J. Med. Chem. **1998,** *41,* 564−578

A Novel Class of Orally Active Non-Peptide Bradykinin B_2 Receptor Antagonists. 1. Construction of the Basic Framework

Yoshito Abe,[†] Hiroshi Kayakiri,*[,†] Shigeki Satoh,[†] Takayuki Inoue,[†] Yuki Sawada,[†] Keisuke Imai,[†] Noriaki Inamura,[‡] Masayuki Asano,[§] Chie Hatori,[§] Akira Katayama,[§] Teruo Oku,[†] and Hirokazu Tanaka[||]

Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 5-2-3 Tokodai, Tsukuba, Ibaraki 300-26, Japan

Received September 4, 1997

A novel class of potent, selective, and orally active non-peptide bradykinin (BK) B_2 receptor antagonists were designed and synthesized starting from 8-benzyloxyimidazo[1,2-*a*]pyridine derivative **2**. The unique screening lead (**2**) was discovered by a two-step intentional random screening process, involving recognition of the relationship between BK and angiotensin II (Ang II) and the common structural features. Systematic chemical modification of **2** elucidated the structural requirements essential for B_2 binding affinity leading to the identification of 8-[[3-(*N*-acylglycyl-*N*-methylamino)-2,6-dichlorobenzyl]oxy]-3-halo-2-methylimidazo[1,2-*a*]pyridine skeleton as the basic framework of this new series of B_2 antagonists. A molecular modeling study suggested the key role of the *N*-methylanilide moiety at the 3-position of the 2,6-dichlorobenzene ring to allow these compounds to adopt the characteristic active conformation. The representative lead compounds inhibited the specific binding of [^{3}H]BK to guinea pig ileum membrane preparations expressing B_2 receptors, with nanomolar IC_{50}s and also displayed in vivo functional antagonistic activities against BK-induced bronchoconstriction in guinea pigs at an oral dose of 1 mg/kg. Pharmacokinetic studies of compounds **47c** and **50b** in rats highlighted their excellent oral bioavailabilities, indicating that they represent the first orally active non-peptide B_2 antagonists reported to date.

Introduction

Bradykinin (BK) is an endogenous nonapeptide produced by tissue and plasma kallikreins from kininogens in the course of inflammatory responses.[1−5] It displays potent and diverse biological activities, such as relaxation of venular smooth muscle, contraction of smooth muscle of airway, plasma extravasation, stimulation of sensory neurons, alteration of ion secretion of epithelial cells and release of nitric oxide, prostaglandins, leukotrienes, and cytokines.[1−7] On the basis of these strong proinflammatory properties, BK is believed to play important roles in a variety of inflammatory diseases including asthma, rhinitis, pancreatitis, sepsis, rheumatoid arthritis, brain edema and angioneurotic edema. BK has at least two subtypes of specific G-protein-coupled cell surface receptors designated as B_1 and B_2,[1,4,8] both of which have been identified by molecular cloning and pharmacological means. B_2 receptors are expressed constitutively in many tissues and are thought to mediate most of the biological actions of BK.[1,8]

A number of peptide B_2 antagonists have been synthesized, and the representative "second-generation" antagonists,[9−13] icatibant (Hoel40)[9,10] and bradycor (CP0127),[11] are in clinical trials. Although they have very strong affinity for B_2 receptors and longer duration of action in vivo than the "first-generation" peptide antagonists,[14,15] their therapeutic use is still limited because of their poor oral bioavailability. Recently some non-peptide B_2 antagonists have been reported,[16,17] but they are much less potent than peptide antagonists and unsatisfactory with regard to selectivity and/or oral bioavailability.

To investigate the pathophysiological roles of BK and to develop a new therapeutic drug for treatment of the inflammatory diseases described above, we started a research program to discover orally active non-peptide B_2 antagonists which could overcome the problems with the peptide analogues. First of all we carried out a two-step directed random screening of the Fujisawa chemical library and discovered the unique non-peptide screening lead **2** (Chart 2). Extensive chemical modification of this simple screening lead, followed by intensive optimization of the side chain, allowed us to build up the basic structure of a novel class of potent and selective non-peptide B_2 antagonists. Herein we describe the structure−activity relationships (SAR) revealed on the way to the discovery of the first orally active lead compounds (**47c**, **50b**).

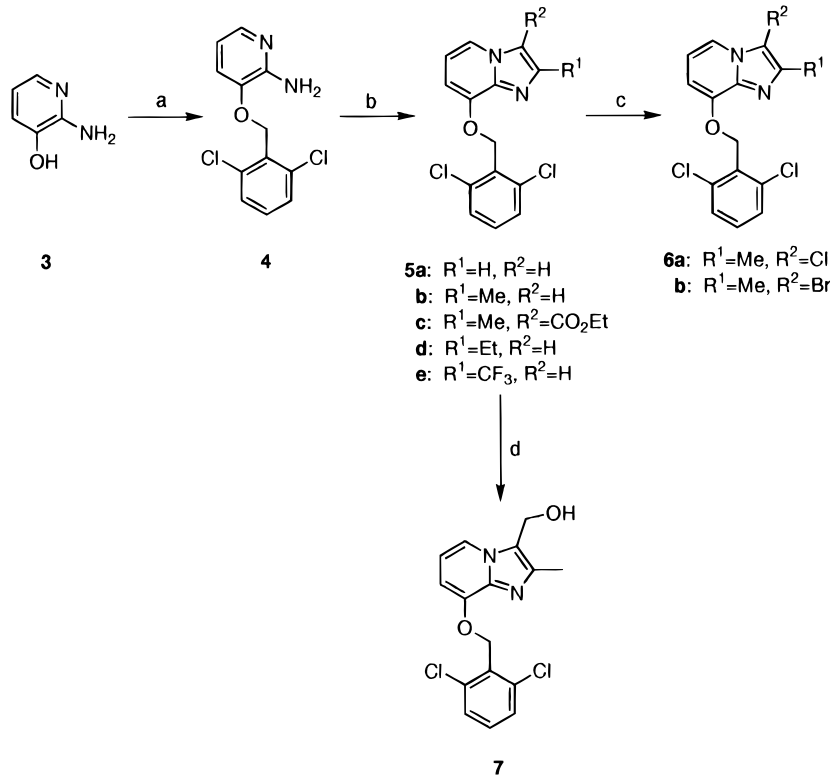
Chemistry

The compounds described in this study are shown in Tables 1−8 and their synthetic methods are outlined in Schemes 1−9. Condensation of 3-[(2,6-dichlorobenzyl)oxy]-2-aminopyridine (**4**) with the corresponding α-halo carbonyl compounds [$XCH(R^2)COR^1$][18,19] gave substituted imidazo[1,2-*a*]pyridines **5a**−**e**. Selective halogenation at the 3-position of **5b** was achieved by means of *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) in EtOH[20] to give **6a,b**. The 3-ester derivative **5c** was reduced with lithium aluminum hydride to give alcohol **7** (Scheme 1).

[†] Department of Medicinal Chemistry.
[‡] Present address: Exploratory Clinical Research, Development Division, Fujisawa Pharmaceutical Co. Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532, Japan.
[§] Department of Pharmacology.
[||] Present address: New Drug Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532, Japan.

S0022-2623(97)00591-8 CCC: $15.00
Published on Web 01/22/1998

Scheme 1[a]



[a] (a) 2,6-Dichlorobenzyl bromide, NaH, DMF; (b) $XCH(R^2)COR^1$, EtOH; (c) NBS or NCS, EtOH; (d) LAH, THF.

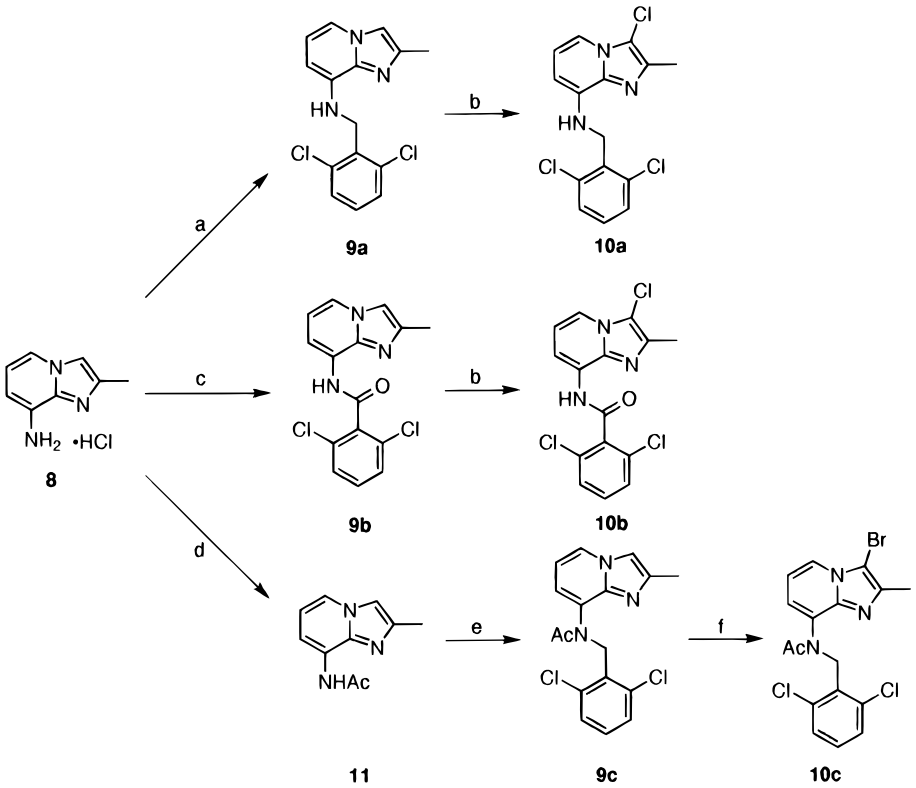
Schemes 2−4 show the synthetic routes for the compounds which have other types of linkers between the imidazo[1,2-*a*]pyridine ring and the 2,6-dichlorophenyl moiety. The benzylamino derivative **10a** was synthesized by reductive alkylation of 8-aminoimidazo-[1,2-*a*]pyridine **8** with 2,6-dichlorobenzaldehyde followed by chlorination with NCS. Coupling of **8** with 2,6-dichlorobenzoyl chloride and successive chlorination gave the benzamido derivative **10b**. The acetamide **11** was alkylated to give **9c**, which was treated with NBS to provide the benzylacetamido derivative **10c** (Scheme 2). The phenoxycarbonyl **15a** and the anilide **15b** were obtained from the acid **14** via its acid chloride. The phenoxymethyl derivative **17** was synthesized by coupling of **16** with 2,6-dichlorophenol via its methanesulfonate (Scheme 3). Wittig reaction of the aldehyde **18**[21] with (2,6-dichlorobenzyl)triphenylphosphonium bromide was performed in DMSO in the presence of sodium hydride to give only the (*E*)-olefin **19**, whose stereochemistry was identified on the basis of the observed coupling constant of 16 Hz between the olefinic protons.[21] Successive bromination at the 3-position yielded **20** (Scheme 4).

Alkylation of 8-hydroxyimidazo[1,2-*a*]pyridine (**21**)[19a] with appropriately substituted benzyl halides or benzyl methanesulfonates followed by halogenation gave the corresponding 8-(benzyloxy)-3-haloimidazo[1,2-*a*]pyridines **23a**−**e** (Scheme 5).

Introduction of the nitrogen atom at the 3-position of the phenyl ring is shown in Scheme 6. Treatment of 2,6-dichlorobenzaldehyde (**24**) with 70% nitric acid in concentrated sulfuric acid provided the 3-nitro derivative **25** exclusively. Similar nitration of 2,6-dichlorobenzoic acid failed to proceed regioselectively (data not shown). Reduction of **25** with sodium borohydride and subsequent mesylation of the alcohol yielded the mesylate **27a**, which was coupled with **21** in the presence of sodium hydride to construct the basic skeleton **28a**. Reduction of the nitro group of **29a** with iron in refluxing concentrated HCl and EtOH gave the highly insoluble aniline **30a**. Acetylation of **30a** followed by treatment with alkyl halides in the presence of sodium hydride yielded the alkylamides **32a** and **32c**. Reduction of the amide **32a** with borane−methyl sulfide complex provided the amine **33**. The 2,4,6-trichlorobenzoic acid **34** was nitrated and was reduced with borane−methyl sulfide complex to give the benzyl alcohol **26b**. Subsequent mesylation, coupling and bromination provided the nitro derivative **29b**, which was reduced with iron in refluxing acetic acid and EtOH to give the aniline **30b**. Acetylation of **30b** with acetic anhydride in pyridine gave the diacetate **31b**. Treatment of **31b** with methyl iodide and sodium hydride afforded the alkylamide **32b**.

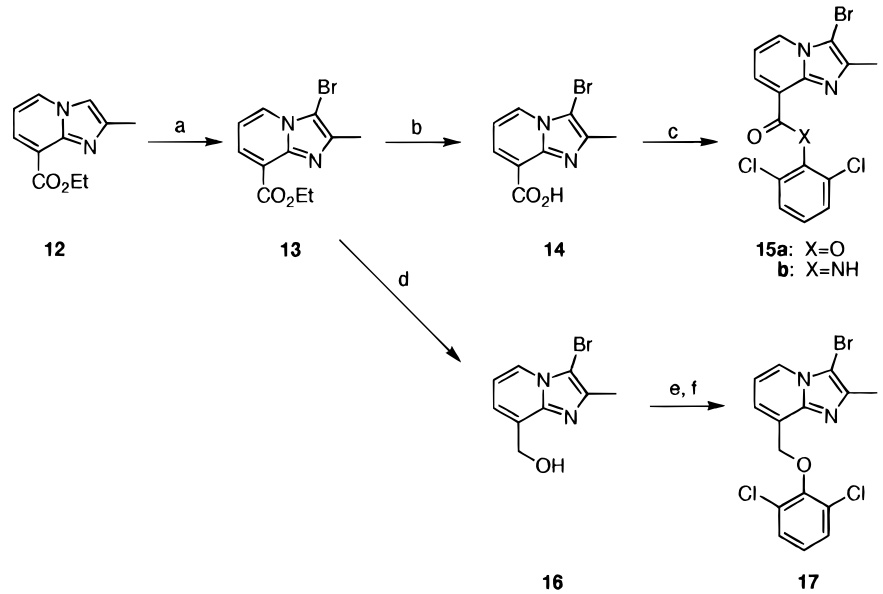
Modifications of the amine at the 3-position of the phenyl ring are shown in Scheme 7 and 8. Removal of the acetyl group of **32a** with sodium methoxide gave the methylaniline **36** which was acylated or sulfonylated to afford **37a**−**e**. Treatment of **37c** with methylamine in methanol yielded the urea **38**. The acetoxyacetamide **37e** was hydrolyzed and alkylated to give the methyl ether **40** (Scheme 7). The *N*-phthaloylglycinamides **42a**−**c** were obtained from **30a** by heating with the acid chlorides (**41a**−**c**) and pyridine in *N*-methylpyrrolidone. Alkylation of **42a**−**c** with methyl iodide in the presence of sodium hydride yielded **43a**−**c**, which were deprotected with hydrazine monohydrate and successively acetylated to give the acetamides **45a**−**c**, respectively. Methylation of **45a** was performed with methyl iodide and sodium hydride to give *N*-methylacetamide **45d**.

Scheme 2[a]



[a] (a) 2,6-$Cl_2C_6H_3CHO$, $NaBH_3CN$, MeOH; (b) NCS, EtOH; (c) 2,6-$Cl_2C_6H_3COCl$, Et_3N, DMAP, CH_2Cl_2; (d) Ac_2O, pyridine; (e) 2,6-$Cl_2C_6H_3CH_2Br$, NaH, DMF; (f) NBS, EtOH.

Scheme 3[a]



[a] (a) NBS, EtOH; (b) 1 N NaOH, EtOH; (c) $(COCl)_2$, DMF, CH_2Cl_2 then 2,6-$Cl_2C_6H_3OH$ or 2,6-$Cl_2C_6H_3NH_2$, Et_3N, CH_2Cl_2; (d) LAH, THF; (e) MsCl, Et_3N, CH_2Cl_2; (f) NaH, 2,6-$Cl_2C_6H_3OH$, DMF.

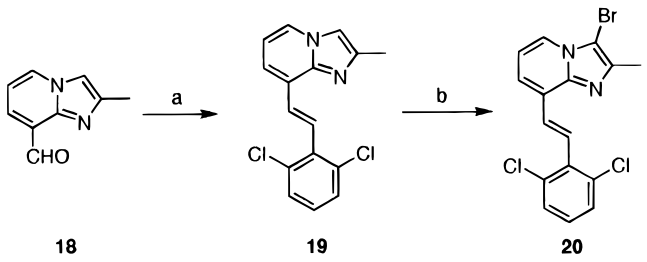
The hydrochloride **46** was obtained by treatment of **45a** with 10% hydrogen chloride in MeOH (Scheme 8).

Further chemical modifications of the amine **44a** are shown in Scheme 9. Reaction of **44a** with sulfonyl chloride or acid chlorides gave **47a**−**d** in good yield. **47a,b** and **47d** were treated with 10% hydrogen chloride in MeOH to give the corresponding hydrochlorides **48a,b** and **48d**, respectively. Acylation of **44a** with bromoacetyl chloride followed by the substitution with dimethylamine yielded **49**. Treatment of **44a** with isocyanates yielded the corresponding ureas **50a**−**c**. **50a** and **50c** were converted to the corresponding hydrochlorides **51a** and **51c**, respectively.

Biology

All compounds were tested for inhibiting the specific binding of [^{3}H]BK to B_2 receptors in guinea pig ileum membrane preparations as previously reported.[22] Com-

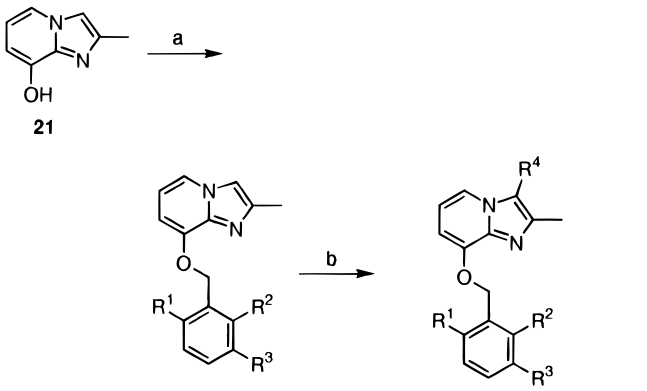
Scheme 4[a]



18 **19** **20**

[a] (a) 2,6-$Cl_2C_6H_3CH_2PPh_3Br$, NaH, DMSO; (b) NBS, EtOH.

Scheme 5[a]



21

22a: $R^1=R^2=Br$, $R^3=H$ **23a**: $R^1=R^2=Br$, $R^3=H$, $R^4=Cl$
b: $R^1=R^2=F$, $R^3=H$ **b**: $R^1=R^2=F$, $R^3=H$, $R^4=Cl$
c: $R^1=Cl$, $R^2=F$, $R^3=H$ **c**: $R^1=Cl$, $R^2=F$, $R^3=H$, $R^4=Br$
d: $R^1=R^2=R^3=Cl$ **d**: $R^1=R^2=R^3=Cl$, $R^4=Br$
e: $R^1=R^2=Cl$, $R^3=OMe$ **e**: $R^1=R^2=Cl$, $R^3=OMe$, $R^4=Br$

[a] (a) NaH, benzyl halide or benzyl methanesulfonate, DMF; (b) NCS or NBS, EtOH.

pounds having the potent binding affinities were then tested for in vivo oral activity in inhibiting BK-induced bronchoconstriction in guinea pigs. Pharmacokinetics of the orally active BK antagonists were also studied.

Results and Discussion

When we started our research program no selective non-peptide BK antagonists had been reported. In seeking a screening lead we took notice of the relationship between BK and Ang II.[17b] Ang II is an octapeptide which plays a key role in regulating cardiovascular homeostasis and electrolyte/fluid balance through specific G-protein-coupled cell surface AT_1 receptors as the active component of the renin−angiotensin−aldosterone system. It acts as a representative vasoconstrictor to increase blood pressure whereas BK causes severe systemic hypotension. Angiotensin-converting enzyme (ACE), which generates Ang II from inactive Ang I, is identical with kininase II which participates in the degradation of BK (Chart 1). Furthermore, AT_1 receptors show the highest homology (29%) to B_2 receptors amongst G-protein-coupled receptors, with the exception of the BK B_1 receptor subtype which has 35% homology. These suggestive relevance between Ang II and BK prompted us to focus our initial screening efforts on AT_1 antagonists and related compounds in the Fujisawa chemical library. This directed random screening of about 300 compounds revealed that a synthetic intermediates for AT_1 antagonists, i.e., compound **1**, weakly bound to B_2 receptors in guinea pig ileum membrane preparations with an IC_{50} value of 3.1×10^{-5} M. Because of its low affinity and simple structure compared to a nonapeptide BK, we supposed that **1** lacks some important pharmacophores. So we carried out a second screening of about 400 more structurally diverse compounds incorporating a benzyloxy heteroaromatic substructure and identified 8-benzyloxyimidazo[1,2-*a*]-pyridine (**2**) with an IC_{50} value of 7.6×10^{-6} M as a better screening lead compound (Chart 2). With this unique lead in hand we started extensive chemical modifications to investigate SAR for B_2 binding activity.

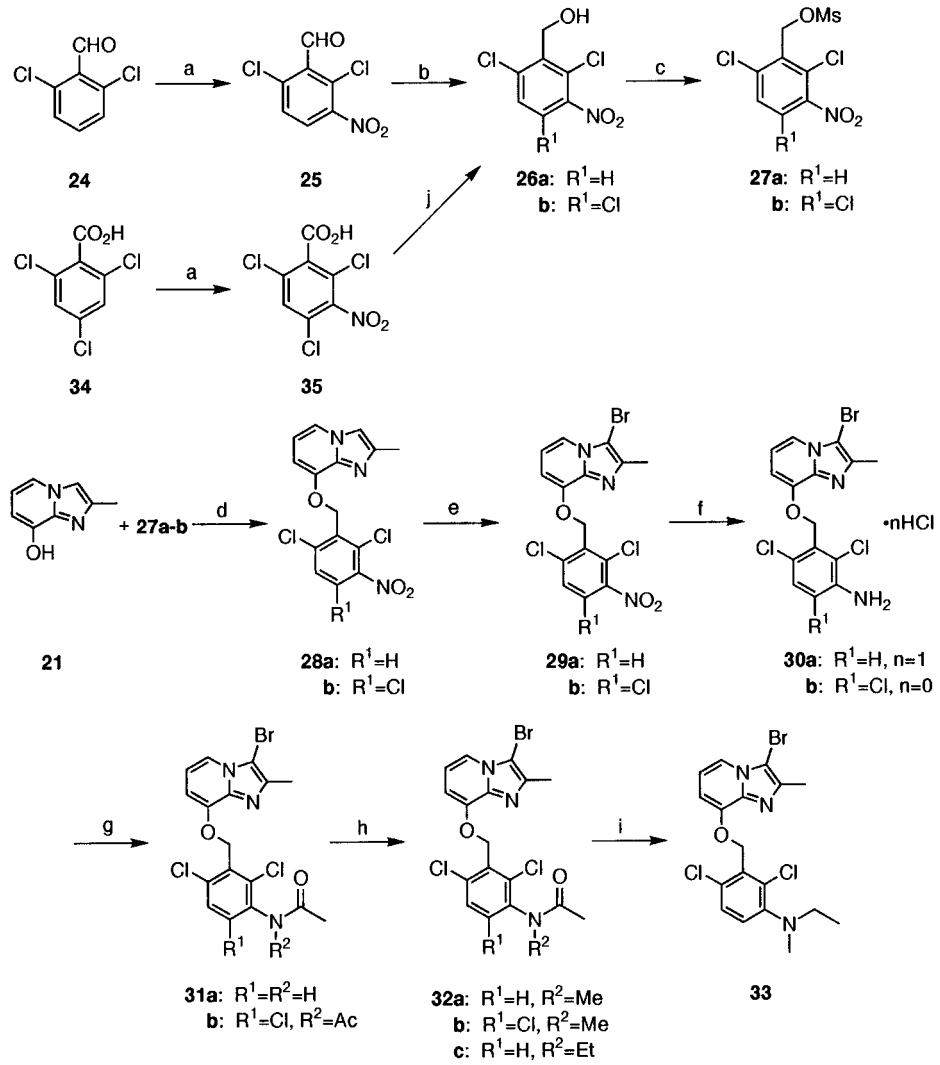
At first we investigated the effect of 2- and 3-substituents on the imidazo[1,2-*a*]pyridine ring (Table 1). Removal of both substituents from the screening lead **2** gave **5a** which was about 4 times less potent; however, introduction of a 2-methyl group (**5b**) recovered the B_2 binding affinity. Enlargement of the 2-substituent gave slightly weaker 2-ethyl derivative **5d**. Replacement of the 2-methyl group with the electron-withdrawing trifluoromethyl moiety (**5e**) resulted in significant loss of activity. Concerning the 3-substituent, hydroxymethyl derivative **7** was slightly weaker than **5b**, and an ester group (**5c**) caused severe loss of activity. On the other hand, incorporation of halogen at the 3-position (**6a,b**) remarkably increased the affinity to submicromolar levels. On the basis of this data we postulated that 2-methyl and 3-chloro or 3-bromo substituents contributed to B_2 binding affinity by hydrophobic interactions with the corresponding pockets of the B_2 receptor and that the pocket for the 2-methyl group was much smaller than that for the 3-substituent. Since chemical modifications at the 5-, 6-, and 7-positions of the imidazo[1,2-*a*]pyridine ring failed to improve the binding affinity (data not shown), we decided to adopt 3-chloro- or 3-bromo-2-methylimidazo[1,2-*a*]pyridine as the common substructure for further modifications.

The SAR of the linker group between the imidazo-[1,2-*a*]pyridine ring and the dichlorophenyl moiety was rather drastic (Table 2). Amino derivative **10a** retained about a 5-fold weaker binding affinity; however, N-acetylation of the corresponding 3-bromo derivative gave inactive compound **10c**. Replacement of the oxymethylene group of **6a** or **6b** with two types of the amides (**10b**, **l5b**), the ester (**l5a**), and the ethenyl (**20**) group resulted in complete loss of the activity. Even the inverse methyleneoxy derivative (**17**) failed to show any appreciable binding affinity, suggesting that the linker group was important not only as a spacer but also as a pharmacophore which had electrostatic interaction with the B_2 receptor via its oxygen atom.

Table 3 shows that the dichloro group was the most favorable among the examined dihalogen substituents at the 2,6-position of the phenyl ring. We also investigated substituents other than halogens in another series of B_2 antagonists and found that the 2,6-dichloro group was superior to others. The data will be reported in future publications.

As the next step, we introduced substituents into the 3- and 4-positions of the 2,6-dichlorophenyl ring to improve the binding affinity (Table 4). Although the 3-chloro (**23d**) and the 3-methoxy group (**23e**) weakened the activity, the 3-nitro derivative (**29a**) afforded an approximately 5-fold increase in binding affinity. Reduction of the nitro group followed by N-acetylation

Scheme 6[a]



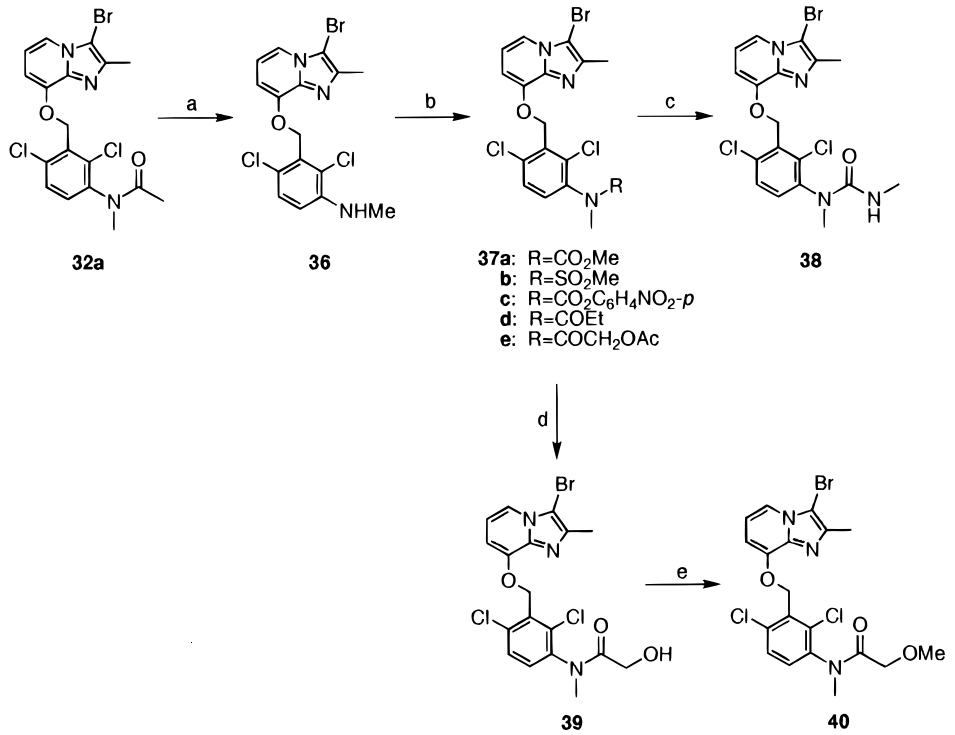
[a] (a) HNO_3, H_2SO_4; (b) $NaBH_4$, MeOH; (c) MsCl, Et_3N, CH_2Cl_2; (d) NaH, DMF; (e) NBS, EtOH; (f) Fe, concentrated HCl (for **29a**) or AcOH (for **29b**), EtOH; (g) Ac_2O, pyridine; (h) R^2X, NaH, DMF; (i) BH_3·SMe_2, THF.

resulted in a severe loss of activity; however, *N*-methylacetamide derivative **32a** was as potent as the nitro derivative **29a**. Additional introduction of chloro to the 4-position of **32a** gave a much less potent compound (**32b**). These results suggest that steric features around this position are much more important for B_2 binding affinity than electrostatic factors.

To investigate more detailed steric requirements for B_2 binding affinity, we carried out conformational analysis of *N*-H and *N*-methyl acetamide model compounds (**31a′**, **32a′,b′**) by ab initio molecular orbital calculations. For each model compound the most stable structures of *cis*- and *trans*-amide conformers were obtained by GAUSSIAN 94 using 6-31G** basis set.[23] The energies and torsion angles for the *cis*- and *trans*-amide conformers are shown in Table 5, and their preferred conformations are drawn in Figure 1. Energetic and conformational features of the most stable structures were as follows. The *N*-H amide compound (**31a′**) adopted a *trans*-amide conformation with the amide and phenyl plane coplanar whereas the *N*-methyl compound (**32a′,b′**) adopted a *cis*-amide conformation with the amide and phenyl plane almost perpendicular. Interestingly, the relative stabilities of the *cis*-amide conformer compared to the *trans*-amide one of the model compounds **3la′**, **32a′**, and **32b′** correlated to the in vitro activities of the corresponding B_2 ligands **31a**, **32a**, and **32b**. These data might suggest that this class of B_2 ligands bind to the receptor as the *cis*-amide conformer and the 2,6-dichloro-3-*N*-methylanilide moiety plays a key role in stabilizing the active conformation.

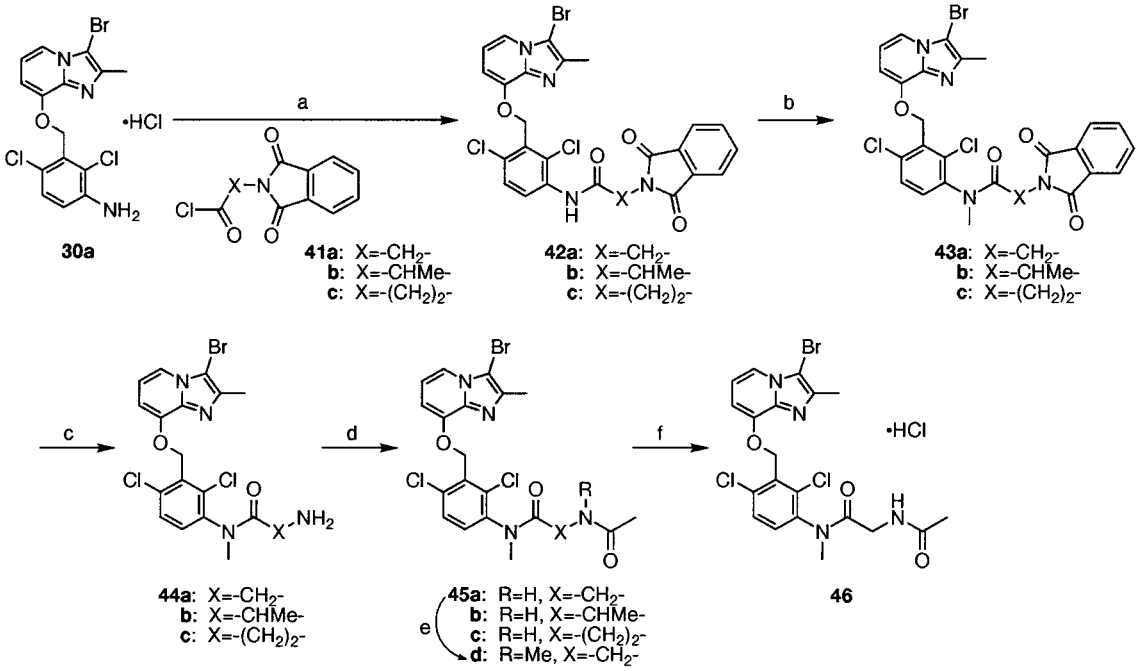
Thus we selected **32a** as a lead compound for further chemical modifications. Obviously **32a** is much smaller than the nonapeptide BK, so there should be many binding sites on the B_2 receptor remaining to be used for interaction with non-peptide ligands. Seeking such possibilities, we concentrated on chemical modifications of the acetamide group of **32a** (Table 6). *N*-Ethyl derivative of **31a** (**32c**) was 3-fold weaker than **32a**, suggesting a strict steric restriction around the amide group. Reduction of the carbonyl group (**33**) significantly reduced the activity consistent with our hypothesis discussed above. The carbamate (**37a**), sulfonamide (**37b**), and urea (**38**) congeners were remarkably less potent and introduction of methyl (**37d**), acetoxy (**37e**), methoxy (**40**), or amino (**44a**) groups gave compounds that were only weakly active. However, acetylation of the terminal amine of **44a** afforded the new lead com-

Scheme 7[a]



[a] (a) NaOMe, MeOH; (b) RCl, Et_3N or pyridine, CH_2Cl_2; (c) $MeNH_2$, MeOH; (d) K_2CO_3, MeOH; (e) MeI, NaH, DMF.

Scheme 8[a]

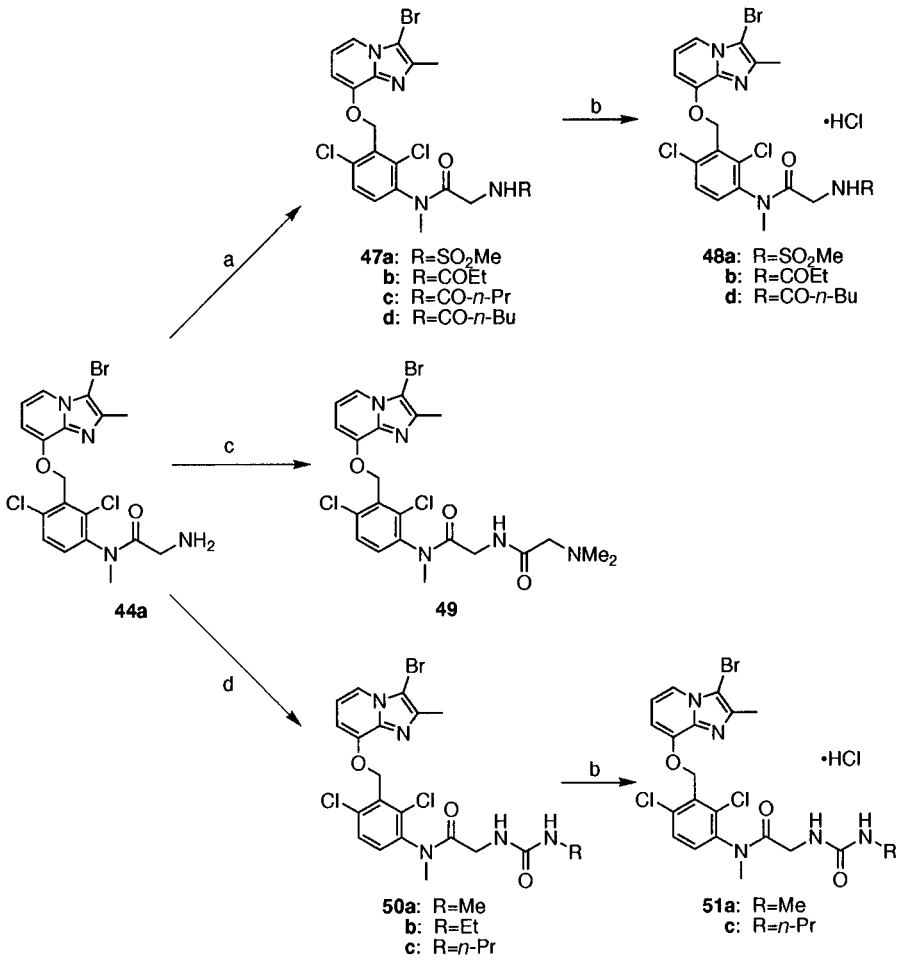


[a] (a) pyridine, DMAP, *N*-methylpyrrolidone; (b) MeI, NaH, DMF; (c) $H_2NNH_2 \cdot H_2O$, EtOH; (d) Ac_2O, pyridine, CH_2Cl_2; (e) MeI, NaH, DMF; (f) HCl−MeOH.

pound **45a**, with an IC_{50} of 16 nM. Since both extending the methylene to ethylene (**45c**) and blocking the terminal amide proton with a methyl group (**45d**) reduced the affinity, it was suggested that the terminal amide group contributed to the interaction with the B_2 receptor as a hydrogen bond donor. Furthermore, introduction of a methyl group at the methylene of the glycine moiety (**45b**) reduced the affinity compared to **45a**, indicating that the methyl group sterically influences the interaction with the receptor or the conformation of the side chain.

Finally, further optimization of the terminal acyl group led us to the discovery of a novel class of highly potent non-peptide BK B_2 antagonists as shown in Table 7. The *n*-butylamide (**47c**), (dimethylamino)acetamide (**49**), and ethyl urea (**50b**) inhibited the specific binding

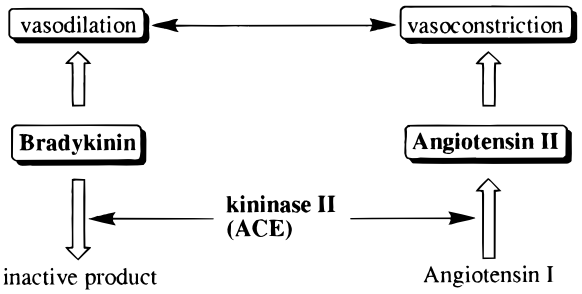
Scheme 9[a]



[a] (a) RCl, Et_3N, CH_2Cl_2; (b) HCl−MeOH; (c) $BrCH_2COCl$, Et_3N, CH_2Cl_2 then $HNMe_2$ in H_2O; (d) RNCO, CH_2Cl_2.

Chart 1

Bradykinin and Angiotensin



of [^{3}H]BK to B_2 receptors with nanomolar IC_{50}s and their functional antagonistic properties were proven in vivo at 1 mg/kg by oral administration in a guinea pig BK-induced bronchoconstriction model. Furthermore, the pharmacokinetic studies in rats revealed their good to excellent oral bioavailabilities (Table 8). To our knowledge these representative compounds are the first non-peptide B_2 antagonists which can inhibit the action of BK in vivo by oral administration.

Conclusion

A unique screening lead (**2**) was found by a two-step directed random screening process taking notice of the relationship between BK and Ang II and structural features. Extensive chemical modification of **2** revealed that hydrophobic contacts via 2-methyl and 3-chloro or 3-bromo groups on the imidazo[1,2-*a*]pyridine ring, electrostatic interactions via linker oxygen, and hydrogen bonds via the terminal amide group significantly contributed to the binding affinity to B_2 receptors. It is also noteworthy that the 2,6-dichloro-3-*N*-methylanilide moiety was suggested to be the key feature to allow these B_2 antagonists to adopt the characteristic active conformations. These speculations are summarized in a pharmacophore model for the interactions between the antagonists and B_2 receptors (Figure 2). The investigation of detailed SAR allowed us to identify 8-[[3-(*N*-acylglycyl-*N*-methylamino)-2,6-dichlorobenzyl]oxy]-3-halo-2-methylimidazo[1,2-*a*]pyridine skeleton as the basic framework and led us to the discovery of the first orally active non-peptide BK B_2 antagonists whose activities represent a 3 order of magnitude increase relative to the screening lead **2**. Further studies aiming at clinical candidates are currently underway using the representative antagonists obtained in this study as the new lead compounds. The expanded SAR will be presented in due course.[25]

Experimental Section

Chemistry. Melting points were determined on Mel-Temp (Mitamura Riken Kogyo, Japan) and are uncorrected. The 200 MHz proton NMR spectra were recorded on a Brucker AM200 spectrometer, and shifts were expressed in δ ppm with TMS as internal standard. Mass spectra were recorded on VG

Chart 2

Seed Finding by a Two-Step Directed Random Screening

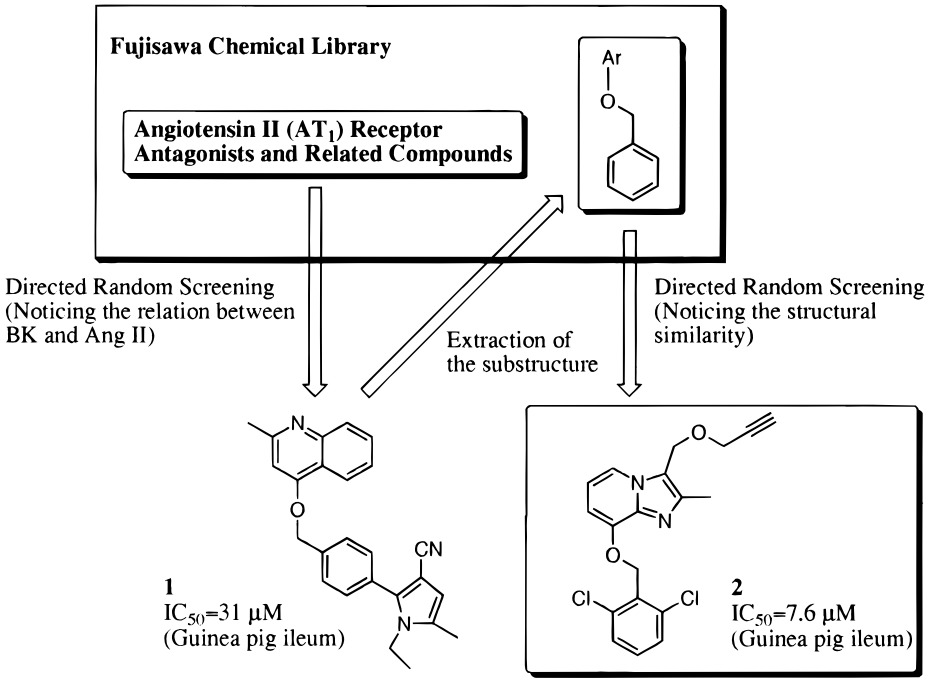
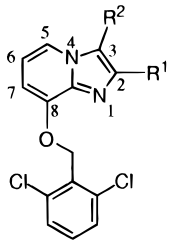


Table 1. SAR at 2,3-Positions of the Imidazo[1,2-*a*]pyridine



compd	R^1	R^2	IC_{50}, nM[a]	method	yield, %	mp, °C	formula[b]
2	Me	$CH_2OCH_2C{\equiv}CH$	7600				
5a	H	H	31000	B	27.0	148−149	$C_{14}H_{10}Cl_2N_2O$
5b	Me	H	4500	C	38.0	165−166	$C_{15}H_{12}Cl_2N_2O$
5d	Et	H	10000	C	25.3	153−154	$C_{16}H_{14}Cl_2N_2O$
5e	CF_3	H	>100000	C	44.6	184−185	$C_{15}H_9Cl_2F_3N_2O$
5c	Me	CO_2Et	>100000	C	29.3	160−161	$C_{18}H_{16}Cl_2N_2O_3$
7	Me	CH_2OH	7500	F	52.5	220−221	$C_{16}H_{14}Cl_2N_2O_2$
6a	Me	Cl	200	D	56.6	185−186	$C_{15}H_{11}Cl_3N_2O$
6b	Me	Br	230	E	82.0	173−174	$C_{15}H_{11}BrCl_2N_2O$

[a] IC_{50} for inhibition of specific binding of [^{3}H]BK (0.06 nM) to B_2 receptors in guinea pig ileum membrane preparations. For details, see the Experimental Section. [b] Analyses for C, H, and N are within ±0.4% of the expected value for the formula.

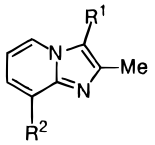
(Fisons) ZAB-SE (FAB). IR spectra were taken with a Perkin-Elmer FTIR 1600 spectrometer in Nujol or KBr and were expressed in cm^{-1}. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer. Analytical results were within ±0.4% of the theoretical values unless otherwise noted. Silica gel thin-layer chromatography was performed on precoated plates Kieselgel $60F_{254}$ (E. Merck, AG, Darmstadt, Germany). Silica gel flash chromatography was performed with Kieselgel 60 (230−400 mesh) (E. Merck, AG, Darmstadt, Germany). Extraction solvents were dried over magnesium sulfate.

Method A. 3-[(2,6-Dichlorobenzyl)oxy]-2-aminopyridine (4). To a solution of 2-amino-3-hydroxypyridine (**3**) (11.0 g, 0.10 mol) in dry DMF (50 mL) was added 60% sodium hydride in oil (4.4 g, 0.11 mol) portionwise in an ice−water bath under nitrogen. The mixture was stirred at the same temperature for 30 min, and 2,6-dichlorobenzyl chloride (25.2 g, 0.105 mol) was added portionwise therein. After 30 min of stirring, the mixture was stirred at ambient temperature for an additional 1 h. The reaction mixture was poured into water, and the formed precipitate was collected by vacuum filtration, washed with water, and dried in vacuo. The crude product was recrystallized from hexane−AcOEt to give **4** (23.9 g, 88.8%) as pale gray crystals: mp 150−152 °C; ^{1}H NMR ($CDCl_3$) δ 4.65 (2H, br s), 5.29 (2H, s), 6.65 (1H, dd, J = 7, 5 Hz), 7.14 (1H, dd, J = 7, 1 Hz), 7.21−7.43 (3H, m), 7.71 (1H, dd, J = 5, 1 Hz); IR (Nujol) 3455, 3270, 3125, 1620. Anal. ($C_{12}H_{10}Cl_2N_2O$) C, H, N.

Compounds **9c** and **22c** were prepared following a procedure similar to method A.

Method B. 8-[(2,6-Dichlorobenzyl)oxy]imidazo[1,2-*a*]-pyridine (5a). Compound **5a** was prepared using the method of Hand and Paudler.[18] To a mixture of 2-(bromomethyl)-1,3-dioxolane (372 mg, 2.23 mmol) and water (15 mL) was added concentrated HCl (0.23 mL, 0.535 mmol) dropwise. The mixture was stirred at ambient temperature for 2.5 h and then

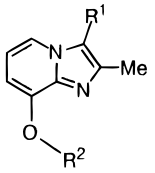
Table 2. SAR at the Linker Group between the Imidazo[1,2-*a*]pyridme and the 2,6-Dichlorobenzene



compd	R^1	R^2	IC_{50}, nM[a]	method	yield, %	mp, °C	formula[b]
6a	Cl	OCH_2Ar[c]	200	D	56.6	185−186	$C_{15}H_{11}Cl_3N_2O$
6b	Br	OCH_2Ar	230	E	82.0	173−174	$C_{15}H_{11}BrCl_2N_2O$
10a	Cl	$NHCH_2Ar$	1200	D	71.9	143−144	$C_{15}H_{12}Cl_3N_3$
10b	Cl	NHCOAr	>100000	D	78.6	191−197	$C_{15}H_{10}Cl_3N_3O$
10c	Br	$NAcCH_2Ar$	>100000	E	63.4	141−142	$C_{17}H_{14}BrCl_2N_2O$
17	Br	CH_2OAr	>100000	I	44.6	158−159	$C_{15}H_{11}BrCl_2N_2O$
15a	Br	CO_2Ar	>100000	H	30.4	165−166	$C_{15}H_9BrCl_2N_2O_2$
15b	Br	CONHAr	>100000	H	34.6	237−239	$C_{15}H_{10}BrCl_2N_3O$
20	Br	(*E*)-CH=CHAr[c]	>100000	E	57.1	121−122	$C_{16}H_{11}BrCl_2N_2$

[a] See Table 1. [b] Analyses for C, H, and N are within ±0.4% of the expected value for the formula. [c] Ar = 2,6-dichlorophenyl.

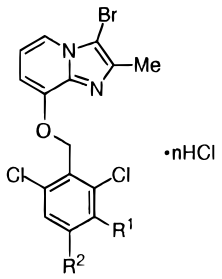
Table 3. SAR at the 2,6-Dihalobenzene



compd	R^1	R^2	IC_{50}, nM[a]	method	yield, %	mp, °C	formula[b]
6b	Br	2,6-Cl_2PhCH_2	230	E	82.0	173−174	$C_{15}H_{11}BrCl_2N_2O$
23a	Cl	2,6-Br_2PhCH_2	1700	D	88.6	157−158	$C_{15}H_{11}Br_2ClN_2O$
23b	Cl	2,6-F_2PhCH_2	1800	D	70.9	168−170	$C_{15}H_{11}ClF_2N_2O$
23c	Br	2-Cl-6-$FPhCH_2$	1500	E	73.2	130−131	$C_{15}H_{11}BrClFN_2O$

[a] See Table 1. [b] Analyses for C, H, and N are within ±0.4% of the expected value for the formula.

Table 4. Introduction of the Substitutents on the 2,6-Dichlorophenyl Ring



compd	R^1	R^2	*n*	IC_{50}, nM[a]	method	yield, %	mp, °C	formula[b]
6b	H	H	0	230	E	82.0	173−174	$C_{15}H_{11}BrCl_2N_2O$
23d	Cl	H	0	490	E	70.9	168−170	$C_{15}H_{12}ClF_2N_2O$
23e	OMe	H	0	540	E	26.6	175−176	$C_{16}H_{13}BrCl_2N_2O_2$
29a	NO_2	H	0	42	E	95.1	217−219	$C_{15}H_{10}BrCl_2N_3O_3$
30a	NH_2	H	1	1500	Ex[c]	77.2	186−187	$C_{15}H_{12}BrCl_2N_3O{\cdot}HCl$
31a	NHAc	H	0	1800	G	93.6	210−212	$C_{17}H_{14}BrCl_2N_3O_2$
32a	NMeAc	H	0	54	M	58.9	201−204	$C_{18}H_{16}BrCl_2N_3O_2$
32b	NMeAc	Cl	0	420	M	29.7	oil	$C_{18}H_{15}BrCl_3N_3O_2$

[a] See Table 1. [b] Analyses for C, H, and N are within ±0.4% of the expected value for the formula. [c] Ex = experimental procedure described.

at 80 °C for 30 min. After the mixture was cooled to ambient temperature, sodium hydrogen carbonate (244 mg, 2.90 mmol) and **4** (479 mg, 1.78 mmol) were added therein, and the mixture was stirred at ambient temperature for 3 h. Dioxane (10 mL) was added to this mixture, and the mixture was heated under reflux for 10 h. The reaction mixture was concentrated in vacuo to about half volume and extracted three times with CH_2Cl_2. The organic extracts were combined, washed with brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting with $CHCl_3$−MeOH (20:1) followed by crystallization from isopropyl ether to give **5a** (140 mg, 27.0%) as colorless crystals: mp 148−149 °C; ^{1}H NMR ($CDCl_3$) δ 5.49 (2H, s), 6.58−6.78 (2H, m), 7.19−7.40 (3H, m), 7.57 (2H, s), 7.82 (1H, d, J = 7.5 Hz). Anal. ($C_{14}H_{10}Cl_2N_2O$) C, H, N.

Method C. 8-[(2,6-Dichlorobenzyl)oxy]-3-(ethoxycarbonyl)-2-methylimidazo[1,2-*a*]pyridine (5c). Substituted imidazo[1,2-*a*]pyridines were prepared by using the method reported by Kaminski et al.[19] A mixture of **4** (15.0 g, 55.8 mmol) and ethyl 2-chloroacetoacetate (11.9 g, 72.5 mmol) in EtOH (150 mL) was refluxed for 24 h. After cooling, the reaction mixture was concentrated in vacuo, and the residue was partitioned between AcOEt and saturated aqueous sodium hydrogen carbonate. The organic layer was washed with water and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting

Table 5. Relative Energies and Torsion Angles for the *cis*- and *trans*-Amide Conformers of Model Compounds[a]

	cis		*trans*	
compd	energy (kcal/mol)	torsion (deg)	energy (kcal/mol)	torsion (deg)
31a′	3.99	100.6	0	180
32a′	0	94.0	2.41	101.3
32b′	0	91.9	1.73	94.4

[a] Geometry optimizations and energy calculations were performed by GAUSSIAN 94 using 6-31G** basis set. Full geometry optimizations were performed to obtain most stable structure starting from the amide and phenyl coplanar and perpendicular structure.

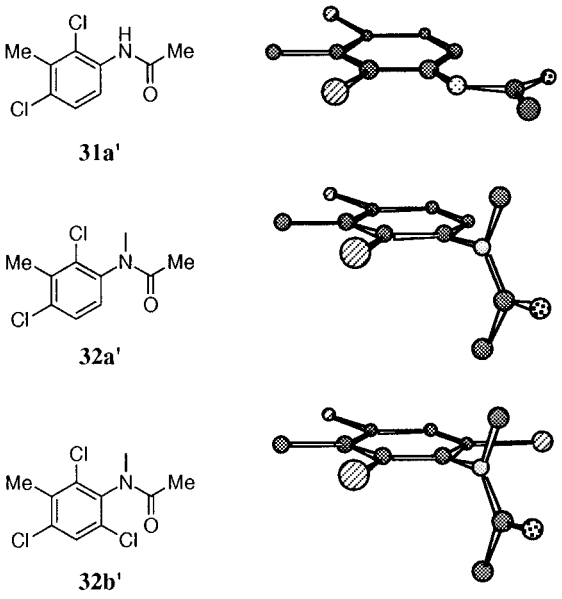


Figure 1. Structures and preferred conformations of model compounds **31a′**, **32a′**, and **32b′**.

with CH_2Cl_2–MeOH (100:1) followed by recrystallization from AcOEt to give **5c** (6.2 g, 29.3%) as colorless crystals: mp 160–161 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (3H, t, J = 8 Hz), 2.71 (3H, s), 4.42 (2H, q, J = 8 Hz), 5.49 (2H, s), 6.83–6.98 (2H, m), 7.19–7.41 (3H, m), 8.99 (1H, dd, J = 5, 1 Hz). Anal. ($C_{18}H_{16}Cl_2N_2O_3$) C, H, N.

Compounds **5b,d,e** and **8** were prepared following a procedure similar to method C.

Method D. 3-Chloro-8-[(2,6-dichlorobenzyl)oxy]-2-methylimidazo[1,2-*a*]pyridine (6a). To a solution of **5b** (100 mg, 0.326 mmol) in EtOH (1 mL) was added *N*-chlorosuccinimide (65 mg, 0.489 mmol) at ambient temperature, and the mixture was stirred the temperature for 1 h. To the mixture was added water, and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting with $CHCl_3$–MeOH (100:1) followed by recrystallization from benzene–hexane to give **6a** (63 mg, 56.6%) as colorless crystals: mp 185–186 °C; ^{1}H NMR ($CDCl_3$) δ 2.43 (3H, s), 5.48 (2H, s), 6.69 (1H, d, J = 8 Hz), 6.81 (1H, t, J = 8 Hz), 7.19–7.40 (3H, m), 7.69 (1H, d, J = 8 Hz). Anal. ($C_{15}H_{11}Cl_3N_2O$) C, H, N.

Compounds **10a,b** and **23a,b** were prepared following a procedure similar to method D.

Method E. 3-Bromo-8-[(2,6-dichlorobenzyl)oxy]-2-methylimidazo[1,2-*a*]pyridine (6b). The title compound was prepared from **5b** (80 mg, 0.260 mmol) and *N*-bromosuccinimide (52 mg, 0.287 mmol) using a similar procedure for **6a** and was crystallized from isopropyl ether to give colorless crystals (82 mg, 82.0%): mp 173–174 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (3H, s), 5.48 (2H, s), 6.70 (1H, d, J = 8 Hz), 6.82 (1H, t, J = 8 Hz), 7.19–7.41 (3H, m), 7.75 (1H, d, J = 8 Hz). Anal. ($C_{15}H_{11}BrCl_2N_2O$) C, H, N.

Compounds **10c**, **13**, **20**, **23c–e**, and **29a,b** were prepared following a procedure similar to method E.

Method F. 8-[(2,6-Dichlorobenzyl)oxy]-3-(hydroxymethyl)-2-methylimidazo[1,2-*a*]pyridine (7). To a suspension of lithium aluminum hydride (716 mg, 18.8 mmol) in dry THF (50 mL) was added **5c** (3.00 g, 7.92 mmol) in portions under nitrogen at 0 °C. The reaction mixture was stirred for 1 h in an ice–water bath. To the mixture was added a 3% aqueous solution of NaOH (3.75 mL) dropwise below 10 °C. The precipitate was removed by vacuum filtration and washed with hot THF (150 mL) and hot $CHCl_3$ (150 mL). The filtrate and washings were combined and evaporated in vacuo. The residue was recrystallized from MeCN to give **7** (1.40 g, 52.5%) as colorless crystals: mp 220–221 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (3H, s), 4.72 (2H, br s), 5.08 (1H, br s), 5.38 (2H, s), 6.76–6.94 (2H, m), 7.45–7.68 (3H, m), 7.98 (1H, d, J = 5 Hz); MS (FAB) m/z 337 (M + 1). Anal. ($C_{16}H_{14}BrCl_2N_2O_2$) C, H, N.

Compound **16b** was prepared following a procedure similar to method F.

8-[(2,6-Dichlorobenzyl)amino]-2-methylimidazo[1,2-*a*]pyridine (9a). To a solution of **8** (367 mg, 2.00 mmol) and 2,6-dichlorobenzaldehyde (350 mg, 2.00 mmol) in MeOH (6 mL) was added sodium cyanoborohydride (138 mg, 2.20 mmol) at ambient temperature under nitrogen. After 30 min, to the mixture was added additional 2,6-dichlorobenzaldehyde (175 mg, 1.00 mmol) and sodium cyanoborohydride (69 mg, 1.10 mmol) at ambient temperature. The reaction mixture was stirred for another 30 min and partitioned between AcOEt and saturated aqueous sodium bicarbonate. The organic layer was washed with water and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting with hexane–AcOEt (1:1) followed by crystallization from isopropyl ether to give **9a** (110 mg, 18.0%) as pale brown crystals: mp 119–121 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s), 4.69 (2H, d, J = 4 Hz), 5.19 (1H, t, J = 4 Hz), 6.29 (1H, d, J = 8 Hz), 6.63 (1H, t, J = 8 Hz), 7.15–7.36 (3H, m), 7.32 (1H, s), 7.47 (1H, d, J = 8 Hz). Anal. ($C_{15}H_{13}Cl_2N_3$) C, H, N.

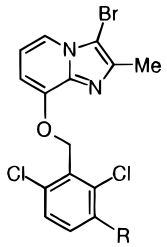
8-(2,6-Dichlorobenzamido)-2-methylimidazo[1,2-*a*]pyridine (9b). To a solution of **8** (410 mg, 2.79 mmol), triethylamine (422 mg, 4.18 mmol), and 4-(dimethylamino)pyridine (8 mg) in CH_2Cl_2 (8 mL) was added 2,6-dichlorobenzoyl chloride (816 mg, 3.90 mmol) in portions, cooling with an ice–water bath under nitrogen. The mixture was stirred at the temperature for 30 min and after that stirred at ambient temperature. After 2 h, the reaction mixture was washed with water, saturated aqueous solution of sodium bicarbonate, and brine, dried, and evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (hexane–AcOEt, 1:2) followed by crystallization from ether to give **9b** (45 mg, 5.0%) as colorless crystals: mp 194–196 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (3H, s), 6.79 (1H, t, J = 8 Hz), 7.30–7.42 (4H, m), 7.84 (1H, d, J = 8 Hz), 8.32 (1H, d, J = 8 Hz), 8.72 (1H, br s). Anal. ($C_{15}H_{11}Cl_2N_3O$) C, H, N.

Method G. 8-Acetamido-2-methylimidazo[1,2-*a*]pyridine (11). A mixture of **8** (235 mg, 1.28 mmol), acetic anhydride (261 mg, 2.56 mmol) and dry pyridine (2.3 mL) was heated at 90 °C for 6 h. After cooling, the mixture was poured into ice–water (10 mL). The precipitated solid was collected by vacuum filtration, washed with water, and dried in vacuo. The solid was crystallized from EtOH to give **11** (151 mg, 62.5%) as pale brown crystals: mp 169–170 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (3H, s), 2.47 (3H, s), 6.79 (1H, t, J = 8 Hz), 7.32 (1H, s), 7.77 (1H, d, J = 8 Hz), 8.19 (1H, br d, J = 8 Hz), 8.82 (1H, br s). Anal. ($C_{10}H_{11}N_3O$) C, H, N.

Compounds **31a,b** and **45a–c** were prepared following a procedure similar to method G.

3-Bromo-2-methylimidazo[1,2-*a*]pyridine-8-carboxylic Acid (14). A solution of **13** (1.00 g, 3.69 mmol) in EtOH (10 mL) containing 1 N NaOH (4.06 mL) was heated at 60 °C for 30 min. Upon cooling, the reaction mixture was diluted with water (20 mL) and adjusted to pH 5 with 1 N HCl. The

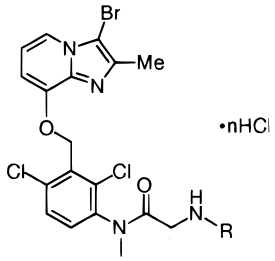
Table 6. SAR at the 3-Position of the 2,6-Dichlorobenzene



compd	R	IC_{50},[a] nM	method	yield, %	mp, °C	formula[b]
31a	NHAc	1800	G	93.6	210−212	$C_{17}H_{14}BrCl_2N_3O_2$
32a	NMeAc	54	M	58.9	201−204	$C_{18}H_{16}BrCl_2N_3O_2$
32c	NEtAc	150	M	63.5	161−162	$C_{19}H_{18}BrCl_2N_3O_2$
33	NMeEt	410	Ex[c]	62.7	oil	$C_{18}H_{18}BrCl_2N_3O$
37a	$NMeCO_2Me$	1400	Ex[c]	94.0	178−179	$C_{18}H_{16}BrCl_2N_3O_3$
37b	$NMeSO_2Me$	2100	N	37.3	161−164	$C_{17}H_{16}BrCl_2N_3O_3S$
38	NMeCONHMe	350	Ex[c]	56.0	192−193	$C_{18}H_{17}BrCl_2N_4O_2$
37d	NMeCOEt	72	N	74.1	168−170	$C_{19}H_{18}BrCl_2N_3O_2$
37e	$NMeCOCH_2OAc$	500	N	71.6	amorphous	$C_{20}H_{18}BrCl_2N_3O_4$
40	$NMeCOCH_2OMe$	580	M	19.4	145−146	$C_{19}H_{18}BrCl_2N_3O_3$
44a	$NMeCOCH_2NH_2$	380	P	95.8	175−178	$C_{18}H_{17}BrCl_2N_4O_2$
45a	$NMeCOCH_2NHAc$	16	G	67.4	187−189	$C_{20}H_{19}BrCl_2N_4O_3$
45c	$NMeCO(CH_2)_2NHAc$	810	G	80.5	amorphous	$C_{21}H_{21}BrCl_2N_4O_3$
45d	$NMeCOCH_2NMeAc$	1600	M	93.5	amorphous	$C_{21}H_{21}BrCl_2N_4O_3$
45b	NMeCOCH(Me)NHAc	770	G	98.0	amorphous	$C_{21}H_{21}BrCl_2N_4O_3$

[a] See Table 1. [b] Analyses for C, H, and N are within ±0.4% of the expected value for the formula. [c] Ex = experimental procedure described.

Table 7. Discovery of Orally Active B_2 Antagonists



compd	R	*n*	in vitro IC_{50},[a] nM	in vivo inhibn %[b] 1 mg/kg, po	method	yield, %	mp, °C	formula[c]
46	Ac	1	16	62.3**	Q	66.8	179−180	$C_{20}H_{19}BrCl_2N_4O_3$·HCl
48b	COEt	1	19	48.4**[d]	Q	86.6	174−176	$C_{21}H_{21}BrCl_2N_4O_3$·HCl
47c	CO-*n*-Pr	0	8.9	52.7	R	82.9	158−159	$C_{22}H_{23}BrCl_2N_4O_3$
48d	CO-*n*-Bu	1	7.8	29.7	Q	86.6	amorphous	$C_{23}H_{25}BrCl_2N_4O_3$·HCl
48a	SO_2Me	1	580	48.4**[d]	Q	94.6	174−176	$C_{19}H_{19}BrCl_2N_4O_4S$·HCl
49	$COCH_2NMe_2$	0	2.4	72.4	Ex[e]	80.0	175−177	$C_{22}H_{24}BrCl_2N_5O_3$
51a	CONHMe	1	46	41.5	Q	94.6	153−155	$C_{20}H_{20}BrCl_2N_5O_3$·HCl
50b	CONHEt	0	9.0	57.2***	S	83.5	171−173	$C_{21}H_{22}BrCl_2N_5O_3$
51c	CONH-*n*-Pr	1	26	62.4**[d]	Q	94.5	168−171	$C_{22}H_{24}BrCl_2N_5O_3$·HCl

[a] See Table 1. [b] BK (5 μg/kg) was administered intravenously to anesthetized guinea pigs, and bronchoconstriction induced by the BK administration was measured by the modified Konzett and Rösseler method as previously reported. After 5 min, compounds were orally administered. After 30 min, BK was administered again and bronchoconstriction was measured. Inhibition % was calculated from the bronchoconstrictions measured before and after the drug administrations. $^{**}P < 0.01$, $^{***}P < 0.001$ vs control (Student's *t*-test). For details, see the Experimental Section. [c] Analyses for C, H, and N are within ±0.4% of the expected value for the formula. [d] Inhibition % at doses of 3.2 mg/kg. [e] Ex = experimental procedure described.

mixture was extracted with $CHCl_3$−MeOH (5:1) three times, and the organic layer was dried and evaporated in vacuo. The residue was crystallized from EtOH to give **14** (800 mg, 85.0%) as colorless crystals: mp 191−195 °C; ^{1}H NMR (DMSO-d_6) δ 2.41 (3H, s), 7.20 (1H, t, J = 8 Hz), 7.98 (1H, d, J = 8 Hz), 8.52 (1H, d, J = 8 Hz). Anal. ($C_9H_7BrN_2O_2$) C, H, N.

Method H. 2,6-Dichlorophenyl 3-Bromo-2-methylimidazo[1,2-*a*]pyridine-8-carboxylate (15a). To a suspension of **14** (100 mg, 0.392 mmol) in dry CH_2Cl_2 (2 mL) were added oxalyl chloride (100 mg, 0.784 mmol) and DMF (1 drop) at ambient temperature under nitrogen. After 1 h of stirring, the reaction mixture was concentrated in vacuo, and the residue was redissolved in CH_2Cl_2 (2 mL) and triethylamine (79 mg, 0.784 mL). To the mixture was added 2,6-dichlorophenol (70 mg, 0.431 mmol) with cooling in an ice water bath. After 30 min, the reaction mixture was washed with saturated aqueous sodium bicarbonate, water, and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting with $CHCl_3$−MeOH (30:1) followed by crystallization from isopropyl ether to give **15a** (57 mg, 30.4%) as colorless crystals: mp 165−166 °C; ^{1}H NMR ($CDCl_3$) δ 2.56 (3H, s), 7.08 (1H, t, J = 8 Hz), 7.21 (1H, m), 7.41 (2H, d, J = 9 Hz), 8.35 (2H, d, J = 8 Hz). Anal. ($C_{15}H_9BrCl_2N_2O_2$) C, H, N.

Table 8. Oral Bioavailabilities of Representative B_2 Antagonists[a]

compd	AUC, μg·h/mL	C_{max}, μg/mL	$T_{1/2}$, h	BA, %
46	3.15	3.64	0.42	NT[b]
47c	11.71	9.97	0.3	90.0
49	0.94	0.29	0.3	32.8
50b	58.9	52.6	0.5	75.0

[a] Drug suspended in 0.5% methyl cellulose at a dose of 10 mg/kg was orally administrered in rats. [b] NT = not tested.

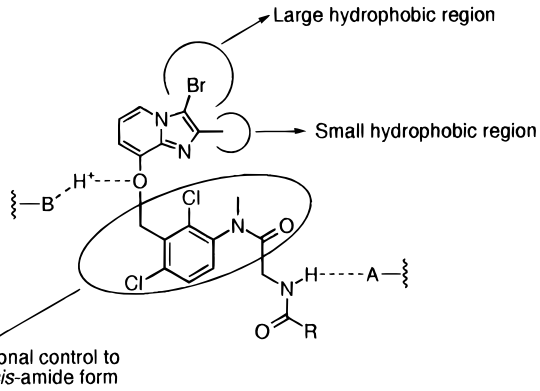


Figure 2. Suggested pharmacophore model for the interactions between the antagonists and B_2 receptors.

Compound **15b** was prepared following a procedure similar to method H.

Method I. 3-Bromo-8-[[(2,6-dichlorophenyl)oxy]methyl]-2-methylimidazo[1,2-*a*]pyridine (17). To a solution of **16** (200 mg, 0.837 mmol) and triethylamine (118 mg, 1.17 mmol) in dry CH_2Cl_2 (4 mL) was added methanesulfonyl chloride (105 mg, 0.921 mmol) cooled in an ice−water bath under nitrogen. After 30 min of stirring, the reaction mixture was washed with water, saturated aqueous sodium bicarbonate, and brine, dried, and evaporated in vacuo. The residue was crystallized from ether to give 3-bromo-8-[(methanesulfonyloxy)methyl]-2-methylimidazo[1,2-*a*]pyridine (172 mg, 64.8%) as colorless crystals: mp 104−106 °C; ^{1}H NMR ($CDCl_3$) δ 2.49 (3H, s), 3.16 (3H, s), 5.15 (2H, s), 6.98 (1H, t, J = 8 Hz), 7.39 (1H, d, J = 8 Hz), 8.09 (1H, d, J = 8 Hz).

To a solution of the above methanesulfonate (100 mg, 0.313 mmol) and 2,6-dichlorophenol (57 mg, 0.347 mmol) in DMF (1 mL) was added potassium carbonate (130 mg, 0.942 mmol) at ambient temperature. After 2 h of stirring, to the mixture was added water and this mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated in vacuo. The residue was crystallized from EtOH to give **17** (82 mg, 82.0%) as colorless crystals: mp 158−159 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (3H, s), 5.51 (2H, s), 6.91−7.10 (2H, m), 7.32 (2H, d, J = 9 Hz), 7.67 (1H, d, J = 8 Hz), 8.03 (1H, d, J = 8 Hz). Anal. ($C_{15}H_{11}BrCl_2N_2O$) C, H, N.

Compounds **22b** and **28a** were prepared following a procedure similar to method I.

***(E)*-8-[2-(2,6-Dichlorophenyl)ethenyl]-2-methylimidazo-[1,2-*a*]pyridine (19).** A suspension of 60% sodium hydride in oil (15 mg, 0.374 mmol) in dry DMSO (1 mL) was stirred at 60 °C for 1 h and cooled to ambient temperature under nitrogen. To this mixture was added (2,6-dichlorobenzyl)-triphenylphosphonium bromide (188 mg, 0.374 mmol), and the mixture was stirred at ambient temperature for 30 min. 2-Methylimidazo[1,2-*a*]pyridine-8-carboxaldehyde (**18**)[19a] (50 mg, 0.310 mmol) was added therein, and the mixture was stirred for 3 h. The mixture was poured into water and extracted three times with AcOEt. The combined organic layers were washed with water and brine, dried, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography to give **19** (64 mg, 65.7%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.50 (3H, s), 6.78 (1H, t, J = 8 Hz), 7.06−7.41 (4H, m), 7.55 (1H, d, J = 16 Hz), 8.00 (1H, d, J = 8 Hz), 8.05 (1H, d, J = 16 Hz); MS (FAB) m/z 303 (M + 1). Anal. ($C_{16}H_{12}Cl_2N_2$) C, H, N.

Method J. 8-[(2,6-Dibromobenzyl)oxy]-2-methylimidazo[1,2-*a*]pyridine (22a). To a solution of 2,6-dibromotoluene (2.5 g, 10 mmol) in dry CH_2Cl_2 (25 mL) was added *N*-bromosuccinimide (1.89 g, 10.5 mmol) and 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (Wako, V-70) (189 mg, 0.61 mmol) at ambient temperature. The reaction mixture was refluxed for 2 h, cooled, and washed twice with water. The organic layer was dried and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting with hexane followed by crystallization from isopropyl ether to give 2,6-dibromobenzyl bromide (2.9 g, 88.4%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.82 (2H, s), 7.01 (1H, t, J =8 Hz), 7.55 (2H, d, J =8 Hz).

To a solution of 8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (**21**)[19a] (100 mg, 0.676 mmol) and 2,6-dibromobenzyl bromide (244 mg, 0.743 mmol) in dry DMF (1 mL) was added potassium carbonate (130 mg, 2.03 mmol) at ambient temperature under nitrogen. The mixture was stirred for 2 h. To the mixture was added water, and the precipitate was collected by vacuum filtration, washed with water, and dried. The solid was crystallized from isopropyl ether to give **22a** (227 mg, 84.8%) as colorless crystals: mp 159−162 °C; ^{1}H NMR ($CDCl_3$) δ 2.43 (3H, s), 5.49 (2H, s), 6.59 (1H, d, J = 8 Hz), 6.67 (1H, t, J = 8 Hz), 7.08 (1H, t, J = 8 Hz), 7.30 (1H, s), 7.58 (2H, d, J = 8 Hz), 7.71 (1H, d, J = 8 Hz). Anal. ($C_{15}H_{12}Br_2N_2O$) C, H, N.

Method K. 8-[(2,6-Dichloro-3-methoxybenzyl)oxy]-2-methylimidazo[1,2-*a*]pyridine (22e). To a solution of 2,6-dichloro-3-methoxybenzoic acid (1.3 g, 5.88 mmol) in dry THF (26 mL) was added 10 M borane−methyl sulfide complex (1.18 mL, 11.76 mmol) under nitrogen at ambient temperature. The reaction mixture was refluxed for 10 h and cooled. The mixture was acidified with 1 N HCl and extracted three times with AcOEt. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting with hexane−AcOEt (3:1) followed by crystallization from hexane to give 2,6-dichloro-3-methoxybenzyl alcohol (973 mg, 79.6%) as colorless crystals: mp 99−101 °C; ^{1}H NMR ($CDCl_3$) δ 2.12 (1H, br s), 3.90 (3H, s), 4.98 (2H, s), 6.86 (1H, d, J = 9 Hz), 7.30 (1H, d, J = 9 Hz). Following a procedure similar to method I, the title compound was obtained in 66.3% yield from **21** and the above alcohol as colorless crystals after crystallization from ether: mp 179−180 °C; ^{1}H NMR ($CDCl_3$) δ 2.43 (3H, s), 3.91 (3H, s), 5.48 (2H, s), 6.70 (1H, d, J = 8 Hz), 6.82 (1H, t, J = 8 Hz), 6.92 (1H, d, J = 9 Hz), 7.31 (1H, d, J = 9 Hz), 7.72 (1H, d, J = 8 Hz). Anal. ($C_{16}H_{17}Cl_2N_2O_2$) C, H, N.

Compounds **22d** and **28b** were prepared following a procedure similar to method K.

Method L. 2,6-Dichloro-3-nitrobenzaldehyde (25). Concentrated sulfuric acid (17.1 mL, 0.321 mol) was added dropwise to 70% nitric acid (24.3 mL, 0.383 mol) for 40 min in an ice−water bath kept below 10 °C. This mixture was added to a solution of 2,6-dichlorobenzaldehyde (**24**) (50.4 g, 0.288 mol) in concentrated sulfuric acid (250 mL) dropwise for 1 h and cooled in an ice−water bath. The mixture was stirred at same temperature for 1.5 h and poured into ice−water (1.5 L) slowly. This mixture was stirred at ambient temperature for 30 min. The precipitate was collected by vacuum filtration and washed with water to give **25** (61.0 g, 96.2%) as yellow crystals: mp 73−74 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (1H, d, J = 9 Hz), 7.90 (1H, d, J = 9 Hz), 10.44 (1H, s). Anal. ($C_7H_3Cl_2NO_3$) C, H, N.

Compound **35** was prepared following a procedure similar to method L.

2,6-Dichloro-3-nitrobenzyl Alcohol (26a). To a solution of **25** (50 g, 0.227 mol) in MeOH (250 mL) was added sodium borohydride (3.43 g, 0.091 mol) portionwise below 10 °C in an ice−water bath under nitrogen. The reaction mixture was stirred at the temperature for 1 h. To the ice-cooled mixture were added dropwise saturated aqueous solution ammonium chloride (125 mL) and water (125 mL). After 30 min the

precipitate was collected by vacuum filtration and washed with water to give **26a** (46.8 g, 92.9%) as yellow crystals: mp 107−108 °C; ^{1}H NMR ($CDCl_3$) δ 2.18 (1H, t, J = 8 Hz), 5.07 (2H, d, J = 8 Hz), 7.50 (1H, d, J = 9 Hz), 7.73 (1H, d, J = 9 Hz). Anal. ($C_7H_5Cl_2NO_3$) C, H, N.

8-[(3-Amino-2,6-dichlorobenzyl)oxy]-3-bromo-2-methylimidazo[1,2-*a*]pyridine Hydrochloride (30a). A suspension of **29a** (2.22 g, 5.15 mmol) and iron (powder, 1.15 g, 20.6 mmol) in a mixture of concentrated HCl (9 mL) and MeOH (9 mL) was refluxed for 30 min. After cooling, the mixture was poured into cooled 1 N HCl (9 mL). The precipitates were collected and washed with water. The crystals were triturated with MeCN to give **30a** (1.74 g, 77.2%) as an off-white solid: mp 186−187 °C; ^{1}H NMR (DMSO-d_6) δ 2.42 (3H, s), 5.48 (2H, s), 6.95 (1H, d, J =8 Hz), 7.24 (1H, d, J = 8 Hz), 7.42 (1H, t, J = 8 Hz), 7.62 (1H, d, J = 8 Hz), 8.25 (1H, d, J = 8 Hz). Anal. ($C_{15}H_{12}BrCl_2N_3O$·HCl) C, H, N.

Method M. 3-Bromo-8-[[2,6-dichloro-3-(*N*-methylacetamido)benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (32a). To a solution of **31a** (222 mg, 0.5 mmol) in dry DMF (2 mL) was added 60% sodium hydride in oil (24 mg, 0.6 mmol) in one portion at ambient temperature. The mixture was stirred at the same temperature for 30 min, and iodomethane (142 mg, 1.0 mmol) was added therein. After 30 min of stirring, the mixture was poured into water and extracted with AcOEt. The extracts were washed with water and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting with hexane−AcOEt (3:1) followed by crystallization from isopropyl ether to give **32a** (135 mg, 58.9%) as colorless crystals: mp 201−204 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (3H, s), 2.46 (3H, s), 3.19 (3H, s), 5.52 (2H, s), 6.72 (1H, d, J = 8 Hz), 6.87 (1H, t, J = 8 Hz), 7.31 (1H, d, J = 8 Hz), 7.48 (1H, d, J = 8 Hz), 7.80 (1H, d, J = 8 Hz). Anal. ($C_{18}H_{16}BrCl_2N_3O_2$) C, H, N.

Compounds **32b,c**, **40**, **43a**−**c**, and **45d** were prepared following a procedure similar to method M.

3-Bromo-8-[[2,6-dichloro-3-(*N*-ethyl-*N*-methylamino)benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (33). To a solution of **32a** (100 mg, 0.242 mmol) in dry THF (2 mL) was added 10 M borane−methyl sulfide complex (0.07 mL, 0.726 mmol) under nitrogen at ambient temperature. The reaction mixture was refluxed for 1 h and cooled. The mixture was acidified with 1 N HCl and refluxed for 15 min. The cooled reaction mixture was neutralized with saturated aqueous solution of sodium bicarbonate and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting with hexane−AcOEt (5:1) to give **33** (67 mg, 62.7%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, t, J = 8 Hz), 2.43 (3H, s), 2.75 (3H, s), 3.00−3.11 (2H, m), 5.50 (2H, s), 6.71 (1H, br d, J = 8 Hz), 6.86 (1H, br t, J = 8 Hz), 7.09 (1H, br d, J = 8 Hz), 7.23−7.31 (1H, m), 7.70 (1H, d, J = 8 Hz). Anal. ($C_{18}H_{18}BrCl_2N_3O$) C, H, N.

8-[(3-Amino-2,4,6-trichlorobenzyl)oxy]-3-bromo-2-methylimidazo[1,2-*a*]pyridine (30b). A suspension of **29b** (1.50 g, 3.22 mmol) and iron (powder, 899 mg, 16.1 mmol) in a mixture of acetic acid (12 mL) and EtOH (6 mL) was refluxed for 40 min. After cooling, the mixture was filtered and washed with CH_2Cl_2−MeOH (4:1). The filtrate was evaporated in vacuo. The residue was partitioned between CH_2Cl_2−MeOH (10:1) and saturated aqueous sodium bicarbonate. The organic layer was dried and evaporated in vacuo. The residue was crystallized from EtOH to give **30b** (1.33 g, 94.8%) as an off-white powder: mp 217−219 °C; ^{1}H NMR (DMSO-d_6) δ 2.30 (3H, s), 5.35 (2H, s), 6.99 (1H, d, J = 8 Hz), 7.58 (1H, s), 7.92 (1H, t, J = 8 Hz). Anal. ($C_{15}H_{11}BrCl_3N_3O$) C, H, N.

3-Bromo-8-[[2,6-dichloro-3-(methylamino)benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (36). To a suspension of **32a** (560 mg, 1.23 mmol) in dry MeOH (2 mL) was added 28% sodium methoxide in MeOH (1.93 g, 10 mmol) at ambient temperature under nitrogen. The mixture was refluxed for 3 days and cooled. The precipitated solid was filtered, washed with MeOH, and dried to give **36** (350 mg, 77.0%) as colorless crystals: mp 184−187 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (3H, s), 2.91 (3H, d, J = 6 Hz), 4.46 (1H, m), 5.46 (2H, s), 6.63 (1H, d, J = 9 Hz), 6.71 (1H, d, J = 7.5 Hz), 6.83 (1H, t, J = 7.5 Hz), 7.24 (1H, d, J = 9 Hz), 7.73 (1H, d, J = 7.5 Hz). Anal. ($C_{16}H_{14}BrCl_2N_3O$) C, H, N.

3-Bromo-8-[[2,6-dichloro-3-[*N*-(methoxylcarbonyl)-*N*-methylamino]benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (37a). To a solution of **36** (100 mg, 0.24 mmol) and 4-(dimethylamino)pyridine (44 mg, 0.36 mmol) in dry CH_2Cl_2 (2 mL) was added methyl chlorocarbonate (45 mg, 0.48 mmol) in portions at ambient temperature under nitrogen. The mixture was stirred for 1 day, and the reaction mixture was washed with water, saturated aqueous sodium bicarbonate, and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (CH_2Cl_2−AcOEt, 10:1) followed by crystallization from ether to give **37a** (107 mg, 94.0%) as colorless crystals: mp 178−179 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (3H, s), 3.22 (3H, s), 3.65 (3H, s), 5.49 (2H, s), 6.78 (1H, br d, J = 7.5 Hz), 6.90 (1H, t, J = 7.5 Hz), 7.25 (1H, d, J = 9 Hz), 7.39 (1H, d, J = 9 Hz), 7.79 (1H, d, J = 7.5 Hz). Anal. ($C_{18}H_{16}BrCl_2N_3O_3$) C, H, N.

Method N. 3-Bromo 8-[[2,6-dichloro-3-(*N*-methyl-*N*-[[(4-nitrophenyl)oxy]carbonyl]benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (37c). To a solution of **36** (100 mg, 0.16 mmol) in dry pyridine (0.5 mL) and dry CH_2Cl_2 (2 mL) was added *p*-nitrophenyl chlorocarbonate (40 mg, 0.20 mmol) in portions at ambient temperature under nitrogen. The mixture was stirred for 1 h, washed with water, saturated aqueous sodium bicarbonate, and brine, dried, and evaporated in vacuo. The residue was crystallized from ether to give **37c** (84 mg, 88.3%) as pale yellow crystals: mp 229−230 °C; ^{1}H NMR ($CDCl_3$−CD_3OD) δ 2.41 (3H, s), 3.32 (3H, s), 5.49 (1H, d, J = 10 Hz), 5.57 (1H, d, J = 10 Hz), 6.73 (1H, d, J = 7.5 Hz), 6.88 (1H, t, J = 7.5 Hz), 7.19−7.57 (4H, m), 7.78 (1H, d, J = 7.5 Hz), 8.20 (2H, d, J = 10 Hz), 7.79 (1H, d, J = 7.5 Hz). Anal. ($C_{23}H_{17}BrCl_2N_4O_5$) C, H, N.

Compounds **37b** and **37d,e** were prepared following a procedure similar to method N.

3-Bromo-8-[[2,6-dichloro-3-(*N*-methyl-*N*′-methylureido)benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (38). A mixture of **37c** (63 mg, 0.109 mmol) and 30% solution of methylamine in MeOH (2 mL) was heated under reflux for 3 h. After addition of another 30% solution of methylamine in MeOH (1 mL), the mixture was heated under reflux for additional 1 h. The reaction mixture was evaporated in vacuo, and the residue was extracted with AcOEt. The extract was evaporated in vacuo, and the residue was purified by preparative thin-layer chromatography (CH_2Cl_2−MeOH, 20:l) followed by crystallization from ether to give **38** (28 mg, 56.0%) as colorless crystals: mp 192−193 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (3H, s), 2.79 (3H, d, J = 5 Hz), 3.20 (3H, s), 4.20 (1H, br d, J = 5 Hz), 5.49 (2H, s), 6.71 (1H, d, J = 7.5 Hz), 6.85 (1H, t, J = 7.5 Hz), 7.32 (1H, d, J = 9 Hz), 7.42 (1H, d, J = 9 Hz), 7.78 (1H, d, J = 7.5 Hz). Anal. ($C_{18}H_{17}BrCl_2N_4O_2$) C, H, N.

3-Bromo-8-[[3-[*N*-(hydroxyacetyl)-*N*-methylamino]-2,6-dichlorobenzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (39). A mixture of **37e** (1.42 g, 2.76 mmol), potassium carbonate (761 mg, 5.51 mmol) in MeOH (7 mL), and THF (7 mL) was stirred at ambient temperature for 1 h. The mixture was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with twice CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated in vacuo. The residue was crystallized from EtOH to give **39** (1.16 g, 89.2%) as colorless crystals: mp 217−218 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (3H, s), 3.19−3.32 (4H, m), 3.69 (1H, d, J = 15 Hz), 3.82 (1H, d, J = 15 Hz), 5.50 (2H, s), 6.70 (1H, d, J = 8 Hz), 6.83 (1H, t, J = 8 Hz), 7.29 (1H, d, J = 9 Hz), 7.49 (1H, d, J = 9 Hz), 7.78 (1H, d, J = 8 Hz). Anal. ($C_{18}H_{16}BrCl_2N_3O_3$) C, H, N.

Method O. 3-Bromo-8-[[2,6-dichloro-3-[*N*-(phthalimidoacetyl)amino]benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (42a). To a mixture of **30a** (15.0 g, 34.2 mmol), 4-(dimethylamino)pyridine (418 mg, 3.42 mmol), dry pyridine (40 mL), and *N*-methylpyrrolidone (120 mL) was added *N*-phthaloylglycyl chloride (**41a**) (11.5 g, 51.3 mmol) at ambient

temperature under nitrogen. The reaction mixture was stirred at 50 °C for 2 h. To the mixture was added water (160 mL) dropwise in an ice−water bath. The precipitated solid was collected by vacuum filtration, washed with water, and dried in vacuo. To the solid was added MeOH (160 mL), and the mixture was stirred for 2 h. The solid was collected by vacuum filtration and washed with MeOH to give **42a** (19.1 g, 95.0%) as pale brown crystals: mp 245−246 °C; ^{1}H NMR ($CDCl_3$−CD_3OD) δ 2.41 (3H, s), 4.71 (2H, s), 5.39 (2H, s), 7.10−7.31 (3H, m), 7.77−7.88 (3H, m), 7.90−8.01 (2H, m), 8.10 (1H, d, J = 9 Hz). Anal. ($C_{25}H_{17}BrCl_2N_4O_4$) C, H, N.

Compounds **42b,c** were prepared following a procedure similar to method O.

Method P. 8-[[3-(*N*-Aminoacetyl-*N*-methylamino)-2,6-dichlorobenzyl]oxy]-3-bromo-2-methylimidazo[1,2-*a*]pyridine (44a). To a suspension of **43a** (450 mg, 0.748 mmol) in EtOH (4.5 mL) was added hydrazine monohydrate (56 mg, 1.12 mmol) at ambient temperature, and the mixture was refluxed for 1 h. After the reaction mixture was cooled, the precipitates formed were filtered off. The filtrate was evaporated in vacuo, CH_2Cl_2 was added to the residue, and precipitates were filtered off. The filtrate was evaporated in vacuo, and the residue was crystallized from ether to give **44a** (338 mg, 95.8%) as colorless crystals: mp 175−178 °C; ^{1}H NMR ($CDCl_3$) δ 2.43 (3H, s), 2.92−3.20 (2H, m), 3.23 (3H, s), 5.49 (2H, s), 6.70 (1H, d, J = 8 Hz), 6.83 (1H, t, J = 8 Hz), 7.29 (1H, d, J = 9 Hz), 7.47 (1H, d, J = 9 Hz), 7.79 (1H, d, J = 8 Hz); MS (FAB) m/z 471, 473 (M + 1). Anal. ($C_{18}H_{17}BrCl_2N_4O_2$) C, H, N.

Compounds **44b,c** were prepared following a procedure similar to method P.

Method Q. 8-[[3-[*N*-(Acetamidoacetyl)-*N*-methylamino]-2,6-dichlorobenzyl]oxy]-3-bromo-2-methylimidazo[1,2-*a*]-pyridine Hydrochloride (46). To a suspension of **45a** (190 mg, 0.37 mmol) in MeOH (1.9 mL) was added 10% hydrogen chloride in MeOH (0.5 mL) at ambient temperature. After 5 min of stirring, the solution was evaporated in vacuo. The residue was crystallized from MeCN−AcOEt, and the product was recrystallized from acetone−water to give **46** (136 mg, 66.8%) as colorless crystals: mp 179−180 °C; ^{1}H NMR (DMSO-d_6) δ 1.83 (3H, s), 2.40 (3H, s), 3.12 (3H, s), 3.37 (1H, dd, J = 16, 5 Hz), 3.67 (1H, dd, J = 16, 5 Hz), 5.59 (2H, s), 7.31−7.78 (4H, m), 8.10 (1H, t, J = 5 Hz), 8.25 (1H, d, J = 8 Hz). Anal. ($C_{20}H_{19}BrCl_2N_4O_3$·HCl) C, H, N.

Compounds **48a,b**, **48d**, **51a**, and **5lc** were prepared following a procedure similar to method Q.

Method R. 3-Bromo-8-[[2,6-dichloro-3-[*N*-(methanesulfonamidoacetyl)-*N*-methylamino]benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (47a). To a solution of **44a** (100 mg, 0.212 mmol) and triethylamine (32 mg, 0.316 mmol) in dry CH_2Cl_2 (2 mL) was added methanesulfonyl chloride (27 mg, 0.236 mmol) cooled in an ice−water bath under nitrogen. The reaction mixture was stirred at the same temperature for 30 min and stirred at ambient temperature for 1 h. The reaction mixture was washed with water, saturated aqueous sodium bicarbonate, and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (CH_2Cl_2−MeOH, 30:1) to give **47a** (103 mg, 88.3%) as a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) δ 2.45 (3H, s), 2.97 (2.7H, s), 3.02 (0.3H, s), 3.27 (2.7H, s), 3.30 (0.3H, s), 3.50 (1H, dd, J = 16, 5 Hz), 3.67 (1H, dd, J = 16, 5 Hz), 5.18 (1H, m), 5.51 (2H, s), 6.71 (1H, d, J = 8 Hz), 6.87 (1H, t, J = 8 Hz), 7.32 (1H, d, J = 9 Hz), 7.51 (1H, d, J = 9 Hz), 7.78 (1H, d, J = 8 Hz). Anal. ($C_{19}H_{19}BrCl_2N_4O_4S$) C, H, N.

Compounds **47b**−**d** were prepared following a procedure similar to method R.

3-Bromo-8-[[2,6-dichloro-3-[*N*-(*N*,*N*-dimethylglycyl)glycyl-*N*-methylamino]benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (49). To a solution of **44a** (500 mg, 1.06 mmol) and triethylamine (160 mg, 1.59 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise bromoacetyl chloride (183 mg, 1.16 mmol) at −60 °C in a dry ice−acetone bath under nitrogen. After 20 min, to the mixture was added 50% dimethylamine−H_2O solution (0.96 mL, 10.6 mmol), and this mixture was stirred at ambient temperature for 1 h. The reaction mixture was washed with aqueous sodium bicarbonate solution, water, and brine. The organic layer was dried and evaporated in vacuo. The residue was purified by flash silica gel column chromatography, eluting CH_2Cl_2−MeOH (50:l) and crystallized from AcOEt. The crystals were recrystallized from MeCN to give **49** (472 mg, 80.0%) as colorless crystals: mp 175−177 °C; ^{1}H NMR ($CDCl_3$) δ 2.32 (6H, s), 2.43 (3H, s), 2.96 (2H, s), 3.25 (3H, s), 3.55 (1H, dd, J = 18, 4 Hz), 3.85 (1H, dd, J = 18, 4 Hz), 5.50 (2H, s), 6.71 (1H, d, J = 8 Hz), 6.86 (1H, t, J = 8 Hz), 7.32 (1H, d, J = 9 Hz),7.49 (1H, d, J = 9 Hz), 7.78 (1H, d, J = 8 Hz), 7.89 (1H, br t, J = 4 Hz); IR (KBr) 3356, 2944, 2856, 2828, 2774, 1684, 1666, 1546, 1512. Anal. ($C_{22}H_{24}BrCl_2N_5O_3$) C, H, N.

Method S. 3-Bromo-8-[[2,6-dichloro-3-[*N*-[(*N*′-ethylureido)acetyl]-*N*-methylamino]benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridine (50b). To a solution of **44a** (100 mg, 0.212 mmol) in dry CH_2Cl_2 (2 mL) was added ethyl isocyanate (45 mg, 0.636 mmol) at ambient temperature under nitrogen. The reaction mixture was stirred for 1 h and evaporated in vacuo. The residue was crystallized from AcOEt and recrystallized from MeCN to give **50b** (94 mg, 83.5%) as colorless crystals: mp 171−173 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 8 Hz), 2.42 (3H, s), 3.09−3.33 (5H, m), 3.56 (1H, dd, J = 17, 5 Hz), 3.80 (1H, dd, J = 17, 5 Hz), 4.71 (1H, br t, J = 5 Hz), 5.49 (2H, s), 6.71 (1H, d, J = 8 Hz), 6.88 (1H, t, J = 8 Hz), 7.31 (1H, d, J = 9 Hz), 7.46 (1H, d, J = 9 Hz), 7.78 (1H, d, J = 8 Hz); IR (KBr) 3328, 3043, 3003, 2970, 2930, 2872, 1667, 1642, 1566, 1547. Anal. ($C_{21}H_{22}BrCl_2N_5O_3$) C, H, N.

Compounds **50a** and **50c** were prepared following a procedure similar to method S.

Biological Methods. Receptor binding: Guinea Pig Ileum. The specific binding of [^{3}H]BK (a high affinity B_2 ligand) was assayed according to the method previously described[26] with minor modifications. Male Hartley guinea pigs (from Charles River Japan, Inc.) were killed by exsanguination under anesthesia. The ilea were removed and homogenized in ice-cold buffer (50 mM sodium (trimethylamino)ethanesulfonate (TES) and 1 mM 1,10-phenanthroline, pH 6.8) with a Polytron. The homogenate was centrifuged to remove cellular debris (1000g, 20 min, 4 °C), and the supernatant was centrifuged (100000g, 60 min, 4 °C). Then, the pellet was resuspended in ice-cold assay buffer (50 mM TES, 1 mM 1,10-phenanthroline, 140, μg mL^{-1} bacitracin, 1 mM dithiothreiol, 1 μM captopril, and 0.1% bovine serum albumin (BSA), pH 6.8) and was stored at −80 °C until use.

In the binding assay, membranes (0.2 mg of protein mL^{-1}) were incubated with [^{3}H]BK (final concentration 0.06 nM) and varying concentrations of test compounds or unlabeled BK at room temperature for 60 min. Receptor-bound [^{3}H]BK was harvested by filtration through Whatman GF/B glass fiber filters under reduced pressure, and the filter was washed five times with 300 μL of ice-cold buffer (50 mM Tris-HCl). The radioactivity retained on the washed filter was measured with a liquid scintillation counter. Specific binding was calculated by subtracting the nonspecific binding (determined in the presence of 1 μM unlabeled BK) from total binding.

BK-Induced Bronchoconstriction in Guinea Pigs. Male Hartley guinea pigs weighing 470−750 g (from Charles River Japan, Inc.) were fasted overnight and anesthetized by intraperitoneal injection of sodium pentobarbital (30 mg kg^{-1}), and the trachea, jugular vein, and esophagus were cannulated. The animals were ventilated at a tidal volume of 10 mL kg^{-1} with a frequency of 60 breaths min^{-1} through the tracheal cannula. To suppress spontaneous respiration, alcuronium chloride (0.5 mg kg^{-1}) was administered intravenously through the jugular vein cannula. Then, propranolol (10 mg kg^{-1}) was also administered subcutaneously. After 10 min, BK (5 μg kg^{-1}, dissolved in saline with 0.1% BSA) was administered intravenously through the jugular vein cannula. Bronchoconstriction was measured by the modified Konzett and Rossler method as the peak increase of pulmonary insufflation pressure (PIP).[27] Each dose of the compound suspended in 0.5% methylcellulose solution or vehicle was administered through

the oesophageal cannula after the first BK-induced bronchoconstriction. After 30 min, BK was administered again and the bronchoconstriction was measured in the same manner. A 0% response was determined as PIP before the administration of BK and the 100% response was determined as the first BK-induced bronchoconstriction before drug administration. The percent response was calculated from the following formula: % response = $(\Delta PIP_{after\ drug}/\Delta PIP_{before\ drug}) \times 100$.

Statistical Analysis. The results are expressed as the mean ± SEM, and statistical significance of between groups was analyzed by Student's *t* test. IC_{50} or ED_{50} value was obtained by using the nonlinear curve-fitting methods with a specific computer program made by our company's engineer.

Measurement of Plasma Level and Bioavailability. Male Sprague−Dawley rats (3) were starved overnight and dosed orally with the compound as a solution in 0.5% methocel (0.5 mL/100 g). Blood was taken from the femoral artery at 0, 0.5, 1, 2, 4, and 6 h after dosing. In the intravenous studies, compounds were dissolved in DMSO and injected intravenously in the femoral vein (dose volume = 0.05 mL). Blood was taken from the femoral artery at 0, 5, 15, and 30 min and 1, 2, 4, and 6 h after dosing. Blood was centrifuged and plasma collected. A 100 μL plasma sample was extracted by 4 mL of $CHCl_3$ for 5 min followed by centrifugation at 700*g* for 5 min. The organic layer was removed and evaporated to dryness under nitrogen at 30 °C. The residue was reconstituted with 100 μL of MeOH and a 20 μL aliquot injected onto the HPLC system. The parent compound was quantitated from the area of the corresponding peak, relative to the standard (plasma sample at time 0 min, spiked with varying concentrations of the compound).

Acknowledgment. We are grateful to Dr. I. Aramori for his valuable suggestions.

Supporting Information Available: The coordinates of ab initio molecular orbital calculations of *cis*-/*trans*-**31a′**, *cis*-/*trans*-**32a′**, and *cis*-/*trans*-**32b′** and physical data of **5b**−**e**, **8**, **9c**, **10a**−**c**, **13**, **15b**, **16**, **20**, **22b**−**d**, **23a**−**e**, **28a,b**, **29a,b**, **31a,b**, **32b,c**, **35**, **37b,d,e**, **40**, **42b,c**, **43a**−**c**, **44b,c**, **45a**−**d**, **47b,d**, **48a**−**d**, **50a,c**, and **51a,c** (20 pages). Ordering information is given on any current masthead page.

References

(1) Regoli, D.; Barabé, J. Pharmacology of Bradykinin and Related Kinins. *Pharmacol. Rev.* **1980**, *32*, 1−46.
(2) Marceau, F.; Lussier, A.; Regoli, D.; Giroud, J. P. Pharmacology of Kinins: Their Relevance to Tissue Injury and Inflammation. *Gen. Pharmacol.* **1983**, *14*, 209−229.
(3) Proud, D.; Kaplan, A. P. Kinin Formation: Mechanisms and Role in Inflammatory Disorders. *Annu. Rev. Immunol.* **1988**, *6*,49−83.
(4) Dray, A.; Parkins, M. Bradykinin and Inflammatory Pain. *Trends. Neurosci.* **1993**, *16*, 99−104.
(5) Greaves, M. W. Inflammation and Mediators. *Br. J. Dermatol.* **1988**, *119*, 419−426.
(6) Bhoola, K. D.; Figueroa, C. D.; Worthy, K. Bioregulation of Kinins: Kallikreins, Kininogens and Kininases. *Pharmacol. Rev.* **1992**, *44*, 1−80.
(7) Farmer, S. G.; Burch, R. M. The Pharmacology of Bradykinin Receptors. In *Bradykinin Antagonists: Basic and Clinical Research*; Burch, R. M., Ed.; Marcel Dekker, Inc.: New York, 1991; pp 1−31.
(8) McEachern, A. E.; Shelton, E. R.; Bhakta, S.; Obernolte, R.; Bach, C.; Zuppan, P.; Fujisaki, J.; Aldrich, R. W.; Jarnagin, K. Expression Cloning of a Rat B_2 Bradykinin Receptor. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 7724−7728.
(9) Hock, F. J.; Wirth, K.; Albus, U.; Linz, W.; Gerhards, H. J.; Wiemer, G.; Henke, S.; Breipohl, G.; König, W.; Knolle, J.; Schölkens, B. A. Hoe 140 A New Potent and Long Acting Bradykinin-Antagonist: In Vitro Studies. *Br. J. Pharmacol.* **1991**, *102*, 769−773.
(10) Wirth, K.; Hock, F. J.; Albus, U.; Linz, W.; Alpermann, H. G.; Anagnostopoulos, H.; Henke, St.; Breipohl, G.; Konig, W.; Knolle, J.; Schölkens, B. A. Hoe 140 A New Potent and Long Acting Bradykinin-Antagonist: In Vivo Studies. *Br. J. Pharmacol.* **1991**, *102*, 774−777.
(11) Cheronis, J. C.; Whalley, E. T.; Nguyen, K. T.; Eubanks, S. R.; Allen, L. G.; Duggan, M. J.; Loy, S. D.; Bonham, K. A.; Blodgett, J. K. A New Class of Bradykinin Antagonists: Synthesis and In Vitro Activity of Bissuccinimidoalkane Peptide Dimers. *J. Med. Chem.* **1992**, *35*, 1563−1572.
(12) Kyle, D. J.; Martin, J. A.; Burch, R. M.; Carter, J. P.; Lu, S.; Meeker, S.; Prosser, J. C.; Sullivan, J. P.; Togo, J.; Noronha-Blob, L; Sinsko, J. A.; Walters, R. F.; Whaley, L. W.; Hiner, R. N. Proving The Bradykinin Receptor: Mapping The Geometric Topography Using Ethers of Hydroxyproline in Novel Peptides. *J. Med. Chem.* **1991**, *34*, 2649−2653.
(13) Kyle, D. J. Structure-Based Drug Design: Progress Toward The Discovery of The Elusive Bradykinin Receptor Antagonists. *Curr. Pharm. Des.* **1995**, *1*, 233−254.
(14) Burch, R. M.; Farmer, S. G.; Steranka, L. R. Bradykinin Receptor Antagonists. *Med. Res. Rev.* **1990**, *10*, 237−269.
(15) Stewart, J. M. Bradykinin Antagonists: Development and Applications. *Biopolymers* **1995**, *37*, 143−155.
(16) Calixto, J. B.; Yunes, R. A.; Rae, G. A.; Medeiros, Y. S. Nonpeptide Bradykinin Antagonists. In *Bradykinin Antagonists, Basic and Clinical Reset*; Burch, R. M., Ed.; Marcel Dekker, Inc.: New York, 1991; pp 97−129.
(17) (a) Salvino, J. M.; Seoane, P. R.; Douty, B. D.; Awad, M. M. A.; Dolle, R. E.; Houck, W. T.; Faunce, D. M.; Sawurtz, D. G. Design of Potent Non-Peptide Competitive Antagonists of the Human Bradykinin B_2 Receptor. *J. Med. Chem.* **1993**, *36*, 2583−2584. (b) Hoyer, D.; Awad, M. M. A.; Salvino, J. M.; Seoane, P. R.; Dolle, R. E.; Houck, W. T.; Sawurtz, D. G. ACE Inhibitors as a Template for the Design of Bradykinin B_2 Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 367−370.
(18) Hand, E. S.; Paudler, W. W. Teleamination of the Imidazo[1,2-*a*]pyridine System. *J. Org. Chem.* **1978**, *43*, 2900−2906.
(19) (a) Kaminski, J. J.; Bristol, J. A.; Puchalski, C.; Lovey, R. G.; Elliott, A. J.; Guzik, H.; Solomon, D. M.; Conn, D. J.; Domalski, M. S.; Wong, S.-C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; Steinberg, M.; McPhail, A. T. Antiulcer Agents. 1. Gastric Antisecretory and Cytoprotective Properties of Substituted Imidazo[1,2-*a*]pyridines. J. *Med. Chem.* **1985**, *28*, 876−892. (b) Kaminski, J. J.; Hilbert, J. M.; Pramanik, B. N.; Solomon, D. M.; Conn, D. J.; Rizvi, R. K.; Elliott, A. J.; Guzik, H.; Lovey, R. G.; Domalski, M. S.; Wong, S.-C.; Puchalski, C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; McPhail, A. T. Antiulcer Agents. 2. Gastric Antisecretory, Cytoprotective, and Metabolic Properties of Substituted Imidazo[1,2-*a*]pyridines and Analogues. J. *Med. Chem.* **1987**, *30*, 2031−2046.
(20) Virgil, S. C. *N*-Bromosuccinimide. *In Encyclopedia of Reagents for Organic Synthesis*, Vol. 1; Paquette, L. A., Editor-in-Chief; John Wiley & Sons Ltd: Chichester, 1995; pp 768−773.
(21) Kaminski, J. J.; Puchalski, C.; Solomon, D. M.; Rizvi, R. K.; Conn, D. J.; Elliott, A. J.; Lovey, R. G.; Guzik, H.; Chiu, P. J. S.; Long, J. F.; McPhail, A. T. Antiulcer Agents. 4. Conformational Considerations and the Antiulcer Activity of Substituted Imidazo[1,2-*a*]pyridines and Related Analogues. J. *Med. Chem.* **1989**, *32*, 1686−1700.
(22) Asano, M.; Inamura, N.; Hatori, C.; Sawai, H.; Fujiwara, T.; Katayama, A.; Kayakiri, H.; Satoh, S; Abe, Y.; Inoue, T.; Sawada, Y.; Nakahara, K.; Oku, T.; Okuhara, M. The Identification of an Orally Active, Non-peptide Bradykinin B_2 Receptor Antagonist, FR173657. *Br. J. Pharmacol.* **1997**, *120*, 617−624.
(23) Gaussian 94, Revision E.1; Gaussian, Inc.: Carnegie Office Park, Building 6, Pittsburgh, PA 15106.
(24) JP patent 4-18091.
(25) Compound **50b** was advanced for evaluation of binding activity to human B_2 receptors expressed on A-431 cells (human epidermoid carcinoma), and showed an IC_{50} value of 3000 nM. It was revealed that there was estrangement of binding affinity in guinea pig ileum and human A-431 cell. Further optimization to overcome this specific differences between human and guinea-pigs will be reported in due course.
(26) Manning, D. C.; Vavrek, R.; Stewart, J. M.; Synder, S. H. Two Bradykinin Binding Sites with Picomolar Affinities. *J. Pharmacol. Exp. Ther.* **1986**, *237*, 504−512.
(27) Asano, M.; Inamura, N.; Nakahara, K.; Nagayoshi, A.; Isono, T.; Hamada, K.; Oku, T.; Notsu, Y.; Kohsaka, M.; Ono, T. A 5-Lipoxygenase Inhibitor, FR110302, Suppresses Airway Hyperresponsiveness and Lung Eosinophilia Induced by Sephadex Particles in Rats. *Agents Actions* **1992**, *36*, 215−221.

JM970591C