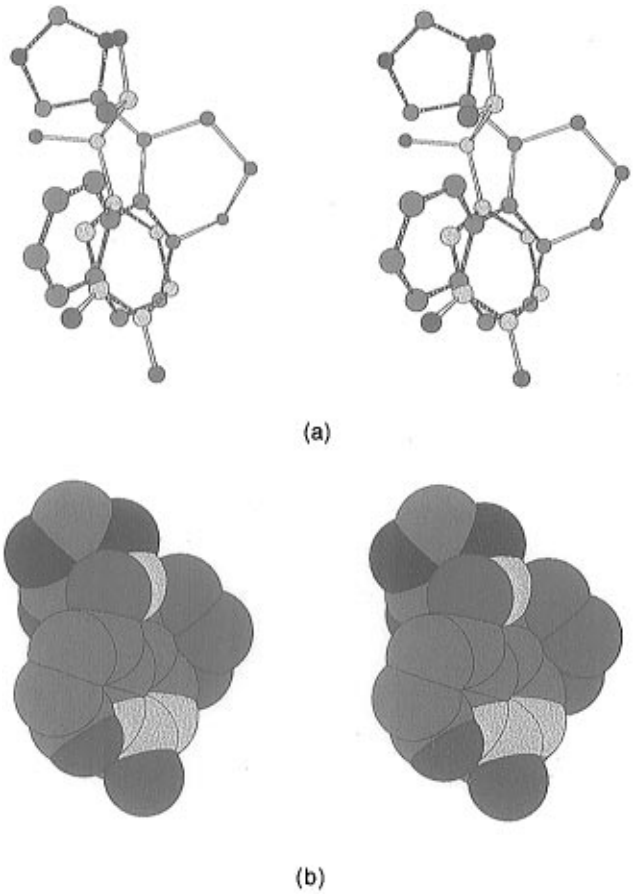


Figure 10. Relaxed stereoview of superimposition of α-rotamer of **21** (yellow) and **7** (green). The rms value is 0.43: (a) model with cylindrical bonds and (b) model of space filling. Nitrogen and oxygen atoms are blue and red, respectively. The α-methyl group of **21** and the benzylic bridge of **7** are pink. All hydrogen atoms were hidden for better visualization.

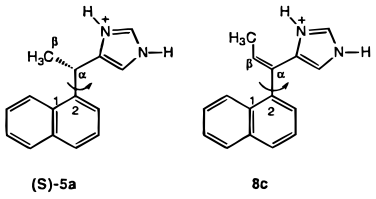


Figure 11. Defined dihedral angle of (*S*)-**5a** and **8c**.

expression of the activity on α_2-adrenoceptors. We are currently working on a more detailed study of the conformation−binding relationships of medetomidine-like compounds in a 3D-α_2-adrenoceptor model which will more clearly define the receptor−ligand binding mode at 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 a Bruker 300 spectrometer, and chemical shift values are reported as parts per million (δ) relative to tetramethylsilane (TMS) as an internal reference. IR spectra were obtained on a System 2000-FTIR instrument. Elemental analyses were performed by Atlantic Microlab, Inc., and the obtained analytical results are 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), methylene chloride (CH_2Cl_2), and toluene 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-[(1-Naphthyl)hydroxymethyl]-*N*-(triphenylmethyl)-imidazole (10a). A 3.0 M solution of EtMgBr (4 mL, 12 mmol) in Et_2O was added to a 0.25 M solution of 4-iodo-*N*-(triphenylmethyl)imidazole[38] (**9a**; 4.36 g, 10 mmol) in dry CH_2Cl_2 at ambient temperature. After stirring for 45 min, 1-naphthylaldehyde (2 mL, 15 mmol) 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 3.95 g (85%) of **10a** as white crystals: mp 235−236 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.52 (bs, 1H, OH), 6.33 (s, 1H), 6.51 (s, 1H), 7.04−6.99 (m, 6H, Ar-H), 7.18−7.29 (m, 9H, Ar-H), 7.36−7.46 (m, 4H, Ar-H), 7.72−7.82 (m, 3H, Ar-H), 7.99−8.02 (m, 1H, Ar-H); MS *m/e* 244 (TrH^+). This compound was used in the synthesis of **11** without further characterization.

4-[(1-Naphthyl)carbonyl]-*N*-(triphenylmethyl)imidazole (11). 4-[(1-Naphthyl)hydroxymethyl]-*N*-(triphenylmethyl)imidazole (**10a**; 4.18 g, 9 mmol) was partially dissolved in 130 mL of dry CH_2Cl_2 with activated MnO_2 (7.82 g, 90 mmol). The mixture was brought to reflux for 4−5 h. The mixture was filtered through Celite, and the CH_2Cl_2 solution was evaporated under reduced pressure. The crude residue was triturated with Et_2O to give 3.98 g (96%) of **11** as a white solid: mp 187−188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13−7.17 (m, 6H), 7.35−7.37 (m, 9H), 7.47−7.54 (m, 4H), 7.64 (d, J = 1.34 Hz, 1H), 7.85−7.87 (m, 2H), 7.95 (d, J = 8.24 Hz, 1H), 8.28−8.31 (m, 1H); IR (KBr) 1631 cm^{-1}; MS *m/e* 244 (TrH^+). This compound was used in the synthesis of **5f** and **8a**,**b** without further characterization.

4-[1-(1-Naphthyl)-1-hydroxyethyl]-*N*-(triphenylmethyl)imidazole (10b). To a cold solution of **11** (0.46 g, 1 mmol) in 10 mL of dry THF was added a 1.4 M solution of CH_3MgBr (1 mL, 1.5 mmol) in toluene/THF (75:25). After the mixture stirred overnight at room temperature, the reaction was quenched with saturated NH_4Cl aqueous solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The crude residue was triturated with Et_2O to give 0.47 g (97%) of **10b** as a white solid: mp 179−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H, CH_3), 3.33 (bs, 1H, OH), 6.52 (d, J = 1.35 Hz, 1 H, Im-H), 7.06−7.11 (m, 6H), 7.25−7.31 (m, 9H), 7.36−7.44 (m, 4H), 7.73−7.82 (m, 3H), 8.17 (d, J = 8.67 Hz, 1H); IR (KBr) 3246, 1490, 1444 cm^{-1}; MS *m/e* calcd for $C_{34}H_{28}N_2O$ 481, found 481. Anal. ($C_{34}H_{28}N_2O$) C, H, N.

4-[1-(1-Naphthyl)ethylene]-1*H*-imidazole Maleate (8a). A solution of **10b** (0.96 g, 2 mmol) in 30 mL of TFA aqueous solution (60%) was stirred overnight. The solvents were evaporated, and the residue was partitioned between 30 mL of CH_2Cl_2 and 30 mL of HCl solution (10%). The organic portion was washed with HCl solution (10%, 3 × 30 mL). The combined acidic solutions were neutralized to pH ∼ 10 and then extracted with CH_2Cl_2 (4 × 100 mL). The organics were dried over Na_2SO_4 and concentrated to yield 0.15 g (33%) of **8a** (free base) as white crystals: ^{1}H NMR (300 MHz, acetone-d_6) δ 5.06 (d, J = 2.21 Hz, 1H), 6.20 (s, 1H), 6.40 (s, 1H), 7.34−7.53 (m, 4H), 7.65 (d, J = 0.83 Hz, 1H), 7.86−7.91 (m, 3H).

A portion of the free base was converted to the maleate which was crystallized from absolute EtOH to give **8a** as a white solid: mp 140−141 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 5.47 (s, 1H), 6.27 (s, 2H, CH=CH), 6.50 (s, 1H), 6.90 (s, 1H, Im-H), 7.42−7.59 (m, 4H), 7.86 (d, J = 8.46 Hz, 1H), 7.96 (d, J = 7.40 Hz, 2H), 8.71 (s, 1H, Im-H); IR (neat) 1456 cm^{-1}; HRMS *m/e* calcd for $C_{15}H_{12}N_2$ (free base) 220.1001, found 220.0997. Anal. ($C_{19}H_{16}N_2O_4 \cdot {}^1/_4H_2O$) C, H, N.

4-[1-(1-Naphthyl)-1-hydroxyethyl]-*N*-(triphenylmethyl)imidazole (10c). To a solution of **11** (1.56 g, 3.35 mmol) in 25 mL of dry benzene was added a 3.0 M solution of EtMgBr (2 mL, 6 mmol) in Et_2O at 0 °C. The mixture was allowed to stir for 25 h at room temperature. The reaction mixture was cooled in an ice bath, and excess EtMgBr was destroyed by addition of saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated. The crude residue was first crystallized with CH_2Cl_2/Et_2O to yield the secondary alcohol **10a** (0.33 g, 21%) and then crystallized in Et_2O to give the desired product **10c** (0.88 g) contaminated with a small amount of **10a**. This mixture was oxidized with MnO_2 in refluxed CH_2Cl_2 for 4 h and filtered through Celite. The resulting CH_2Cl_2 solution was concentrated, and the crude residue was crystallized in Et_2O to give 0.66 g (40%) of **10c** as white crystals: mp 178−179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J = 7.35 Hz, 3H, CH_3), 2.40−2.62 (m, 2H, CH_2), 3.17 (b, 1H, OH), 6.59 (d, J = 1.40 Hz, 1H, Im-H), 7.06−7.14 (m, 6H), 7.24−7.34 (m, 10H), 7.39−7.44 (m, 3H), 7.74 (d, J = 8.00 Hz, 1H), 7.81 (d, J = 8.09 Hz, 2H), 8.13 (d, J = 8.65 Hz, 1H); IR (KBr) 3184, 1492, 1446 cm^{-1}; MS *m/e* calcd for $C_{35}H_{30}N_2O$ 495, found 495. Anal. ($C_{35}H_{30}N_2O\cdot{}^3/_2H_2O$) C, H, N.

4-[1-(1-Naphthyl)-1-propenyl]-*N*-(triphenylmethyl)imidazole (12a,b). Sodium hydride (95%, 0.27 g, 11.1 mmol) was suspended in 10 mL of dry DMSO and heated to 80 °C for 0.5 h. The resulting deep-green solution of dimsyl sodium was cooled to 0 °C. A solution of the ethyltriphenylphosphonium bromide (4.115 g, 11.1 mmol) in 10 mL of dry DMSO was added, and the resulting deep-red solution was maintained for a further 10 min at room temperature. A solution of ketone **11** (3.43 g, 7.39 mmol) in 10 mL of dry DMSO was added, and the mixture was heated to 80 °C for 3 h. After cooling to 0 °C, the mixture was poured into 50 mL of cold water. The heterogeneous mixture was extracted with EtOAc (3 × 50 mL). The combined organics were washed with H_2O (5 × 100 mL), dried over $MgSO_4$, and concentrated. The crude residue was triturated with Et_2O, and the white precipitate (triphenyl phosphoxide) was removed by filtration. The Et_2O solution was concentrated, and the resulting mixture of two alkene isomers was separated by flash chromatography on silica gel, eluting with EtOAc/hexane (1:4).

4-[1-(1-Naphthyl)-(1*E*)-propenyl]-*N*-(triphenylmethyl)-imidazole (12a): 1.0 g, 28%; mp 130−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, J = 7.05 Hz, 3H, CH_3), 5.99 (s, 1H, Im-H), 6.89 (q, J = 7.09 Hz, 1H, HC=C), 7.00−7.03 (m, 6H), 7.17−7.34 (m, 10H), 7.36−7.45 (m, 4H), 7.73 (d, J = 8.16 Hz, 1H), 7.78−7.85 (m, 2H); IR (KBr) 1493, 1445 cm^{-1}; MS *m/e* calcd for $C_{35}H_{28}N_2$ 476, found 476. Anal. ($C_{35}H_{28}N_2$) C, H, N.

4-[1-(1-Naphthyl)-(1*Z*)-propenyl]-*N*-(triphenylmethyl)-imidazole (12b): 1.90 g, 54%; mp 154−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (d, J = 7.19 Hz, 3H, CH_3), 5.82 (q, J = 7.03 Hz, 1H, HC=C), 6.36 (d, J = 1.06 Hz, 1H, Im-H), 7.04−7.07 (m, 6H), 7.21−7.29 (m, 9H), 7.34−7.43 (m, 5H), 7.71 (t, J = 4.08 Hz, 1H), 7.76−7.85 (m, 2H); IR (KBr) 1494, 1445 cm^{-1}; MS *m/e* calcd for $C_{35}H_{28}N_2$ 476, found 476. Anal. ($C_{35}H_{28}N_2$) C, H, N.

4-[1-(1-Naphthyl)-1-propenyl]-1*H*-imidazole Maleate (8b,c). Compound **10c** (1.50 g, 3.03 mmol) was deoxygenated and deprotected in TFA aqueous solution (60%, 25 mL) as previously described in the preparation of **8a** to afford a mixture of *E*/*Z*-isomers with a ratio of 3:1. The isomers were separated by flash chromatography, eluting with EtOAc/hexane (5:2), to yield 0.38 g (51%) of **8b** and 0.13 g (17%) of **8c**.

Alternatively, **8c** could be prepared from the deprotection of **12b**. A solution of **12b** (1.95 g, 4.1 mmol) in 60 mL of AcOH aqueous solution (90%) was stirred at 60 °C for 2 h. The solvents was removed under reduced pressure, and the residue was partitioned between 50 mL of EtOAc and 20 mL of H_2O. The water layer was made basic to pH ∼ 10 and extracted with EtOAc (3 × 30 mL). The organics were washed with brine and dried over Na_2SO_4. Removal of the solvent and flash chromatography, eluting with EtOAc/hexane (2:1), gave 0.69 g (97%) of **8c** (free base) as white needles.

4-[1-(1-Naphthyl)-(1*E*)-propenyl]-1*H*-imidazole (8b): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40 (d, J = 7.00 Hz, 3H, CH_3), 6.07 (b, 1H, Im-H), 6.62 (q, J = 7.02 Hz, 1H, HC=C), 7.30 (dd, J = 1.05, 6.95 Hz, 1H), 7.41 (m, 1H), 7.49 (m, 1H), 7.55 (m, 1H), 7.61 (s, 1H), 7.68 (d, J = 8.20 Hz, 1H), 7.93 (m, 2H), 12.02 (bs, 1H, NH).

4-[1-(1-Naphthyl)-(1*Z*)-propenyl]-1*H*-imidazole (8c): ^{1}H NMR (300 MHz, CD_3OD) δ 2.12 (d, J = 7.12 Hz, 3H, CH_3), 5.84 (q, J = 7.12 Hz, 1H, HC=C), 6.90 (s, 1H, Im-H), 7.26−7.32 (m, 1H), 7.35−7.47 (m, 3H), 7.54 (s, 1H, Im-H), 7.73 (d, J = 8.46 Hz, 1H), 7.79−7.83 (m, 2H).

The free bases were converted to the maleates, respectively.

4-[1-(1-Naphthyl)-(1*E*)-propenyl]-1*H*-imidazole maleate (8b): mp 159−160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.46 (d, J = 6.90 Hz, 3H, CH_3), 6.07 (d, J = 0.77 Hz, 2H, HC=HC), 6.70−6.67 (m, 2H), 7.36 (d, J = 6.96 Hz, 1H), 7.46−7.66 (m, 4H), 7.97−8.01 (m, 2H), 8.74 (s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 14.72 (CH_3), 167.11 (C=O); IR (KBr) 1507, 1457 cm^{-1}; MS *m/e* calcd for $C_{16}H_{14}N_2$ (free base) 234, found 234. Anal. ($C_{20}H_{18}N_2O_4$) C, H, N.

4-[1-(1-Naphthyl)-(1*Z*)-propenyl]-1*H*-imidazole maleate (8c): mp 139.0−140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.09 (d, J = 7.13 Hz, 3H, CH_3), 6.01 (q, J = 7.14 Hz, 1H, HC=C), 6.08 (s, 2H, HC=HC), 7.38−7.46 (m, 3H), 7.48−7.55 (m, 2H), 7.68 (d, J = 8.35 Hz, 1H), 7.93 (t, J = 6.23 Hz, 2H), 8.55 (s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 15.63 (CH_8), 166.99 (C=O); IR (KBr) 1576, 1474, 1442 cm^{-1}; MS *m/e* calcd for $C_{16}H_{14}N_2$ (free base) 234, found 234. Anal. ($C_{20}H_{18}N_2O_4$) C, H, N.

4-[1-(1-Naphthyl)propyl]-1*H*-imidazole Maleate (5f). To a solution of **8c** (0.45 g, 2 mmol) in absolute EtOH (25 mL) was added 5% Pd/C (0.05 g). The mixture was subjected to 40 psi of H_2 for 24 h. The mixture was filtered through Celite, and the solvent was evaporated to give 0.43 g (95%) of **5f** (free base) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 0.95 (t, J = 7.33 Hz, 3H, CH_3), 2.07−2.25 (m, 2H, CH_2), 4.68 (t, J = 7.46 Hz, 1H, CH), 6.80 (t, J = 0.87 Hz, 1H, Im-H), 7.37−7.39 (m, 2H), 7.41−7.48 (m, 2H), 7.55 (d, J = 1.13 Hz, 1H, Im-H), 7.69 (dd, J = 4.55, 2.36 Hz, 1H), 7.80−7.83 (m, 1H), 8.14−8.18 (m, 1H).

A portion of the free base was converted to the maleate and recrystallized in CH_2Cl_2/hexane to give the title compound as white crystals: mp 112−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J = 7.28 Hz, 3H, CH_3), 2.26−2.39 (m, 2H, CH_2), 4.78 (t, J = 7.66 Hz, 1H, CH), 6.39 (s, 2H, CH=CH), 6.80 (s, 1H, Im-H), 7.45−7.54 (m, 4H), 7.79 (dd, J = 2.54, 6.78 Hz, 1H), 7.86−7.89 (m, 1H), 8.00−8.03 (m, 1H), 9.09 (d, J = 1.35 Hz, 1H, Im-H), 14.30 (bs, 2H, CO_2H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 12.25 (CH_3), 27.61 (CH_2), 38.11 (CH), 167.08 (C=O); IR (KBr) 1696, 1575, 1514, 1475 cm^{-1}; MS *m/e* calcd for $C_{16}H_{16}N_2$ (free base) 236, found 236. Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

4-(1-Hydroxy-1-perinaphthenyl)-*N*-(triphenylmethyl)-imidazole (14a). A 3.0 M solution of EtMgBr (0.80 mL, 2.4 mmol) in Et_2O was added to a 0.25 M solution of 4-iodo-*N*-(triphenylmethyl)imidazole (**9a**; 0.87 g, 2 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of perinaphthenone (**13a**; 0.40 g, 2.2 mmol) in 1 mL of dry CH_2Cl_2 was added, and stirring was continued overnight. The reaction mixture was worked up in a manner identical with that previously described for the synthesis of **10a**. The resulting solid was recrystallized from CH_2Cl_2/hexane to provide 0.49 g (49%) of the titled compound as an orange solid: mp 199−200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (d, J = 3.78 Hz, 1H), 6.00 (dd, J = 4.40, 9.77 Hz, 1H), 6.59 (s, 1H, Im-H), 6.68 (dd, J = 9.81, 1.67 Hz, 1H), 6.98−7.16 (m, 8H), 7.21 (s, 1H), 7.27−7.33 (m, 9H), 7.40 (d, J = 1.32 Hz, 1H), 7.52 (d, J = 7.93 Hz, 1H), 7.58 (d, J = 8.72 Hz, 1H); IR (KBr) 3413, 1617 cm^{-1}; MS *m/e* 243 (Tr^+). Anal. ($C_{35}H_{26}N_2O$) C, H, N.

2,3-Dihydro-1*H*-phenalenone (13b). A solution of 3-(1-naphthyl)propionic acid[21] (**15**; 1.0 g, 5 mmol) in 4 mL of $SOCl_2$ was brought to reflux for 2 h. Removal of the solvent under reduced pressure gave 3-(1-naphthyl)propionic acid chloride as a light brown oil: ^{1}H NMR (300 MHz, acetone-d_6) δ 3.46−3.54 (m, 4H, $2CH_2$), 7.41−7.47 (m, 2H), 7.49−7.60 (m, 2H), 7.80−7.83 (m, 1H), 7.91−7.94 (m, 1H), 8.12−8.15 (m, 1H).

The oily residue was dissolved in 8 mL of dry benzene, and $SnCl_4$ (0.6 mL, 5.1 mmol) was added via syringe at 0 °C. After 15 min, the mixture was hydrolyzed by dumping into a slurry of ice water and aqueous HCl solution (10%). The water layer was extracted with an equal amount of Et_2O. The combined organics were washed successively with water, saturated $NaHCO_3$, water, and brine and then dried and concentrated. The residue was purified over aluminum oxide (activated, neutral, Brockmann I), eluting with CH_2Cl_2/hexane (5:1) to yield 0.33 g (36%) of the title compound as a light yellow solid: mp 78−81 °C (lit.[17] mp 85 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (m, 2H, CH_2), 3.34 (t, J = 7.09 Hz, 2H, CH_2), 7.36−7.45 (m, 2H), 7.52 (t, J = 7.67 Hz, 1H), 7.72 (d, J = 7.61 Hz, 1H), 8.00 (d, J = 2.11 Hz, 1H), 8.29 (dd, J = 7.18, 0.92 Hz, 1H); ^{13}C NMR (300 MHz, CD_3OD) δ 29.24 (CH_2), 39.34 (CH_2), 200.59 (C=O); IR (KBr) 1681 cm^{-1}. The spectral data were consistent with the structure of the product; the product was immediately used in the synthesis of **14c** without further characterization.

4-(1-Hydroxy-2,3-dihydro-1-perinaphthanyl)-*N*-(triphenylmethyl)imidazole (14c). A 3.0 M solution of EtMgBr (0.55 mL, 1.65 mmol) in Et_2O was added to a 0.25 M solution of 4-iodo-*N*-(triphenylmethyl)imidazole (**9a**; 0.72 g, 1.65 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of perinaphthanone (**13b**; 0.20 g, 1.1 mmol) in 1 mL of dry CH_2Cl_2 was added, and stirring was continued overnight. The reaction mixture was worked up in a manner similar to that previously described for the synthesis of **10a**. The crude product was recrystallized from CH_2Cl_2/hexane to provide 0.40 g (73%) of the title compound as a white solid: mp 206−208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30−2.37 (m, 1H), 2.61−2.69 (m, 1H), 2.91−2.94 (m, 1H), 3.23−3.31 (m, 1H), 3.34 (bs, 1H, OH), 6.25 (s, 1H, Im-H), 7.05−7.08 (m, 6H), 7.26−7.28 (m, 9H), 7.34−7.44 (m, 4H), 7.55 (d, J = 7.20 Hz, 1H), 7.66 (d, J = 8.16 Hz, 1H), 7.72 (d, J = 8.18 Hz, 1H); IR (KBr) 3208, 1492, 1446 cm^{-1}; HRMS *m/e* calcd for $C_{35}H_{28}N_2O$ 492.2202, found 292.2211. Anal. ($C_{35}H_{28}N_2O$) C, H, N.

4-(1-Perinaphthanyl)-1*H*-imidazole Maleate (6). To a mixture of Me_3SiCl (1.54 mL, 12 mmol), NaI (1.8 g 12 mmol), and dry CH_3CN (0.6 mL, 12 mmol) was added a solution of **14c** (0.5 g, 1 mmol) in dry CH_2Cl_2 (6 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 0.15 g (63%) of **6** (free base) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.18−2.27 (m, 1H), 2.40−2.47 (m, 1H), 2.99−3.06 (m, 2H, Ar-CH_2), 4.46 (t, J = 4.63 Hz, 1H, CH), 6.63 (s, 1H, Im-H), 7.11−7.14 (m, 1H), 7.23 (dd, J = 6.95, 1.17 Hz, 1H), 7.34−7.39 (m, 2H), 7.66−7.73 (m, 3H).

A portion of the free base was converted to the maleate and recrystallized in CH_2Cl_2 to afford the title compound as white crystals: mp 143−145 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.34−2.41 (m, 2H, CH_2), 3.05−3.09 (m, 1H), 3.14−3.19 (m, 1H), 4.69 (t, J = 5.48 Hz, 1H, CH), 6.24 (s, 2H, HC=CH), 6.98−6.99 (m, 1H), 7.12 (dt, J = 7.09 Hz, 1H), 7.31 (dd, J = 7.00, 1.16 Hz, 1H), 7.39−7.45 (m, 2H), 7.73−7.76 (m, 1H), 7.81 (d, J = 8.27 Hz, 1H), 8.80 (d, J = 1.39 Hz, 1H, Im-H); ^{13}C NMR (300 MHz, CD_3OD) δ 28.98 (CH_2), 30.03 (CH_2), 38.42 (CH), 170.75 (C=O); IR (KBr) 1571, 1507, 1465 cm^{-1}; MS *m/e* calcd for $C_{16}H_{14}N_2$ (free base) 234, found 234. Anal. ($C_{20}H_{18}N_2O_4$) C, H, N.

4-(1,2,3,4-Tetrahydro-1-hydroxy-1-phenanthrenyl)-*N*-(triphenylmethyl)imidazole (20). 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 (**9a**; 2.09 g, 4.8 mmol) in dry CH_2Cl_2 at ambient temperature. After 1 h, a solution of 2,3-dihydro-4(1*H*)-phenanthrone[25] (**19**; 0.47 g, 2.4 mmol) in 2 mL of dry CH_2Cl_2 was added, and stirring was continued overnight. The reaction mixture was worked up in a manner similar to that previously described for the synthesis of **10a**. The crude product was recrystallized from CH_2/Cl_2/hexane to provide 0.87 g (72%) of the title compound as a white solid: mp 195−196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (m, 1H), 1.94 (m, 1H), 2.30 (t, 4.63H, 2H, CH_2), 2.83−2.88 (m, 1H), 2.90−3.00 (m, 1H), 3.88 (bs, 1H, OH), 6.04 (d, J = 1.34 Hz, 1H, Im-H), 6.95−7.07 (m, 6H), 7.12−7.25 (m, 9H), 7.28−7.38 (m, 3H), 7.41 (d, J = 1.24 Hz, 1H, Im-H), 7.61 (d, J = 8.41 Hz, 1H), 7.71 (m, 1H), 8.17 (d, J = 8.70 Hz, 1H); IR (KBr) 3218, 1493, 1445 cm^{-1}; HRMS *m/e* calcd for $C_{36}H_{30}N_2O$ 506.2358, found 506.2356. Anal. ($C_{36}H_{30}N_2O\cdot{}^1/_4H_2O$) C, H, N.

4-(1,2,3,4-Tetrahydro-1-phenanthrenyl)-1*H*-imidazole Maleate (7). To a mixture of triethylsilane (3 mL, 20 mmol) and **20** (1.015 g, 2 mmol) was added TFA (3 mL, 40 mmol). After stirring at 50−55 °C for 28 h, the mixture was cooled to room temperature and diluted with 25 mL of EtOAc and 15 mL of NaOH aqueous solution (10%) at 0 °C. The layers were separated; the pH of water layer was adjusted to 8−9. The aqueous portion was extracted with EtOAc (15 × 3 mL). The combined organics were washed with H_2O and brine and dried over Na_2SO_4. The crude product was purified by flash chromatography, eluting with EtOAc/CH_3OH (10:1), to yield 0.28 g (56%) of the product (free base): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.67−1.75 (m, 2H, CH_2), 1.89−1.98 (m, 1H), 2.15−2.20 (m, 1H), 2.90 (t, J = 7.21 Hz, 2H, CH_2), 4.69 (d, J = 3.22 Hz, 1H, CH), 6.03 (s, 1H, Im-H), 7.25 (d, J = 8.42 Hz, 1H), 7.32−7.38 (m, 2H), 7.50 (s, 1H, Im-H), 7.68−7.76 (m, 2H), 7.78−7.81 (m, 1H), 11.65 (b, 1H, NH).

A portion of the free base was converted to the maleate, and the salt was crystallized in Et_2O to give **7**: mp 169−170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56−1.64 (m, 1H), 1.78−7.82 (m, 1H), 2.05−2.14 (m, 2H, CH_2), 2.92−2.97 (m, 2H, CH_2), 4.90 (d, J = 2.45 Hz, 1H, CH), 6.04 (s, 2H, HC=CH), 6.69 (s, 1H, Im-H), 7.32 (d, J = 9.47 Hz, 1H), 7.39−7.43 (m, 2H), 7.66−7.69 (m, 1H), 7.79 (d, J = 8.46 Hz, 1H), 7.85−7.88 (m, 1H), 8.82 (d, J = 1.09 Hz, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 17.37 (CH_2), 28.91 (CH_2), 29.23 (CH_2), 31.22 (CH), 167.07 (C=O); IR (KBr) 1702 cm^{-1}; MS *m/e* calcd for $C_{17}H_{16}N_2$ (free base) 248, found 248. Anal. ($C_{21}H_{20}N_2O_4\cdot{}^1/_4H_2O$) C, H, N.

Receptor Isolation and Preparation. α_1- And α_2-adrenergic receptors were isolated using established methods.[7,39] Briefly, frozen rat brain were purchased from Harlan Bioproducts for Science, Inc. and stored at −70 °C until use (Indianapolis, IN). Brains were rapidly thawed, frontal cortices dissected, and the cortices homogenized in approximately 30 vol/wet wt of ice-cold buffer containing 50 mM Tris-HCl and 10 mM $MgCl_2$, pH 7.4. The homogenate was first centrifuged at 48000*g* for 30 min. The resulting pellet, representing the membrane fraction, was then resuspended in buffer and recentrifuged. This process was repeated twice. The final pellet was then resuspended in approximately 10 vol and stored at −70 °C until use in competitive binding studies.

Radioligand Binding Studies. All radioligand binding assays were performed in triplicate in polypropylene tubes. α_1-Adrenergic receptors were labeled using 0.1 nM [^{3}H]-prazosin (78.7 Ci/mL) dissolved in 50 mM Tris buffer, pH 7.4, containing 10 mM $MgCl_2$. α_2-Adrenergic receptors were labeled using 2.0 nM [^{3}H]rauwolscine (80.5 Ci/mL) in 50 nM Tris buffer, pH 7.4, containing 10 mM EDTA. The final protein concentrations were approximately 300 and 500 μg/mL for the α_1- and α_2-assays, respectively. Phentolamine (10 μM) was used to determine the fraction of nonspecific binding in both assays. Samples were incubated at 30 °C for 30 min and then rapidly filtered (Whatman GF/C glass fiber filters presoaked in 10 μM phentolamine) and washed with 20 mL of ice-cold assay buffer on a Brandel cell harvester.[40] Individual filters were inserted into scintillation vials, shaken, and allowed to equilibrate for 5 h with 5 mL of aqueous scintillation fluid before radioactivity counting on a Beckman LS 6800 liquid scintillation counter. The IC_{50} for each compound in each of the receptor systems was then determined by plotting the percentage specific binding at each sigmoidal E_{max} model. The equilibrium dissociation constant of each compound (K_i) was then calculated using the standard equation.

Aorta Contraction Activities. Rats, weighing 150−300 g, of either sex were killed by a sharp blow to the head and thoracic. Abdominal aorta was removed and placed in a Petri dish containing oxygenated Krebs solution of the following composition (mM): NaCl, 94.8; KCl, 4.7; $MgSO_4$, 1.2; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; and glucose, 11.7. Fat and connective tissues were trimmed away using fine curved scissors, and helical strips were prepared. The specimen was mounted vertically in a 10-mL organ bath containing the

oxygenated Krebs solution kept at 37 °C and connected to an isometric tension transducer (Grass FT-03C) with initial loads of 1 g. The experiment was begun after a 90-min equilibration period. The responsiveness of each preparation was first tested by applications of 30 nM of phenylephrine (PE). Then, PE was added cumulatively to the organ bath. After 90 min, the compound was added to the organ bath, cumulatively. The responses were expressed as percentage of the maximum contraction to 1 μM of PE. When the compound caused more than 20% of the contraction, it was considered as an agonist; however, when the contraction was less than 20%, the compound was considered as an antagonist. When the compound was considered to be an antagonist, it was added 60 min before a second application of PE. A maximal response to PE in the tissue was 100%, and the percentage of response for each agonist was adjusted from this value. The EC_{50} values of agonists and pK_B values were determined as described previously.[27]

Platelet Antiaggregatory Activities. All aggregation studies were performed using human platelet-rich plasma, according to methods reported previously.[27] Various concentrations of inhibitors were added 1 min prior to activation of platelets by epinephrine (30−100 μM). Aspirin (1 mM) was routinely added to platelet preparations in experiments to examine drug effects on the primary wave aggregation response to epinephrine. IC_{50} values of drugs were analyzed by computer programs as described previously.[27]

X-ray Analysis of 8c. A clear colorless 0.36 × 0.36 × 0.52 mm data crystal of **8c** ($C_{16}H_{15}N_2^+ \cdot C_4H_3O_4^-$, fw = 350.4) was crystallized from $CHCl_3$/hexane. Data were collected on a computer-controlled diffractometer with an incident beam graphite monochromator (Siemens R3m/V with Cu Kα radiation, λ = 1.541 78 Å, T = 295 K). A least-squares refinement using 25 centered reflections within 60° < 2θ < 720° gave the $P2_1/c$ monoclinic cell, a = 7.050(1) Å, b = 34.165(5) Å, c = 7.899(1) Å, and β = 110.80(1)°, with V = 1776.3(4) Å^3, Z = 4, and D_{calcd} = 1.310 gm/cm^3. A total of 2627 reflections were measured in the $\theta/2\theta$ mode to $2\theta_{max}$ = 1150°, of which 2432 were unique (R_{int} = 1.66%). The scan width was [2$\theta(K_{\alpha 1})$ − 1.1]−[2$\theta(K_{\alpha 2})$ + 1.1]°, and scan rate was a function of count rate (7.5°/min minimum, 30.0°/min maximum in ω). Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved by direct methods with the aid of the program SHELXTL (version 5.0; Siemens Analytical Instruments, Madison, WI) and refined on F_o^2 with full matrix least-squares. The 255 parameters refined included the coordinates and anisotropic thermal parameters for all nonhydrogen atoms. Carbon hydrogens used a riding model of C−H = 0.96 Å and idealized angles. Hydroxyl hydrogens and those on the heterocyclic ring were refined isotropically with fixed thermal parameters. Atomic scattering factors are from the *International Tables for X-ray Crystallography* (1974). The maximum excursions for the final Fourier difference map were 0.20 and −0.29 eÅ^{-3}. The final R values for the 2115 observed reflections with $F_o > 4\sigma(|F_o|)$ were R = 0.044 and R^2_w = 0.121. Tables of coordinates, bond distances, and bond angles have been deposited with the Crystallographic Data Center, Cambridge CB2 1EW, England.

Molecular Modeling. Molecular modeling studies were conducted using the program SYBYL 5.32 (Tripos Associates, St. Louis, MO) running on a Silicon Graphics Iris workstation. The structures of model compounds were constructed from their X-ray atomic coordinates using the Crysin interface of SYBYL. The X-ray crystal coordinates of (*S*)-medetomidine[41] were obtained from the published atomic coordinates. The X-ray analyses of (*S*)-**5a**[33] and **8c** were provided by the Naval Research Laboratory. Energy minimizations were performed using Maximin2, a molecular mechanics method available in SYBYL. Atomic charges were calculated by the Gasteiger−Hückel method. Conformational analysis of each compound was performed by using systematic search, rotating bonds and distance constraints as depicted in Figure 4. The low-energy conformations of each molecule were minimized prior to superimposition. Molecules were superimposed using the FIT ATOM command in SYBYL. The selected 3D-features were read into the program CSC Chem3D Plus for printed representations. Hydrogen atoms were hidden in Figures 7−10 for better visualization.

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Supporting Information Available: Elemental analyses of the new compounds and X-ray data for **8c** (5 pages). Ordering information can be found on any current masthead page.

References

(1) Ruffolo, R. R., Jr.; Nichols, A. J.; Stadel, J. M.; Hieble, J. P. Pharmacologic and Therapeutic Applications of α_2-Adrenoceptor Subtypes. *Annu. Rev. Pharmacol. Toxicol.* **1993**, *32*, 243−279.
(2) Urban, R.; Szabo, B.; Starke, K. Is the Sympathoinhibitory Effect of Rilmenidine Mediated by Alpha-2 Adrenoceptors or Imidazoline Receptors? *J. Pharmacol. Exp. Ther.* **1994**, *270*, 572−578.
(3) Ernsberger, P.; Damon, T. H.; Graff, L. M.; Schafer, S. G.; Christen, M. O. Moxonidine, a Centrally Acting Antihypertensive Agent, Is a Selective Ligand for I_1-Imidazoline Sites. *J. Pharmacol. Exp. Ther.* **1993**, *264*, 172−182.
(4) Hayashi, Y.; Maze, M. Alpha$_2$ Adrenoceptor Agonists and Anaesthesia. *Br. J. Anaesth.* **1993**, *71*, 108−118.
(5) Aantaa, R.; Kallio, A.; Virtanen, R. Dexmedetomidine, a Novel α_2-Adrenergic Agonist. A Review of Its Pharmacodynamic Characteristics. *Drugs Future* **1993**, *18*, 49−56.
(6) Savola, J.-M.; Virtanen, R. Central α_2-Adrenoceptors are Highly Stereoselective for Dexmedetomidine, the Dextro Enantiomer of Medetomidine. *Eur. J. Pharmacol.* **1991**, *195*, 193−199.
(7) Hong, S.-S.; Romstedt, K. J.; Feller, D. R.; Hsu, F.-L.; Cupps, T. L.; Lyon, R. A.; Miller, D. D. A Structure-Activity Relationship Study of Benzylic Modifications of 4-[1-(1-Naphthyl)ethyl]-1*H*-imidazoles on α_1- and α_2-Adrenergic Receptors. *J. Med. Chem.* **1994**, *37*, 2328−2333.
(8) Mutschler, E.; Lambrecht, G. Stereoselectivity and Conformation: Flexible and Rigid Compounds. In *Stereochemistry and Biological Activity of Drugs*; Ariens, E. J., Soudijn, W., Timmermans, P. B. M. W. M., Eds.; Blackwell: Oxford, 1983; pp 63−79.
(9) Erhardt, P. W. Conformational Analogues of Dopamine. Synthesis and Pharmacological Activity of (E)- and (Z)-2(3,4-Dihydroxyphenyl)cyclopropylamine Hydrochlorides. *J. Med. Chem.* **1979**, *22*, 907−911.
(10) Ruffolo, R. R., Jr.; Anderson, K. S.; Miller, D. D. Conformational Requirements of Alpha$_2$-Adrenergic Receptors. *Mol. Pharmacol.* **1982**, *21*, 259−261.
(11) Hicks, P. E.; Waldron, C.; Bum, P.; Crooks, P. A. α_2-Adrenoceptor Agonist Properties of Exo- and Endo-isomers of 2-Amino-6,7-dihydroxybenzonorbornene Designed as Rigid Catecholamines. *J. Pharm. Pharmacol.* **1983**, *35*, 94−99.
(12) DeBernardis, J. F.; Kerkman, D. J.; Winn, M.; Bush, E. N.; Arendsen, D. L.; McClellan, W. J.; Kyncl, J. J.; Basha, F. Z. Conformationally Defined Adrenergic Agents. 1. Design and Synthesis of Novel α_2 Selective Adrenergic Agents: Electrostatic Repulsion Based Conformational Prototypes. *J. Med. Chem.* **1985**, *28*, 1398−1404.
(13) Macchia, B.; Balsamo, A.; Breschi, M. C.; Lapucci, A.; Lucacchini, A.; Macchia, F.; Mamera, C.; Martinelli, A.; Martini, C.; Martinotti, E.; Nencetti, S. Conformational Effects on the Activity of Drugs. 13. A Revision of Previously Proposed Models for the Activation of α- and β-Adrenergic Receptors. *J. Med. Chem.* **1992**, *35*, 1009−1018.
(14) Turner, R. M.; Lindell, S. D. A Facile Route to Imidazol-4-yl Anions and Their Reaction with Carbonyl Compounds. *J. Org. Chem.* **1991**, *56*, 5739−5740.
(15) Hsu, F.-L.; Zhang, X.; Hong, S.-S.; Berg, F. J.; Miller, D. D. Imidazole-Assisted Intramolecular Phenoxythiocarbonylation of Tertiary Alcohols. A Key Reaction for the Deoxygenation of α-trifluoromethylarylmethyl Alcohols. *Heterocyclic* **1994**, *39*, 801−809.
(16) Prinzbach, H.; Freudenberger, V.; Scheidegger, U. Cyclische, Gekreuzt-Konjugierte Bindungssysteme. XIII. NMR.-Untersuchungen am Phenafulven-System. (Cyclic Cross-conjugated Binding Systems. XIII. NMR Investigations with the Phenafulvene System.) *Helv. Chim. Acta* **1967**, *50*, 1087−1107.
(17) Boekelheide, V.; Larrabee, C. E. An Investigation of the Preparation and Some Properties of Perinaphthene. *J. Am. Chem. Soc.* **1950**, *72*, 1245−1249.
(18) Ganem, B. Conjugate Reduction and Reductive Alkylation of α,β-Unsaturated Cyclohexenones Using Potassium Tri-sec-butylborohydride. *J. Org. Chem.* **1975**, *40*, 146−147.

(19) Hoffman Jun, J. M.; Schlessinger, R. H. Sodium Metaperiodate: a Mild Oxidizing Agent for the Generation of Di-imide from Hydrazine. *Chem. Commun.* **1971**, 1245−1255.
(20) Djerassi, C.; Gutzwiller, J. Selective Reduction of Steroids by Homogeneous Catalytic Hydrogenation. *J. Org. Chem.* **1969**, *34*, 4537−4538.
(21) Fieser, L. F.; Gates, M. D., Jr. Synthetic Experiments Utilizing Perinaphthanone-7. *J. Am. Chem. Soc.* **1940**, *62*, 2335−2341.
(22) Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. Me_3SiCl-NaI-CH_3-CN as an Efficient and Practical Reducing Agent for Benzylic Alcohols. *Tetrahedron Lett.* **1987**, *28*, 3817−3818.
(23) Denney, D. B.; Smith, L. C. Preparation and Reaction of Some Phosphobetaines. *J. Org. Chem.* **1962**, *27*, 3404−3408.
(24) Sally, J. J., Jr.; Glennon, R. A. Studies on Simplified Ergoline Derivatives. A General Six-Step Synthesis of Phenyl-Substituted 4-Methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-1-(2H)-one Analogs (1). *J. Heterocycl. Chem.* **1982**, *19*, 545−550.
(25) Bachmann, W. E.; Cortes, G. D. Phenanthrene Derivatives. XI. Accetylation and Succinoylation of 3-Methylphenanthrene. *J. Am. Chem. Soc.* **1943**, *65*, 1329−1334.
(26) Agranat, I.; Shih, Y.-S. Haworth Synthesis as a Route to the Anthracene Ring System. *Synthesis* **1974**, 865−866.
(27) Amemiya, Y.; Hong, S.-S.; Venkataraman, B. V.; Patil, P. N.; Shams, G.; Romstedt, K.; Feller, D. R.; Hsu, F.-L.; Miller, D. D. Synthesis and α-Adrenergic Activities of 2- and 4-Substituted Imidazoline and Imidazole Analogs. *J. Med. Chem.* **1992**, *35*, 750−755.
(28) Ruffolo, R. R., Jr. Medicinal Chemistry of Adrenoceptor Agonists. *Drug. Des. Discovery* **1993**, *9*, 351−367.
(29) Ruffolo, R. R., Jr.; Stadel, J. M.; Hieble, J. P. α-Adrenoceptors: Recent Developments. *Med. Res. Rev.* **1994**, *14*, 229−270.
(30) Timmermans, P. B. M. W. M.; Chiu, A. T.; Thoolen, M. J. M. C. α-Adrenergic receptors. In *Comprehensive of Medicinal Chemistry*; Hansch, C., Ed.; Pergamon Press: Oxford, **1990**; pp 133−185.
(31) Ruffolo, R. R., Jr.; Waddell, J. E. Stereochemical Requirements of α_2-Adrenergic Receptors for α-Methyl Substituted Phenethylamines. *Life Sci.* **1982**, *31*, 2999−3007.
(32) Wang, C. D.; Buck, M. A.; Fraser, C. M. Site-Directed Mutagenesis of α_{2A}-Adrenergic Receptors: Identification of Amino Acids Involved in Ligand Binding and Receptor Activation by Agonists. *Mol. Pharmacol.* **1991**, *40*, 168−179.
(33) Hong, S.-S.; Romstedt, K. J.; Feller, D. R.; Hsu, F.-L.; George, C.; Cupps, T. L.; Lyon, R. A.; Miller, D. D. Resolution and Adrenergic Activities of the Optical Isomers of 4-[1-(1-Naphthyl)-ethyl]-1*H*-imidazole. *Chirality* **1992**, *4*, 432−438.
(34) Squier, G. J.; van der Schyf, C. J.; Oliver, D. W.; Venter, D. P. Comparative α- and *β*-Adrenoceptor Activity of 2- and 6-Ring-chlorinated Noradrenaline Analogues. *Arzneim.-Forsch. Drug Res.* **1986**, *36*, 457−460.
(35) DeBernardis, J. F.; Arendsen, D. L.; Kyncl, J. J.; Kerkman, D. J. Conformationally Defined Adrenergic Agents. 4. 1-(Aminomethyl)phthalans: Synthesis and Pharmacological Consequences of the Phthalan Ring Oxygen Atom. *J. Med. Chem.* **1987**, *30*, 178−184.
(36) Li, Y. O.; Bergsma, D. J.; Ganguly, S.; Swift, A. M.; Ruffolo, R. R., Jr.; Hieble, J. P. Presentation at XII International Congress of Pharmacology, Montreal, Canada, July 24−29, 1994.
(37) Easson, L. H.; Stedman, E. Studies on the Relationship Between Chemical Constitution and Physiological Action. V. Molecular Dissymetry and Physiological Activity. *Biochem. J.* **1933**, *27*, 1257−1266.
(38) Kirk, K. L. 4-Lithio-1-tritylimidazole as a Synthetic Intermediate. Synthesis of Imidazole-4-carboxyaldehyde. *J. Heterocycl. Chem.* **1985**, *22*, 57−59.
(39) Pitha, J.; Szabo, L.; Szurmai, Z.; Buchowiecki, W.; Kusiak, J. W. Alkylating Prazosin Analog: Irreversible Label for α_1-Adrenoceptors. *J. Med. Chem.* **1989**, *32*, 96−100.
(40) Veenstra, D. M. J.; van Buuren, K. J. H.; Krielaart, M. J.; Nijkamp, F. P. Errors Introduced in Radioligand Binding Studies Due to Displaceable, Cation Dependent, [^{3}H]Prazosin Binding to Glass-Fiber and Glass Surface. *J. Recept. Res.* **1993**, *13*, 801−814.
(41) Kivikoski, J. H.; Rissanen, K. T.; Parhi, S. S. L. Crystal Structures and Absolute Configurations of Dexmedetomidine and its Tosyl Derivative. *Tetrahedron*: *Asymmetry* **1993**, *4*, 45−58.

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