A Novel Class of Orally Active Non-Peptide Bradykinin B_2 Receptor Antagonists. 4. Discovery of Novel Frameworks Mimicking the Active Conformation

Yoshito Abe,[†] Hiroshi Kayakiri,*[,†] Shigeki Satoh,[†] Takayuki Inoue,[†] Yuki Sawada,[†] Noriaki Inamura,[‡] Masayuki Asano,[§] Ichiro Aramori,[||] Chie Hatori,[§] Hiroe Sawai,[§] Teruo Oku,[†] and Hirokazu Tanaka[⊥]

Exploratory Research Laboratories, Fujisawa Pharmaceutical Ltd., 5-2-3, Tokodai, Tsukuba, Ibaraki 300-2698, Japan

Received May 27, 1998

In recent articles we reported the identification of a series of 8-[[2,6-dichloro-3-[*N*-methyl-*N*-[(*E*)-(substituted)acryloylglycyl]amino]benzyl]oxy]-2-methylimidazo[1,2-*a*]pyridines as the first orally active non-peptide bradykinin (BK) B_2 receptor antagonists. Optimization of the terminal glycine part and the imidazo[1,2-*a*]pyridine moiety led to the discovery of a clinical candidate (**5**, FR173657). With the aim of completion of the structure−activity relationship (SAR) study, we next investigated the roles of the substituents on the central phenyl ring. The results suggested that the 2,6-dichloro or 2,6-dimethyl groups may play important roles in regulating the conformations of the 1- and 3-substituents and also may interact with hydrophobic pockets of the B_2 receptors. Furthermore, according to the results of a molecular modeling study reported in part 1 of this series, we designed and synthesized a series of sterically constrained analogues by replacing the *N*-methylamide group with *cis*-amide-like rigid moieties. We discovered several bioisosteres and chemically proved that the *N*-methylamide moiety adopts the *cis*-amide form in the active conformation. Extensive chemical modification led to the identification of a novel class of highly potent and orally active non-peptide B_2 antagonists represented by a pyrrole derivative (**52a**, FR193517). Compound **52a** inhibited the specific binding of [^{3}H]BK to recombinant human B_2 receptors expressed in Chinese hamster ovary (CHO) cells and guinea pig ileum membrane preparations expressing B_2 receptors with IC_{50}s of 0.37 and 0.56 nM, respectively. This compound also displayed excellent in vivo functional antagonistic activity against BK-induced bronchoconstriction in guinea pigs at 1 mg/kg by oral administration.

Introduction

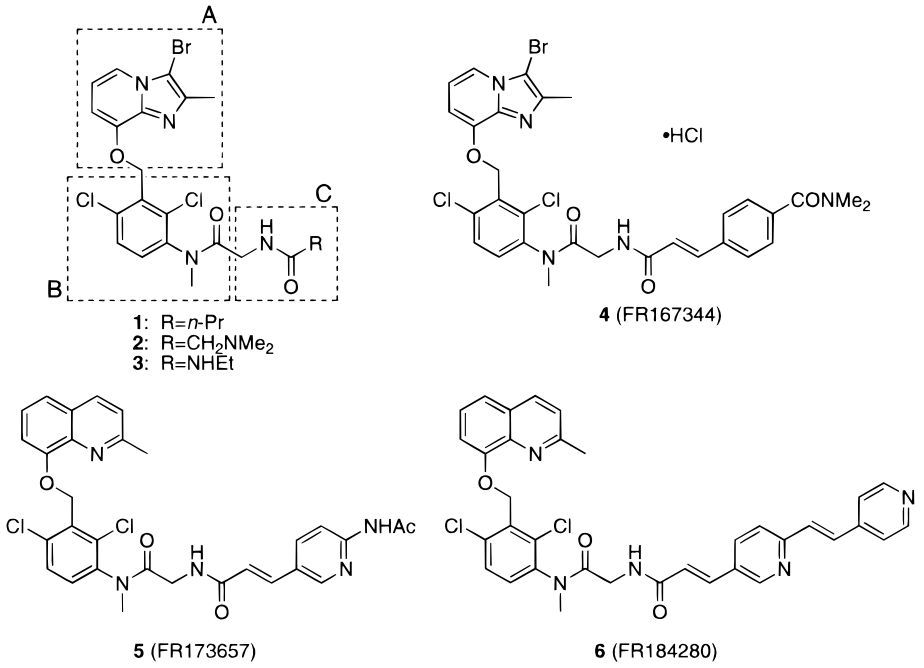
Bradykinin (BK) is an endogenous proinflammatory nonapeptide which is believed to play important roles in pain, inflammation, asthma, rhinitis, and hypotension.[1−8] Two types of kinin receptors, designated as B_1 and B_2, have been identified by molecular cloning and pharmacological methods,[1,4,9−11] and most of the biological actions of BK are mediated by B_2 receptors.[1,9] Since BK B_2 receptor antagonists have therapeutic potential as novel analgesics and antiinflammatory agents, a number of antagonists have been investigated.[12−16] The second-generation peptide B_2 antagonists, including Icatibant (Hoe140),[12,13] have highly potent affinity for B_2 receptors; however, therapeutic use is still limited because of their peptidic nature. On the other hand, few non-peptide antagonists have been disclosed.[17−19] Indeed, until our work[20] there were no reports of orally active non-peptide B_2 antagonists.

Recently, we reported the identification of a series of 8-[[3-(*N*-acylglycyl-*N*-methylamino)-2,6-dichlorobenzyl]-oxy]-3-halo-2-methylimidazo[1,2-*a*]pyridines represented by compounds **1**−**3** as the first orally active non-peptide BK B_2 receptor antagonists (Chart 1).[20] Although their affinities for human B_2 receptors were found to be much lower, discovery of novel key pharmacophores enabled us to overcome the species difference between humans and guinea pigs and to enhance the in vivo activities leading to the identification of **4** (FR167344).[21,22] Furthermore, intensive research seeking bioisosteres of the imidazo[1,2-*a*]pyridine ring afforded the quinoline derivatives **5** (FR173657)[21b,23,24] and **6** (FR184280)[24] with highly potent in vitro and excellent in vivo activities. A molecular modeling study in part 1 of this series had suggested that the *N*-methylamide group at the 3-position of the 2,6-dichlorobenzene ring adopts a *cis*-amide form as the active conformation.[20] To verify this suggested active conformation, we designed and synthesized a series of sterically constrained analogues by replacing the *N*-methylamide group with *cis*-amide-like rigid moieties and discovered several promising bioisosteres. Herein we wish to describe the structure−activity relationship (SAR) revealed on the way to the discovery of a new series of highly potent and orally active non-peptide BK B_2 receptor antagonists which incorporate a novel framework mimicking the active conformation.

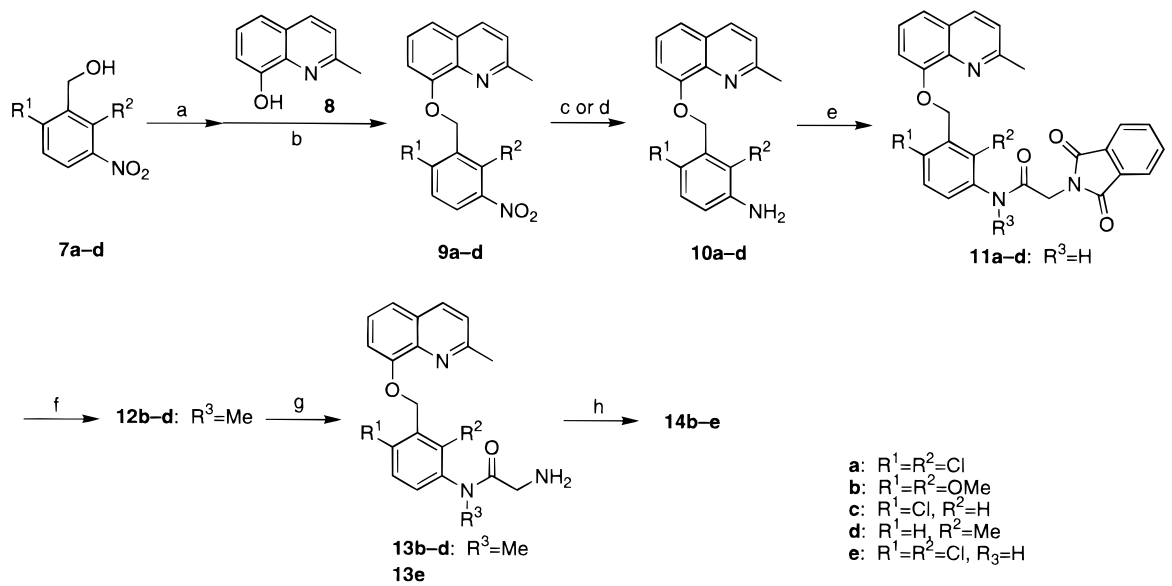
[†] Department of Medicinal Chemistry.
[§] Department of Pharmacology.
[||] Molecular Biological Research Laboratory.
[‡] Present address: Exploratory Clinical Research, Development Division, Fujisawa Pharmaceutical Co. Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan.
[⊥] Present address: New Drug Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan.

10.1021/jm980330i CCC: $15.00
Published on Web 10/08/1998

Chart 1



Scheme 1[a]



[a] (a) MsCl, Et_3N, CH_2Cl_2; (b) NaH, DMF; (c) $N_2H_4 \cdot H_2O$, $FeCl_3 \cdot 6H_2O$, C, aqueous MeOH; (d) Fe, AcOH, EtOH; (e) *N*-phthaloylglycyl chloride, pyridine, DMF; (f) MeI, NaH, DMF; (g) $N_2H_4 \cdot H_2O$, EtOH; (h) (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid or (*E*)-3-(6-acetamidopyridin-3-yl)acrylic acid, WSCD·HCl, HOBt, DMF.

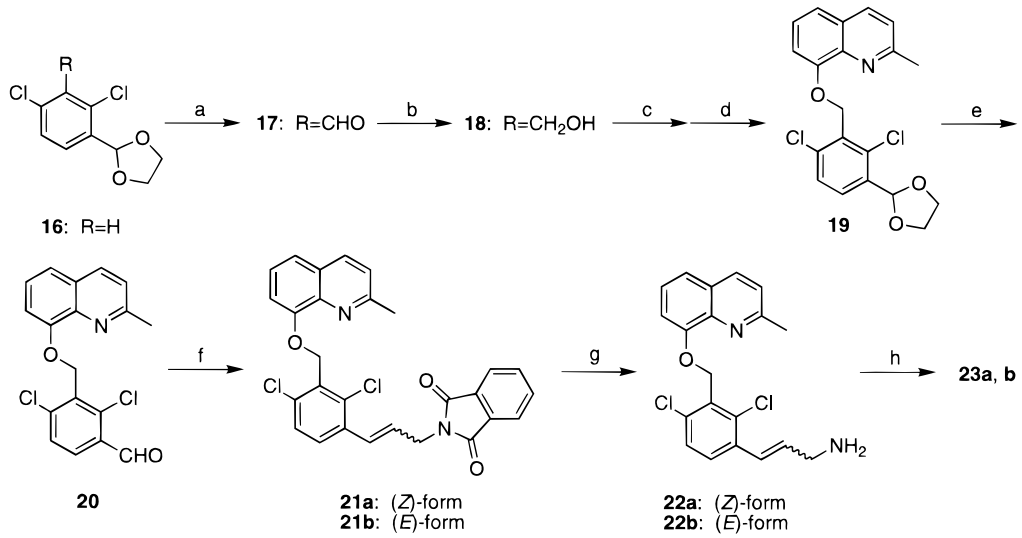
Chemistry

The compounds described in this study are shown in Tables 1−3, and their synthetic methods are outlined in Schemes 1−6.

Modification of the substituents at the 2,6-dichlorobenzene ring and the *N*-methylamide group is shown in Scheme 1. Appropriate benzyl alcohols **7a**−**d** were treated with methanesulfonyl chloride and triethylamine in CH_2Cl_2, and subsequent coupling with 2-methyl-8-hydroxyquinoline (**8**) in the presence of sodium hydride as a base gave the corresponding quinolines **9a**−**d**, respectively. Reduction of the nitro group with hydrazine monohydrate, iron(II) chloride hexahydrate, and carbon or iron in AcOH and EtOH gave the anilines **10a**−**d**. The *N*-phthaloylglycinamides **11a**−**d** were obtained from **10a**−**d** by coupling with *N*-phthaloylglycyl chloride in pyridine and DMF. Alkylation of **11b**−**d** with methyl iodide in the presence of sodium hydride yielded **12b**−**d**. The *N*-phthaloyl groups of **10a** and **12b**−**d** were deprotected with hydrazine monohydrate followed by coupling with (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid[22] or (*E*)-3-(6-acetamidopyridin-3-yl)-acrylic acid[22] in the presence of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) and 1-hydroxybenzotriazole (HOBt) to give the acrylamides **14b**−**e**.

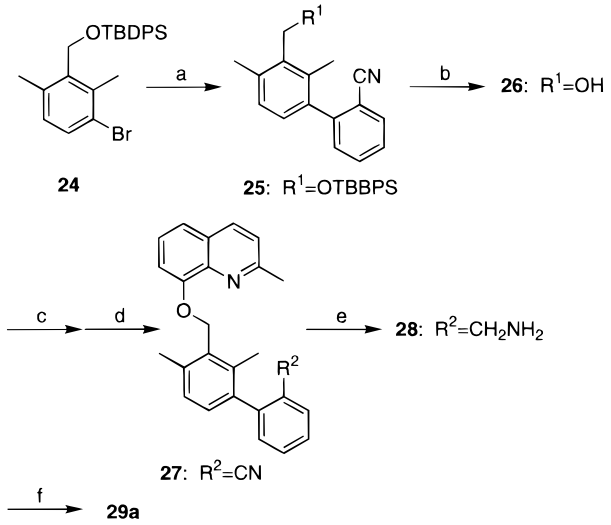
Schemes 2−6 show the synthetic routes for the various *cis*- or *trans*-amide-like rigid moieties, which were introduced in place of the *N*-methylamide group. Replacement of the *N*-methylamide group with a double

Scheme 2[a]



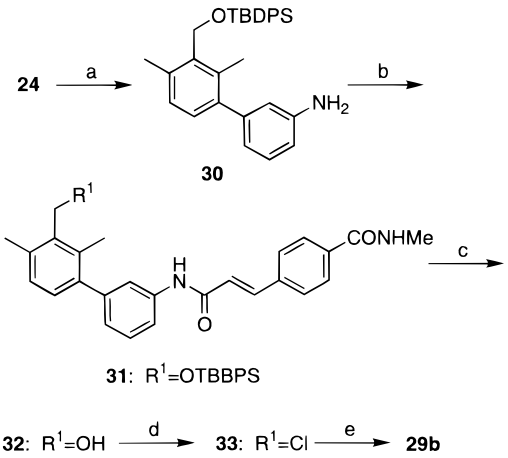
[a] (a) *n*-BuLi, DMF, THF; (b) $NaBH_4$, MeOH; (c) MsCl, Et_3N, CH_2Cl_2; (d) **8**, NaH, DMF; (e) AcOH, H_2O; (f) 2-(*N*-phthaloyl)ethyltriphenylphosphonium bromide, NaH, DMSO; (g) $N_2H_4 \cdot H_2O$, EtOH; (h) (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid, WSCD·HCl, HOBt, DMF.

Scheme 3[a]



[a] (a) *n*-BuLi, $ZnCl_2$, 2-bromobenzonitrile, $Pd(PPh_3)_4$, THF; (b) *n*-Bu_4NF, THF; (c) MsCl, Et_3N, CH_2Cl_2; (d) **8**, NaH, DMF; (e) LAH, THF; (f) (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid, WSCD·HCl, HOBt, DMF.

Scheme 4[a]



[a] (a) 3-Aminophenylboronic acid hemisulfate, 2 M Na_2CO_3, $Pd(PPh_3)_4$, toluene; (b) (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid, WSCD·HCl, HOBt, DMF; (c) *n*-Bu_4NF, THF; (d) MsCl, Et_3N, CH_2Cl_2; (e) **8**, NaH, DMF.

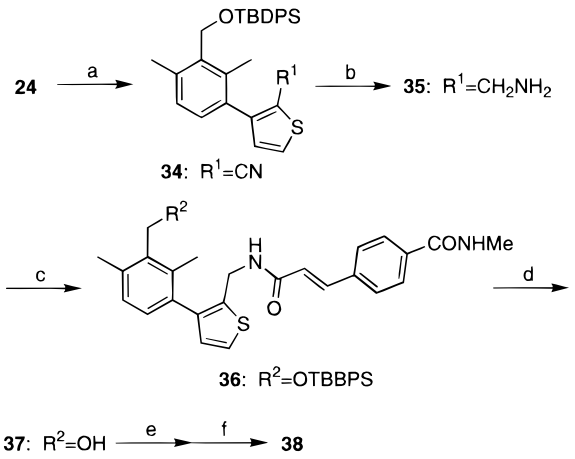
bond is shown in Scheme 2. Treatment of 2-(2,4-dichlorophenyl)-1,3-dioxolane (**16**) with *n*-butyllithium followed by reaction with DMF gave the benzaldehyde **17**. Reduction of **17** with sodium borohydride provided the benzyl alcohol **18**, which was treated with methanesulfonyl chloride followed by coupling with **8** to afford the quinoline **19**. Deprotection of the 1,3-dioxolane group of **19** under acidic conditions, followed by Wittig reaction using sodium hydride and DMSO, gave a 3:4 mixture of (*Z*)- and (*E*)-isomers (**21a**,**b**), whose stereochemistry was identified on the basis of the observed coupling constants of 10 and 15 Hz between the olefinic protons for (*Z*)- and (*E*)-isomers, respectively. The *N*-phthaloyl groups of **21a**,**b** were removed, and the resultant amines **22a**,**b** were condensed with (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid[22] in the presence of WSCD·HCl and HOBt to furnish the cinnamamides **23a**,**b**.

Introduction of the 1,2-disubstituted benzene ring in place of the *N*-methylamide group is illustrated in Scheme 3. Coupling of the bromobenzene **24** with 2-bromobenzonitrile and subsequent deprotection of the silyl group with tetra-*n*-butylammonium fluoride provided the benzyl alcohol **26**. Treatment of **26** with methanesulfonyl chloride, coupling with **8**, reduction of the cyano group of **27** with lithium aluminum hydride, and condensation with (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid[22] gave the cinnamamide **29a**.

Scheme 4 shows replacement of the *N*-methylamide group with a 1,3-disubstituted benzene ring. Suzuki coupling of **24** with 3-aminophenylboronic acid hemisulfate in the presence of tetrakis(triphenylphosphine)-palladium(0), condensation with (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid,[22] and deprotection of the silyl group afforded the benzyl alcohol **32**. Reaction of **32** with methanesulfonyl chloride and alkylation with **8** yielded the quinoline **29b**.

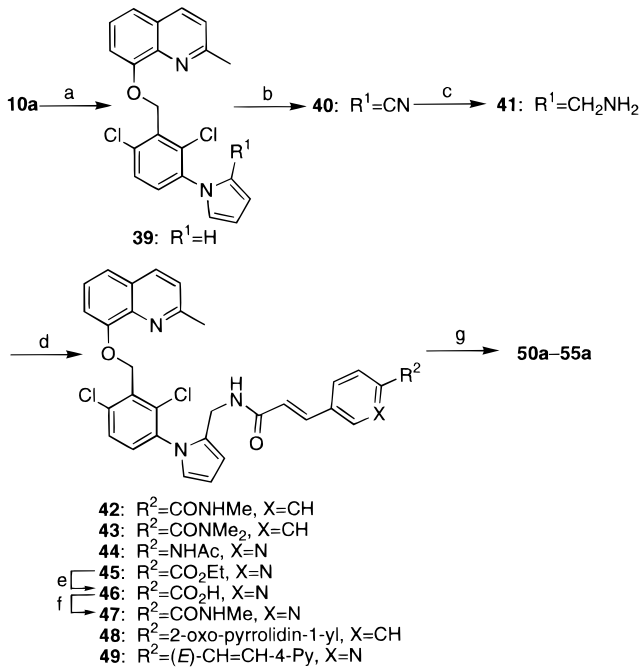
Synthesis of the thienyl derivative was performed as shown in Scheme 5. Coupling of **24** with 3-bromo-2-cyanothiophene, reduction of the cyano group with

Scheme 5[a]



[a] (a) *n*-BuLi, $ZnCl_2$, 3-bromo-2-cyanothiophene, $Pd(PPh_3)_4$, THF; (b) BH_3·THF, THF; (c) (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid, WSCD·HCl, HOBt, DMF; (d) *n*-Bu_4NF, THF; (e) MsCl, Et_3N, CH_2Cl_2; (f) **8**, NaH, DMF.

Scheme 6[a]



[a] (a) 2,5-Dimethoxytetrahydrofuran, AcOH, 90 °C; (b) $ClSO_2NCO$, DMF, CH_2Cl_2; (c) LAH, THF; (d) substituted acrylic acid, WSCD·HCl, HOBt, DMF; (e) 1 N NaOH, EtOH, 60 °C; (f) H_2NMe·HCl, WSCD, HOBt, DMF; (g) HCl−MeOH.

borane−THF complex, and condensation with (*E*)-4-(*N*-methylcarbamoyl)cinnamic acid[22] provided **36**. Deprotection, sulfonylation, and alkylation afforded the 2,3-disubstituted thiophene **38**.

Replacement of the *N*-methylamide group with the pyrrole ring and modification of the terminal acrylamide moiety are shown in Scheme 6. The pyrrole **39** was obtained from **10a** by heating 2,5-dimethoxytetrahydrofuran in AcOH. Reaction of **39** with chlorosulfonyl isocyanate provided the 2-cyano derivative **40**. The cyano group of **40** was reduced to give the amine **41**, which was condensed with appropriate acrylic acids to furnish the corresponding acrylamides **42**−**45**, **48**, and **49**, respectively. Hydrolysis of the ester **45** followed by coupling with methylamine hydrochloride yielded the carbamoyl **47**. The acrylamides **42**−**45** and **47**−**49** were converted to the corresponding hydrochlorides **50a**−**55a**, respectively.

Biology

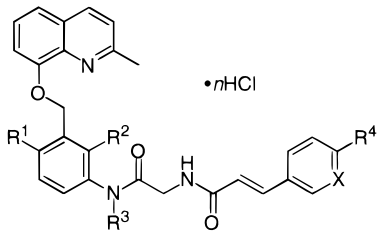
All compounds were tested for inhibition of the specific binding of [^{3}H]BK to B_2 receptors in guinea pig ileum membrane preparations as previously reported,[20−23a,24] and they were also evaluated for inhibition of the specific binding of [^{3}H]BK to human recombinant B_2 receptors expressed in CHO cells.[21b,24] Compounds having potent binding affinities were then tested for in vivo functional antagonistic activity in inhibiting BK-induced bronchoconstriction in guinea pigs by oral administration.[20,21a,22,23a,24]

Results and Discussion

Recently, we reported the first series of orally active non-peptide BK B_2 receptor antagonists, incorporating a 8-[[3-(*N*-acylglycyl-*N*-methylamino)-2,6-dichlorobenzyl]oxy]-3-halo-2-methylimidazo[1,2-*a*]pyridine skeleton as the basic framework.[20] Using the representatives (**1**−**3**) as lead compounds, we then investigated SAR for B_2 binding affinities to both human and guinea pig receptors and demonstrated an obvious species difference in the ligand selectivity. Intensive chemical modification of the terminal amide part (C part in Chart 1) led to identification of the essential pharmacophores for human B_2 binding affinity and to speculation of their interaction with B_2 receptors.[22] Further extensive research on the imidazo[1,2-*a*]pyridine part (A part) led to several bioisosteres and resulted in the identification of the highly potent quinoline series.[24] Thus, we have discovered a novel class of potent, selective, and orally active non-peptide B_2 antagonists represented by **4**,[21,22] **5**,[21b,23,24] and **6**.[24] To complete the SAR of our B_2 antagonists, we next aimed to elucidate the roles of each substituent on the central phenyl ring in the B part.

At first we investigated replacement of the chloro atoms in the B part. 2,6-Dimethyl derivative **15** retained high B_2 binding affinities, while the 2,6-dimethoxy congener **14b** showed 191- and 33-fold decreased activity against the human and guinea pig receptors, respectively (Table 1). Removal of the 2-chloro atom from **14a** and the 6-methyl group from **15** resulted in greater loss of B_2 binding affinity to the human receptor (100- and 31-fold) than to the guinea pig one (10- and 18-fold). These results suggest that both the 2- and 6-chloro or -methyl groups may be important, not only for conformational restriction of the 1- and 3-substituents but also for hydrophobic interactions with B_2 receptors. We next examined the steric effect of the N-substituent R^3. Removal of the *N*-methyl group from **5** gave **14e** which displayed a 3 orders of magnitude reduction in binding affinity to both human and guinea pig B_2 receptors, consistent with the results in the imidazo[1,2-*a*]pyridine series.[20] This dramatic loss of activity may be postulated to be the result of a critical conformational change for the whole molecule. As reported in part 1 of this series,[20] a molecular modeling study suggested that the *N*-methylamide preferred the *cis*-amide conformation, while the *trans*-amide form was favorable for the N-H amide. It was also suggested that the planes of the *N*-methylamide and the 2,6-dichlorophenyl moieties

Table 1. Modification of Substituents at the 2,6-Dichlorobenzene Ring



compd	R^1	R^2	R^3	R^4	X	*n*	in vitro IC_{50} (nM) guinea pig ileum[a]	in vitro IC_{50} (nM) human recombinant[b]	method	mp (°C)	formula[c]
14a	Cl	Cl	Me	CONHMe	CH	1	0.51	1.1	ref[24]		
15	Me	Me	Me	CONHMe	CH	0	0.97	4.8	ref[24]		
14b	OMe	OMe	Me	CONHMe	CH	0	17	210	B	amorphous	$C_{33}H_{34}N_4O_6$
14c	Cl	H	Me	CONHMe	CH	0	5.1	110	B	223–227	$C_{31}H_{29}ClN_4O_4$
14d	H	Me	Me	CONHMe	CH	0	17	150	B	amorphous	$C_{32}H_{32}N_4O_4$
14e	Cl	Cl	H	NHAc	N	0	280	4200	B	274–279	$C_{29}H_{25}Cl_2N_5O_4$
5	Cl	Cl	Me	NHAc	N	0	0.46	1.4	ref[24]		

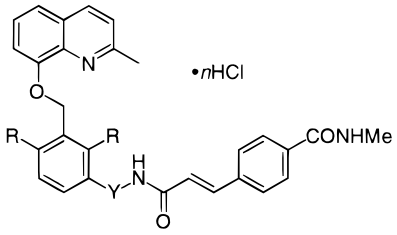
[a] Concentration required to inhibit specific binding of [^{3}H]BK (0.06 nM) to B_2 receptors in guinea pig ileum membrane preparations by 50%. Values are expressed as the average of at least three determinations, with variation in individual values of <15%. See the Experimental Section for further details. [b] Concentration required to inhibit specific binding of [^{3}H]BK (1.0 nM) to human B_2 receptors which was expressed in CHO (Chinese hamster ovary) cells by 50%. Values are expressed as the average of at least three determinations, with variation in individual values of <15%. See the Experimental Section for further details. [c] Analyses for C, H, and N are within ±0.4% of the expected value for the formula.

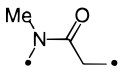
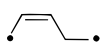
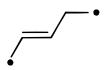
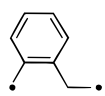
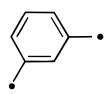
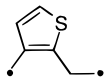
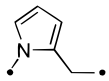
were almost perpendicular, whereas those of the N-H amide and the 2,6-dichlorophenyl moieties were almost coplanar. Such a conformational change at the central anilide can cause significant topological differences in the important pharmacophores in the C part. On this point, it seems reasonable that the B_2 binding affinity for human receptors is more sensitive to chemical modification of the B part than that for guinea pig receptors, because the terminal pharmacophore of the C part is essential for the former but not so important for the latter. These results prompted us to design and synthesize sterically constrained derivatives by replacing the *N*-methylamide group with *cis*-amide-like rigid moieties.

Table 2 summarizes the results of the bioisosteric transformation of the *N*-methylamide group into rigid moieties mimicking *cis*- and *trans*-conformers. Upon replacement of the *N*-methylamide group by a double bond, the *cis*-isomer (**23a**) exhibited 51-fold more potent human B_2 binding affinity compared with the corresponding *trans*-isomer (**23b**), supporting the results of the molecular modeling study. Although binding affinity to both receptors was lower for **23a** compared to *N*-methylamide derivative **14a**, this might be due to insufficient steric features to regulate the molecule to adopt the active conformation. Next we replaced the *N*-methylamide group with bulkier aromatic rings. Introduction of a 1,2-disubstituted benzene ring (**29a**), corresponding to the *cis*-amide form, recovered binding affinities to the same level as **14a**, while replacement with a 1,3-disubstituted benzene ring (**29b**), corresponding to some degree to the *trans*-amide form, resulted in complete loss of human B_2 affinity and a 184-fold decrease in guinea pig activity. Furthermore, we investigated substitution of the benzene ring of **29a** with five-membered rings. Bioisosteric conversion of the 1,2-disubstituted phenyl ring of **29a** to a 2,3-disubstituted thienyl derivative (**38**) retained activity. On the other hand, a pyrrole derivative (**50a**) afforded a remarkable increase in binding affinities, to both human and guinea pig receptors, with IC_{50}s of 0.26 and 0.64 nM, respectively. These results revealed that the *cis*-*N*-methylamide moiety, along with the 2,6-dichloro group, play key roles to allow the whole molecule to adopt the characteristic active conformation.

For optimization of the pyrrole series, we investigated introduction of several acrylic acid moieties to the C part, which afforded potent binding affinities for both human and guinea pig B_2 receptors in the *N*-methylamide series. Table 3 shows a comparison of these pyrrole derivatives with the corresponding *N*-methylamide congeners. All pyrroles exhibited highly potent binding affinities for both species. Although the pyrrole derivatives tend to be weaker in vivo, compounds **51a**, **52a**, and **53a** retained excellent antagonistic activities. It is noteworthy that most of the pyrroles afforded a 3−10-fold increase in human B_2 binding activity compared with the *N*-methylamide counterparts. In particular, compound **50a** is almost twice as potent as the second-generation peptide B_2 antagonist, Icatibant. These results indicate that the SAR at the terminal substituent in the pyrrole series is consistent with that

Table 2. Modification of the *N*-Methylacetamide Moiety



compd	Y	R	*n*	in vitro IC_{50} (nM) guinea pig ileum[a]	in vitro IC_{50} (nM) human recombinant[b]	method	mp (°C)	formula[c]
14a		Cl	1	0.51	1.1	ref[24]		
23a		Cl	0	17	14	B	194–196	$C_{31}H_{27}Cl_2N_3O_3$
23b		Cl	0	220	710	B	amorphous	$C_{31}H_{27}Cl_2N_3O_3$
29a		Me	0	2.3	2.6	B	amorphous	$C_{37}H_{35}N_3O_3$
29b		Me	0	94	>10000	A	234–238	$C_{36}H_{33}N_3O_3$
38		Me	0	2.8	5.8	A	amorphous	$C_{35}H_{33}N_3O_3S$
50a		Cl	1	0.64	0.26	C	amorphous	$C_{33}H_{28}Cl_2N_4O_3$•HCl

[a–c] See corresponding footnotes in Table 1.

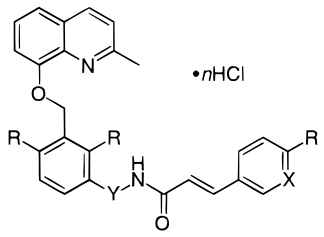
in the *N*-methylamide series and that the pyrrole derivatives bind to human B_2 receptors in a similar but conformationally more refined mode compared with the *N*-methylamide bioisosteres.

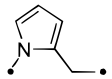
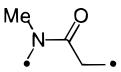
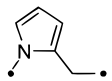
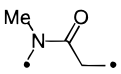
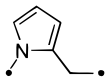
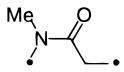
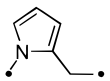
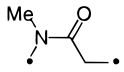
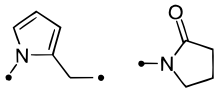
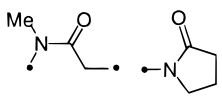
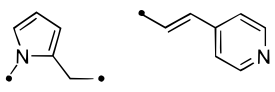
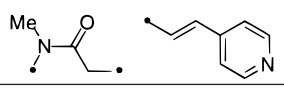
Conclusion

In this study we investigated the roles of substituents on the central phenyl ring in the B part to complete the SAR of our non-peptide B_2 antagonists. The results suggested that the 2,6-dichloro substituents may play important roles not only to regulate the conformation of the 1- and 3-substituents but also to interact with the corresponding hydrophobic pockets of the B_2 receptors and that the 3-*N*-methylamide moiety may critically contribute to prescribe the conformation of the C part.

According to the results of a molecular modeling study, reported in part 1 of this series,[20] we designed and synthesized a series of sterically constrained analogues by replacing the *N*-methylamide group with *cis*-amide-like rigid moieties and found that it could be successfully replaced by several bioisosteres. Thus, we have chemically proven that the active conformation of the *N*-methylamide moiety for both guinea pig and human B_2 receptors is the *cis*-amide form. Extensive optimization of these new heteroaromatic derivatives allowed us to identify a novel series of highly potent and orally active non-peptide B_2 antagonists, incorporating a pyrrole moiety instead of the *N*-methylamide group. Several pyrrole derivatives exhibited equipotent binding affinities for human B_2 receptors to the second-generation peptide B_2 antagonist, Icatibant. Since the representative pyrrole **52a** afforded highly potent B_2 binding affinities to both human and guinea pig receptors, with IC_{50} values of 0.37 and 0.56 nM, respectively, along with an excellent in vivo antagonistic activity at 1 mg/kg po, it is expected to be a novel class of drug for various inflammatory diseases.

Table 3. Comparison of the Pyrrole Series with the *N*-Methylamide Series



compd	Y	R	X	*n*	in vitro IC_{50} (nM) guinea pig ileum[a]	in vitro IC_{50} (nM) human recombinant[b]	in vivo % inhibn[c] 1 mg/kg, po	method	mp (°C)	formula[d]
50a		CONHMe	CH	1	0.64	0.26	67.9±9.5*	C	amorphous	$C_{33}H_{28}Cl_2N_4O_3$•HCl
14a		CONHMe	CH	1	0.51	1.1	81.9±8.0***	ref[24]		
51a		$CONMe_2$	CH	1	0.25	0.41	80.6±4.2***	C	amorphous	$C_{34}H_{30}Cl_2N_4O_3$•HCl
51b		$CONMe_2$	CH	1	1.3	3.9	89.7±0.5**	ref[24]		
52a		NHAc	N	2	0.56	0.37	82.1±5.2*	C	amorphous	$C_{32}H_{27}Cl_2N_5O_3$•2HCl
5 (FR173657)		NHAc	N	0	0.46	1.4	94.4±3.0**	ref[24]		
53a		CONHMe	N	2	0.87	1.5	90.0±1.9***	C	amorphous	$C_{32}H_{27}Cl_2N_5O_3$•2HCl
53b		CONHMe	N	2	0.68	4.6	93.9±1.3**	ref[24]		
54a			CH	1	0.58	0.41	36.0±7.6	C	amorphous	$C_{35}H_{30}Cl_2N_4O_3$•HCl
54b			CH	1	0.55	3.2	85.3±5.1*	ref[24]		
55a			N	3	2.6	0.52	26.5±14.3	C	amorphous	$C_{37}H_{29}Cl_2N_5O_2$•3HCl
6			N	0	0.76	0.51	87.3±4.3**	ref[24]		

[a,b,d] See corresponding footnotes in Table 1. [c] 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[27] as previously reported. After 5 min, compounds were orally administered. After 30 min, BK was administered again and bronchoconstriction was measured. Percent inhibition was calculated from the values of percent responses of drug-treated and control groups ($n = 3-4$). The results are expressed as the mean ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs control (Student's *t*-test). See the Experimental Section for further details. [e] NT, not tested.

Experimental Section

Chemistry. Melting points were determined on a Mel-Temp instrument (Mitamura Riken Kogyo, Japan) and are uncorrected. Proton NMR spectra (300 MHz) were recorded on a Varian Gemini 300 spectrometer, and shifts are expressed in δ (ppm) with TMS as internal standard. Mass spectra were recorded with a VG (Fisons) ZAB-SE (FAB) or Micromass Platform (ESI) system. 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.

8-[(2,6-Dichloro-3-nitrobenzyl)oxy]-2-methylquinoline (9a). To a solution of **7a** (2.00 g, 9.01 mmol) and triethylamine (1.19 g, 11.7 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise methanesulfonyl chloride (1.14 g, 9.91 mmol) in an ice−water bath under nitrogen. After 30 min, the reaction mixture was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried and evaporated in vacuo to give 2.70 g of a pale-yellow oil. Following a similar procedure to method A, the title compound was obtained in 87.6% yield from **8** and the preceding oil as pale-yellow crystals after crystallization from MeOH: mp 183−186 °C; ^{1}H NMR ($CDCl_3$) δ 2.76 (3H, s), 5.70 (2H, s), 7.21−7.57 (5H, m), 7.76 (1H, d, J = 8 Hz), 8.02 (1H, d, J = 8 Hz). Anal. ($C_{17}H_{12}Cl_2N_2O_3$) C, H, N.

Compounds **9b**−**d**, **19**, **27**, and **38** were prepared using a similar procedure to that used for **9a**.

8-[(3-Amino-2,6-dichlorobenzyl)oxy]-2-methylquinoline (10a). To a mixture of **9a** (1.82 g, 5.00 mmol), iron(III) chloride (55 mg), and carbon (55 mg) in 80% aqueous MeOH (27 mL) was added dropwise hydrazine monohydrate (1.00 g, 20.0 mmol) at 70 °C. After the mixture stirred for 4 h at 70 °C, MeOH (10 mL) and hydrazine monohydrate (500 mg, 10.0 mmol) were added therein, and the mixture stirred for a further 2 h. The reaction mixture was then cooled to ambient temperature and filtered through Celite. The filtrate was concentrated in vacuo, and the residue was partitioned between $CHCl_3$ 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 ($CHCl_3$−MeOH, 30:1) followed by crystallization from MeOH to give **10a** (1.10 g, 65.8%) as pale-brown crystals: mp 231−234 °C; ^{1}H NMR (DMSO-d_6) δ 2.60 (3H, s), 5.33 (2H, s), 5.68 (2H, br s), 6.91 (1H, d, J = 8 Hz), 7.23 (1H, d, J = 8 Hz), 7.35−7.52 (4H, m), 8.11 (1H, d, J = 8 Hz); MS (ESI) m/z 333 (M + 1). Anal. ($C_{17}H_{14}Cl_2N_2O$) C, H, N.

Compound **10b** was prepared using a similar procedure to that used for **10a**.

8-[(5-Amino-2-chlorobenzyl)oxy]-2-methylquinoline (10c). A suspension of **9c** (3.28 g, 10.0 mmol) and iron (powder, 2.80 g, 50.0 mmol) in a mixture of AcOH (32 mL) and EtOH (15 mL) was refluxed for 3 h. After cooling, the mixture was filtered and washed with CH_2Cl_2−MeOH (4:1). The filtrate was evaporated in vacuo, and the residue was partitioned between CH_2Cl_2−MeOH (4:1) and saturated aqueous sodium bicarbonate. The organic layer was dried and evaporated in vacuo and the residue purified by flash silica gel column chromatography ($CHCl_3$−MeOH, 50:1) followed by crystallization from diethyl ether to give **10c** (1.64 g, 54.8%) as pale-brown crystals: mp 176−178 °C; ^{1}H NMR (DMSO-d_6) δ 2.67 (3H, s), 5.22 (2H, s), 5.31 (2H, s), 6.55 (1H, d, J = 8, 2 Hz), 6.80 (1H, d, J = 2 Hz), 7.10−7.16 (2H, m), 7.37−7.48 (3H, m), 8.19 (1H, d, J = 8 Hz). Anal. ($C_{17}H_{15}ClN_2O$) C, H, N.

Compound **10d** was prepared using a similar procedure to that used for **10c**.

8-[[2,6-Dichloro-3-(*N*-phthalimidoacetylamino)benzyl]oxy]-2-methylquinoline (11a). To a mixture of **10a** (1.00 g, 3.01 mmol), 4-(dimethylamino)pyridine (37 mg, 0.301 mmol), dry pyridine (2.5 mL), and *N*-methylpyrrolidone (7.5 mL) was added *N*-phthaloylglycyl chloride (1.01 g, 4.52 mmol) at ambient temperature under nitrogen. The reaction mixture was then stirred at 50 °C for 2 h. To the mixture was added dropwise water (10 mL) in an ice−water bath. The precipitate was collected by vacuum filtration, washed with water, and dried in vacuo. This crude solid was purified by flash silica gel column chromatography ($CHCl_3$−MeOH, 40:1) followed by crystallization from AcOEt to give **11a** (1.38 g, 87.9%) as pale-yellow crystals: mp 133−135 °C; ^{1}H NMR ($CDCl_3$) δ 2.86 (3H, s), 4.74 (2H, s), 5.51 (2H, s), 7.20−7.50 (5H, m), 7.63−7.93 (4H, m), 8.03 (1H, d, J = 8 Hz), 8.29 (1H, d, J = 8 Hz). Anal. ($C_{27}H_{19}Cl_2N_3O_4$) C, H, N.

Compounds **11b**,**c** were prepared using a similar procedure to that used for **11a**.

8-[[3-(*N*-Aminoacetyl-*N*-methylamino)-2,6-dimethoxybenzyl]oxy]-2-methylquinoline (13b). To a suspension of **12b** (1.14 g, 2.17 mmol) in EtOH (11 mL) was added hydrazine monohydrate (217 mg, 4.34 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 (6 mL) was added to the residue, and precipitates were filtered off. The filtrate was again evaporated in vacuo and the residue purified by flash silica gel column chromatography (CH_2Cl_2−MeOH, 20:1) to give **13b** (786 mg, 91.6%) as a pale-yellow amorphous solid: ^{1}H NMR ($CDCl_3$) δ 2.69 (3H, s), 3.10 (1H, d, J = 17 Hz), 3.22 (1H, d, J = 17 Hz), 3.30 (3H, s), 3.85 (6H, s), 5.33 (1H, d, J = 10 Hz), 5.44 (1H, d, J = 10 Hz), 6.72 (1H, d, J = 8 Hz), 7.12 (1H, d, J = 8 Hz), 7.21−7.45 (4H, m), 8.00 (1H, d, J = 8 Hz); MS (ESI) m/z 395 (M + 1). Anal. ($C_{22}H_{25}N_3O_4$) C, H, N.

Compounds **13c**−**e** and **22a**,**b** were prepared using a similar procedure to that used for **13b**.

2,6-Dichloro-3-(2,5-dioxolanyl)benzaldehyde (17). To a solution of **16** (31.9 g, 146 mmol) in dry THF (220 mL) was added dropwise 1.6 M *n*-butyllithium in hexane (110 mL) below −50 °C in a dry ice−acetone bath under nitrogen. After 1 h, to the reaction mixture was added dry DMF (56.4 mL, 728 mmol). After 15 min, the mixture was stirred at ambient temperature for 1 h. The mixture was partitioned between AcOEt (200 mL) and water (200 mL); the organic layer was washed with water (2×), dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (hexane−AcOEt, 10:1) followed by crystallization from isopropyl ether to give **17** (4.91 g, 13.6%) as colorless crystals: mp 96−98 °C; ^{1}H NMR ($CDCl_3$) δ 4.04−4.20 (4H, m), 6.16 (1H, s), 7.44 (1H, d, J = 8 Hz), 7.75 (1H, d, J = 8 Hz), 10.05 (1H, s). Anal. ($C_{10}H_8Cl_2O_3$) C, H, N.

2,6-Dichloro-3-(2,5-dioxolanyl)benzyl Alcohol (18). To a solution of **17** (3.90 g, 15.8 mol) in dry MeOH (20 mL) was added sodium borohydride (299 mg, 7.89 mmol) portionwise below 10 °C in an ice−water bath under nitrogen. The reaction mixture was then stirred at the temperature for 1 h. To the ice-cooled mixture was added dropwise water (125 mL) and the whole extracted with AcOEt. The organic layer was washed with water and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (hexane−AcOEt, 3:1) followed by crystallization from isopropyl ether to give **18** (3.69 g, 93.8%) as colorless crystals: mp 82−85 °C; ^{1}H NMR ($CDCl_3$) δ 2.08 (1H, t, J = 7 Hz), 4.02−4.18 (4H, m), 5.00 (2H, d, J = 7 Hz), 6.13 (1H, s), 7.38 (1H, d, J = 8 Hz), 7.54 (1H, d, J = 8 Hz); MS (ESI) m/z 249 (M + 1). Anal. ($C_{10}H_{10}Cl_2O_3$) C, H, N.

8-[(2,6-Dichloro-3-formylbenzyl)oxy]-2-methylquinoline (20). A solution of **19** (2.00 g, 5.12 mmol) in 80% AcOH (20 mL) was heated at 60 °C for 2 h. The cooled reaction mixture was then concentrated in vacuo. To the residue was added aqueous sodium bicarbonate solution, followed by extraction with $CHCl_3$. The organic layer was washed with water, dried, and evaporated in vacuo. The residue was crystallized from AcOEt to give **20** (1.53 g, 86.3%) as colorless crystals: mp 184−186 °C; ^{1}H NMR ($CDCl_3$) δ 2.73 (3H, s), 5.69

(2H, s), 7.23−7.52 (5H, m), 7.89 (1H, d, J = 8 Hz), 8.02 (1H, d, J = 8 Hz); MS (ESI) m/z 346 (M + 1). Anal. ($C_{18}H_{13}Cl_2NO_2$) C, H, N.

8-[[2,6-Dichloro-3-[(*Z*)-3-(*N*-phthalimido)propenyl]benzyl]oxy]-2-methylquinoline (21a) and 8-[[2,6-Dichloro-3-[(*E*)-3-(*N*-phthalimido)propenyl]benzyl]oxy]-2-methylquinoline (21b). A mixture of 60% sodium hydride in oil (428 mg, 10.7 mmol) and DMSO (24 mL) was stirred at 60 °C under nitrogen for 1 h. To the mixture was added 2-(*N*-phthaloyl)-ethyltriphenylphosphonium bromide (5.53 g, 10.7mol) at ambient temperature. After the mixture stirred for 30 min, **20** (1.23 g, 3.55 mmol) was added therein in an ice−water bath and stirring continued at ambient temperature overnight. To the ice-cooled reaction mixture was added water, and the mixture was extracted with $CHCl_3$. The organic layer was washed with water (3×) and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel chromatography, eluting with hexane−AcOEt (3:1), followed by crystallization from isopropyl ether to give **21a** (464 mg, 30.0%) as colorless crystals. Further elution of the column with hexane−AcOEt (1:1) followed by crystallization from isopropyl ether gave **21b** (629 mg, 35.2%) as colorless crystals. **21a**: mp 187−190 °C; ^{1}H NMR ($CDCl_3$) δ 2.75 (3H, s), 4.42 (2H, d, J = 7 Hz), 5.65 (2H, s), 5.83 (1H, dt, J = 10, 7 Hz), 6.67 (1H, br d, J = 10 Hz), 7.24−7.31 (2H, m), 7.36−7.47 (3H, m), 7.59 (1H, d, J = 8 Hz), 7.69−7.77 (2H, m), 7.82−7.90 (2H, m), 8.01 (1H, d, J = 8 Hz); MS (ESI) m/z 503 (M + 1). Anal. ($C_{28}H_{20}Cl_2N_2O_3$) C, H, N. **21b**: mp 213−215 °C; ^{1}H NMR ($CDCl_3$) δ 2.73 (3H, s), 4.49 (2H, d, J = 7 Hz), 5.61 (2H, s), 6.22 (1H, dt, J = 15, 7 Hz), 7.07 (1H, br d, J = 15 Hz), 7.20−7.30 (3H, m), 7.33−7.46 (3H, m), 7.70−7.78 (2H, m), 7.84−7.91 (2H, m), 8.00 (1H, d, J = 8 Hz); MS (ESI) m/z 503 (M + 1). Anal. ($C_{28}H_{20}Cl_2N_2O_3$) C, H, N.

2-[3-(*tert*-Butyldiphenylsiloxymethyl)-2,4-dimethylphenyl]benzonitrile (25). To a solution of **24** (454 mg, 1.00 mmol) in dry THF (2.5 mL) was added dropwise 1.6 N *n*-butyllithium in hexane (0.63 mL) in a dry ice−acetone bath under nitrogen. After stirring for 1 h in a dry ice−acetone bath, to this mixture was added dropwise a solution of zinc chloride (141 mg, 1.03 mmol) in dry THF (1.4 mL) under dry ice−acetone cooling. The bath was removed, and the reaction mixture was stirred at ambient temperature for 1 h. This mixture was added to a solution of 2-bromobenzonitrile (182 mg, 1.00 mmol) and tetrakis(triphenylphosphine)palladium-(0) (23 mg, 0.020 mmol) in dry THF (1 mL) dropwise at ambient temperature. The reaction mixture was then stirred at this temperature for 20 h in the dark. The mixture was diluted with AcOEt, washed with 1 N HCl, water, saturated aqueous sodium bicarbonate solution, and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (hexane−AcOEt, 25:1) to give **25** (233 mg, 48.9%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s), 2.08 (3H, s), 2.28 (3H, s), 4.79 (2H, s), 7.04 (1H, d, J = 8 Hz), 7.08 (1H, d, J = 8 Hz), 7.32−7.75 (14H, m); MS (ESI) m/z 476 (M + 1). Anal. ($C_{32}H_{33}NOSi$) C, H, N.

Compound **33** was prepared using a similar procedure to that used for **25**.

2-(3-Hydroxymethyl-2,4-dimethylphenyl)benzonitrile (26). To a solution of **25** (228 mg, 0.479 mmol) in THF (2.5 mL) was added 1 M tetrabutylammonium fluoride in THF (1.00 mL) at ambient temperature. After 1 h, the mixture was partitioned between AcOEt and 1 N HCl. The organic layer was washed with water and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (hexane−AcOEt, 4:1) to give **26** (72 mg, 63.3%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.27 (3H, s), 2.50 (3H, s), 4.82 (2H, s), 7.07 (1H, d, J = 8 Hz), 7.17 (1H, d, J = 8 Hz), 7.36 (1H, d, J = 8 Hz), 7.45 (1H, t, J = 8 Hz), 7.63 (1H, t, J = 8 Hz), 7.74 (1H, d, J = 8 Hz). Anal. ($C_{16}H_{15}NO$) C, H, N.

Compounds **32** and **37** were prepared using a similar procedure to that used for **26**.

3-(3-Aminophenyl)-1-(*tert*-butyldiphenylsiloxymethyl)-2,6-dimethylbenzene (30). To a suspension of 3-aminophenylboronic acid hemisulfate (472 mg, 2.54 mmol) in toluene (11 mL) were added tetrakis(triphenylphosphine)palladium(0) (64 mg, 0.055 mmol), 2 M sodium carbonate in H_2O (5.5 mL), MeOH (2.8 mL), and **24** (1.00 g, 2.21 mmol) at ambient temperature, and the mixture was heated at 80 °C. After 5 h, the cooled reaction mixture was extracted with $CHCl_3$, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (hexane−AcOEt, 5:1) to give **30** (350 mg, 34.1%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s), 2.14 (3H, s), 2.26 (3H, s), 3.67 (2H, br s), 4.77 (2H, s), 6.56−6.80 (3H, m), 7.00 (1H, d, J = 8 Hz), 7.06 (1H, d, J = 8 Hz), 7.16 (1H, t, J = 8 Hz), 7.32−7.48 (6H, m), 7.70 (4H, br d, J = 8 Hz); MS (ESI) m/z 466 (M + 1). Anal. ($C_{31}H_{35}NOSi$) C, H, N.

1-Chloromethyl-2,6-dimethyl-3-[3-[(*E*)-4-(*N*-methylcarbamoyl)cinnamamidoacetyl]phenyl]benzene (33). To a solution of **32** (104 g, 0.251 mmol) and triethylamine (38 mg, 0.376 mmol) in dry DMF (1 mL) was added methanesulfonyl chloride (34 mg, 0.297 mmol) in an ice−water bath under nitrogen. After 30 min, the reaction mixture was stirred at ambient temperature for 4 h. The mixture was partitioned between CH_2Cl_2 and water. The organic layer was washed with water (4×) and brine, dried, and evaporated in vacuo. The residue was crystallized from MeCN to give **33** (102 mg, 93.9%) as colorless crystals: mp 238−241 °C; ^{1}H NMR (DMSO-d_6) δ 2.30 (3H, s), 2.44 (3H, s), 2.79 (3H, d, J = 5 Hz), 4.88 (2H, s), 4.78 (1H, t, J = 6 Hz), 6.90 (1H, d, J = 15 Hz), 6.99 (1H, br d, J = 8 Hz), 7.09−7.21 (2H, m), 7.40 (1H, t, J = 8 Hz), 7.58−7.74 (5H, m), 7.89 (2H, d, J = 8 Hz), 8.50 (1H, br d, J = 5 Hz); MS (ESI) m/z 433 (M + 1). Anal. ($C_{26}H_{25}ClN_2O_2$) C, H, N.

Method A. 8-[[2,6-Dimethyl-3-[3-[(*E*)-4-(*N*-methylcarbamoyl)cinnamamido]phenyl]benzyl]oxy]-2-methylquinoline (29b). To a solution of **8** (100 mg, 0.628 mmol) in dry DMF (2 mL) was added 60% sodium hydride in oil (27 mg, 0.659 mmol) in an ice−water bath under nitrogen. After 30 min, **33** (272 mg, 0.628 mmol) was added therein, and the mixture stirred at ambient temperature for 2 h. The mixture was poured into water and the precipitated solid collected by vacuum filtration, washed with water, and dried in vacuo. The solid was purified by flash silica gel column chromatography ($CHCl_3$−MeOH, 30:1), followed by crystallization from MeOH to give **29b** (250 mg, 71.6%) as colorless crystals: mp 234−238 °C; ^{1}H NMR ($CDCl_3$) δ 2.31 (3H, s), 2.46 (3H, s), 2.70 (3H, s), 2.98 (3H, s), 5.32 (2H, s), 6.74 (1H, d, J = 15 Hz), 7.02−7.12 (2H, m), 7.18 (1H, br d, J = 8 Hz), 7.29−7.59 (7H, m), 7.64−7.81 (4H, m), 8.01 (1H, br d, J = 8 Hz), 8.09 (1H, d, J = 8 Hz); MS (ESI) m/z 556 (M + 1). Anal. ($C_{36}H_{33}N_3O_3$) C, H, N.

Compounds **12b**−**d** were prepared using a similar procedure to that used for method A.

3-(2-Aminomethylthiophene-3-yl)-1-(*tert*-butyldiphenylsiloxymethyl)-2,6-dimethylbenzene (35). To a solution of **34** (471 mg, 0.978 mmol) in dry THF (2 mL) was added 1 M borane−THF complex (3 mL) under nitrogen at ambient temperature and the reaction mixture was stirred for 14 h. To the mixture was added 1 N HCl (1.5 mL) dropwise in an ice−water bath, and the mixture stirred for 1 h at ambient temperature. The mixture was partitioned between AcOEt and water. The organic layer was washed with water and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography ($CHCl_3$−MeOH, 50:1) to give **35** (67 mg, 62.7%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s), 2.02 (3H, s), 2.27 (3H, s), 3.78 (2H, s), 4.76 (2H, s), 6.83 (1H, d, J = 6 Hz), 7.00 (2H, br s), 7.20 (1H, d, J = 6 Hz), 7.30−7.48 (6H, m), 7.63−7.75 (4H, m). Anal. ($C_{30}H_{35}NOSSi$) C, H, N.

8-[[2,6-Dichloro-3-(pyrrol-1-yl)benzyl]oxy]-2-methylquinoline (39). A solution of **10a** (3.33 g, 10.0 mmol) and 2,5-dimethoxytetrahydrofuran (1.32 g, 10.0 mmol) in AcOH (8.3 mL) was heated at 100 °C for 2 h. To the reaction mixture were added 2,5-dimethoxytetrahydrofuran (661 mg, 5.00 mmol) and AcOH (8.3 mL) at ambient temperature, and the mixture

was heated at 100 °C for 2 h. The mixture was evaporated in vacuo, and the residue was dissolved in $CHCl_3$. The solution was washed with saturated aqueous sodium bicarbonate solution, water, and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (hexane-$CHCl_3$, 2:1) to give **39** (3.14 g, 81.9%) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 2.75 (3H, s), 5.68 (2H, s), 6.33 (2H, d, J = 3 Hz), 6.87 (2H, d, J = 3 Hz), 7.24−7.48 (6H, m), 8.02 (1H, d, J = 8 Hz). Anal. ($C_{21}H_{16}Cl_2N_2O$) C, H, N.

8-[[3-(2-Cyanopyrrol-1-yl)-2,6-dichlorobenzyl]oxy]-2-methylquinoline (40). To a solution of **39** (1.00 g, 2.61 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise a solution of chlorosulfonyl isocyanate (500 mg, 3.53 mmol) in dry CH_2Cl_2 (1 mL) in a dry ice−acetone bath below −20 °C under nitrogen. The reaction mixture was stirred in a dry ice−acetone bath for 30 min and then at ambient temperature for 1 h. The mixture was cooled to −78 °C and treated with dry DMF (0.5 mL). The reaction mixture was stirred at the same temperature for 30 min and at ambient temperature for 1 h. To the mixture was added dropwise 4 N HCl (4 mL) in an ice−water bath, and the mixture stirred for 30 min at that temperature. To the mixture was added 4 N NaOH (8 mL) in an ice−water bath, and the mixture was filtered through Celite. The filtrate was extracted with $CHCl_3$, washed with water and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (hexane−$CHCl_3$, 2:1) to give **40** (575 mg, 54.0%) as a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) δ 2.76 (3H, s), 5.69 (2H, s), 6.39 (1H, t, J = 4 Hz), 6.95−7.02 (2H, m), 7.23−7.56 (6H, m), 8.03 (1H, d, J = 8 Hz). Anal. ($C_{22}H_{15}Cl_2N_3O$) C, H, N.

8-[[3-(2-Aminomethylpyrrol-1-yl)-2,6-dichlorobenzyl]oxy]-2-methylquinoline (41). To a suspension of lithium aluminum hydride (168 mg, 4.43 mmol) in dry THF (25 mL) was added a solution of **39** (1.51 g, 3.70 mmol) in dry THF (5 mL) dropwise in an ice−water bath under nitrogen. After 2 h, further lithium aluminum hydride (84 mg, 2.21 mmol) was added thereto, and the reaction mixture was stirred at ambient temperature for 1 h. To the mixture was added H_2O (30 mL) dropwise in an ice−water bath, followed by AcOEt. The precipitate was removed by vacuum filtration through Celite, which was then washed with AcOEt. The filtrate and washings were combined, and the organic layer was separated, dried, and evaporated in vacuo. The residue was purified by flash silica gel chromatography ($CHCl_3$−MeOH, 50:1) to give **41** (797 mg, 52.2%) as a brown amorphous solid: ^{1}H NMR ($CDCl_3$) δ 2.75 (3H, s), 3.55 (1H, d, J = 16 Hz), 3.66 (1H, d, J = 16 Hz), 5.70 (2H, s), 6.21 (1H, d, J = 4 Hz), 6.28 (1H, t, J = 4 Hz), 6.64 (1H, d, J = 4 Hz), 7.23−7.51 (6H, m), 8.02 (1H, d, J = 8 Hz). Anal. ($C_{22}H_{19}Cl_2N_3O$) C, H, N.

Compound **28** was prepared using a similar procedure to that used for **41**.

Method B. 8-[[3-[2-[(*E*)-3-(6-Acetamidopyridin-3-yl)acryloylaminomethyl]pyrrol-1-yl]-2,6-dichlorobenzyl]oxy]-2-methylquinoline (44). To a solution of **41** (100 mg, 0.243 mmol), (*E*)-3-(6-acetamidopyridin-3-yl)acrylic acid[22] (58 mg, 0.279 mmol), and 1-hydroxybenzotriazole (HOBt; 49 mg, 0.364 mmol) in dry DMF (1 mL) was added WSCD·HCl (56 mg, 0.291 mmol) in an ice−water bath under nitrogen. After 30 min, the reaction mixture was stirred at ambient temperature for 2 h. The mixture was partitioned with $CHCl_3$ and saturated aqueous sodium bicarbonate solution. The organic layer was washed with water (3×) and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography ($CHCl_3$−MeOH, 40:1) to give **44** (108 mg, 74.2%) as a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) δ 2.11 (3H, s), 2.59 (3H, s), 4.10 (1H, m), 4.24 (1H, m), 5.42 (2H, d, J = 3 Hz), 6.16−6.25 (2H, m), 6.57 (1H, d, J = 15 Hz), 6.86 (1H, d, J = 3 Hz), 7.25 (1H, d, J = 8 Hz), 7.31 (1H, d, J = 15 Hz), 7.36−7.47 (2H, m), 7.53 (1H, d, J = 8 Hz), 7.63 (1H, d, J = 8 Hz), 7.71 (1H, d, J = 8 Hz), 7.95 (1H, m), 8.11 (1H, d, J = 8 Hz), 8.17−8.30 (2H, m), 8.45 (1H, br s), 10.66 (1H, br s); MS (ESI) m/z 600 (M + 1). Anal. ($C_{32}H_{27}Cl_2N_5O_3$) C, H, N.

Compounds **14b**−**e**, **23a**,**b**, **29a**, **31**, **36**, **42**, **43**, **45**, **48**, and **49** were prepared using a similar procedure to that used for method B.

8-[[3-[2-[(*E*)-3-(6-Carboxypyridin-3-yl)acryloylaminomethyl]pyrrol-1-yl]-2,6-dichlorobenzyl]oxy]-2-methylquinoline (46). A solution of **45** (100 mg, 0.162 mmol) in EtOH (1 mL) containing 1 N NaOH (0.3 mL) was heated at 60 °C for 1 h. Upon cooling, the reaction mixture was evaporated in vacuo and dissolved with water. The water layer was washed with ether, adjusted to pH 5 with 1 N HCl, and extracted with $CHCl_3$−MeOH (10:1, 4×). The organic layer was dried and evaporated in vacuo. The residue was triturated with AcOEt to give **46** (75 mg, 78.8%) as a colorless amorphous solid: ^{1}H NMR (DMSO-d_6) δ 2.60 (3H, s), 4.15 (1H, m), 4.26 (1H, m), 5.43 (2H, s), 6.18−6.27 (2H, m), 6.80 (1H, d, J = 16 Hz), 6.88 (1H, m), 7.27 (1H, d, J = 8 Hz), 7.37−7.49 (3H, m), 7.53 (1H, d, J = 8 Hz), 7.62 (1H, d, J = 8 Hz), 7.72 (1H, d, J = 8 Hz), 8.02−8.14 (2H, m), 8.21 (1H, d, J = 8 Hz), 8.41 (1H, br s), 8.85 (1H, d, J = 2 Hz); MS (FAB) m/z 587 (M + 1). Anal. ($C_{31}H_{24}Cl_2N_4O_4$) C, H, N.

8-[[2,6-Dichloro-3-[[(*E*)-3-[6-(*N*-methylcarbamoyl)pyridin-3-yl]acryloylaminomethyl]pyrrol-1-yl]benzyl]oxy]-2-methylquinoline (47). To a solution of **46** (100 mg, 0.170 mmol) in dry DMF (1 mL) were added methylamine hydrochloride (13 mg, 0.193 mmol), WSCD (32 mg, 0.206 mmol), and HOBt (35 mg, 0.259 mmol) at ambient temperature. After 5 h, this mixture was partitioned between $CHCl_3$ and saturated aqueous sodium bicarbonate solution. The organic layer was washed with water (4×) and brine, dried, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (CH_2Cl_2−MeOH, 40:1) to give **47** (86 mg, 84.3%) as a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) δ 2.60 (3H, s), 3.00 (3H, d, J = 6 Hz), 4.34 (1H, dd, J = 15, 4 Hz), 4.52 (1H, dd, J = 15, 4 Hz), 5.54 (1H, d, J = 10 Hz), 5.61 (1H, d, J = 10 Hz), 6.28 (1H, m), 6.35 (1H, m), 6.47−6.61 (2H, m), 6.69 (1H, m), 7.18−7.31 (2H, m), 7.36−7.58 (6H, m), 7.78 (1H, d, J = 8 Hz), 7.86 (1H, m), 8.04 (1H, d, J = 8 Hz), 8.39 (1H, br s); MS (FAB) m/z 600 (M + 1). Anal. ($C_{32}H_{27}Cl_2N_5O_3$) C, H, N.

Method C. 8-[[3-[2-[(*E*)-3-(6-Acetamidopyridin-3-yl)acryloylaminomethyl]pyrrol-1-yl]-2,6-dichlorobenzyl]oxy]-2-methylquinoline Dihydrochloride (52a). To a suspension of **44** (100 mg, 0.167 mmol) in MeOH (2 mL) was added 10% hydrogen chloride in MeOH (2 mL) at ambient temperature. To the mixture was added $CHCl_3$ (0.5 mL), and the mixture stirred for 10 min. The solution was evaporated in vacuo and the residue washed with AcOEt to give **52a** (106 mg, 94.3%) as a colorless amorphous solid: ^{1}H NMR (DMSO-d_6) δ 2.11 (3H, s), 2.91 (3H, s), 4.17 (1H, m), 4.57 (1H, m), 5.56 (1H, d, J = 10 Hz), 5.65 (1H, d, J = 10 Hz), 6.19−6.27 (2H, m), 6.51 (1H, d, J = 15 Hz), 6.84 (1H, m), 7.27 (1H, d, J = 15 Hz), 7.57 (1H, d, J = 8 Hz), 7.67 (1H, d, J = 8 Hz), 7.77−8.03 (5H, m), 8.09 (1H, d, J = 8 Hz), 8.41 (1H, br s), 8.47 (1H, m), 9.03 (1H, m), 10.72 (1H, br s). Anal. ($C_{32}H_{27}Cl_2N_5O_3$·2HCl) C, H, N.

Compounds **50a**, **51a**, and **53a**−**55a** were prepared using a similar procedure to that used for method C.

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[25] 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 homogenizer. The homogenate was centrifuged to remove cellular debris (1000g, 20 min, 4 °C), and the supernatant was centrifuged (100000g, 60 min, 4 °C). The pellet was then resuspended in ice-cold binding buffer I (50 mM TES, 1 mM 1,10-phenanthroline, 140 μg/mL bacitracin, 1 mM dithiothreitol, 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, the membranes (0.2 mg of protein/

mL) were incubated with 0.06 nM [^{3}H]BK 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. All experiments were carried out three times.

Recombinant Human B_2 Receptors Expressed in CHO cells. CHO (dhfr$^-$) cells that were transferred with and stably expressed human B_2 receptors have been described previously.[21b] Cells were maintained in an α-minimum essential medium supplemented with penicillin (100 μg/mL), streptomycin (100 μg/mL), and 10% fetal bovine serum. The cells were seeded in 48-well tissue culture plates at a density of 3.0×10^4 cells/well and cultured for 1 day. The cells were washed three times with phosphate-buffered saline containing 0.1% BSA and incubated with 1.0 nM [^{3}H]BK and test compounds for 2 h at 4 °C in 0.25 mL of binding buffer III (20 mM HEPES, 125 mM *N*-methyl-D-glucamine, 5.0 mM KCl, 1.8 mM $CaCl_2$, 0.8 mM $MgSO_4$, 0.05 mM bacitracin, 5 μM enalaprilat, and 0.1% BSA, pH 7.2). All experiments were carried out three times. Nonspecific binding was determined in the presence of 1 μM unlabeled BK. At the end of the incubation, the buffer was aspirated, and the cells were washed twice with ice-cooled phosphate-buffered saline containing 0.1% BSA. The specific binding was calculated by subtracting the nonspecific binding, determined in the presence of 1 μM unlabeled BK, from the total binding. Bound radioactivity was determined by solubilizing with 1% sodium dodecyl sulfate containing 0.05 N NaOH and quantitating in a liquid scintillation counter.

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), and the trachea, jugular vein, and esophagus were cannulated. The animals were ventilated at a tidal volume of 10 mL/kg with a frequency of 60 breaths/min through the tracheal cannula. To suppress spontaneous respiration, alcuronium chloride (0.5 mg/kg) was administered intravenously through the jugular vein cannula. Then, propranolol (10 mg/kg) was also administered subcutaneously. After 10 min, BK (5 μg/kg, dissolved in saline with 0.1% BSA) was administered intravenously through the jugular vein cannula. Bronchoconstriction was measured by the modified Konzett and Rössler method[26] 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 esophageal 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 = $(\Delta PIP_{\text{after drug}}/\Delta PIP_{\text{before drug}}) \times 100$. Percent response obtained from the vehicle-administered animals was regarded as the control. Three or four animals were used in each dose. The potency of the drug was expressed as percent inhibition which was calculated from the values of percent responses of drug-treated and control groups as follows: % inhibition = $(1 - \%\ \text{response}_{\text{drug}}/\%\ \text{response}_{\text{mean value of vehicle}}) \times 100$.

Statistical Analysis. Statistical significance was analyzed with the results of percent inhibition between groups by Student's *t*-test. IC_{50} or ED_{50} value was obtained by using nonlinear curve-fitting methods with a computer program developed in-house.

Acknowledgment. We are grateful to Dr. D. Barrett (Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., Osaka) for his valuable suggestions.

Supporting Information Available: Physical data of **9b−d**, **10b**,**d**, **11b**,**c**, **12b−d**, **13c−e**, **14b−e**, **19**, **22a**,**b**, **23a**,**b**, **27−29a**, **31−33**, **36−38**, **42**, **43**, **45**, **48−51a**, and **53a−55a** (12 pages). Ordering information is found 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.; Perkins, 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: New York, 1991; pp 1−31.
(8) Burch, R. M.; Farmer, S. G.; Steranka, L. R. Bradykinin Receptor Antagonists. *Med. Res. Rev.* **1990**, *10*, 237−269.
(9) 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.
(10) Hess, J. F.; Borkowski, J. A.; Young, G. S.; Strader, C. D.; Ransom, R. W. Cloning and Pharmacological Characterization of a Human Bradykinin (BK-2) Receptor. *Biochem. Biophys. Res. Commun.* **1992**, *184*, 260−268.
(11) Menke, J. G.; Borkowski, J. A.; Bierilo, K. K.; MacNeil, T.; Derrick, A. W.; Schneck, K. A.; Ransom, R. W.; Strader, C. D.; Linemeyer, D. L.; Hess, J. F. Expression Cloning of a Human B_1 Bradykinin Receptor. *J. Biol. Chem.* **1994**, *269*, 21583−21586.
(12) 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.
(13) Wirth, K.; Hock, F. J.; Albus, U.; Linz, W.; Alpermann, H. G.; Anagnostopoulos, H.; Henke, St.; Breipohl, G.; König, 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.
(14) 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.
(15) 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. Probing The Bradykinin Receptor: Mapping The Geometric Topography Using Ethers of Hydroxyproline in Novel Peptides. *J. Med. Chem.* **1991**, *34*, 2649−2653.
(16) Kyle, D. J. Structure-Based Drug Design: Progress Toward The Discovery of The Elusive Bradykinin Receptor Antagonists. *Curr. Pharm. Des.* **1995**, *1*, 233−254.
(17) Calixto, J. B.; Yunes, R. A.; Rae, G. A.; Medeiros, Y. S. Nonpeptide Bradykinin Antagonists. In *Bradykinin Antagonists*, *Basic and Clinical Research;* Burch, R. M., Ed.; Marcel Dekker: New York, 1991; pp 97−129.
(18) Salvino, J. M.; Seoane, P. R.; Douty, B. D.; Awad, M. M. A.; Dolle, R. E.; Houck, W. T.; Faunce, D. M.; Sawutz, D. G. Design of Potent Non-Peptide Competitive Antagonists of the Human Bradykinin B_2 Receptor. *J. Med. Chem.* **1993**, *36*, 2583−2584.
(19) Hoyer, D.; Awad, M. M. A.; Salvino, J. M.; Seoane, P. R.; Dolle, R. E.; Houck, W. T.; Sawutz, D. G. ACE Inhibitors as a Template for the Design of Bradykinin B_2 Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 367−370.
(20) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Imai, K.; Inamura, N.; Asano, M.; Hatori, C.; Katayama, A.; Oku, T.; Tanaka, H. A Novel Class of Orally Active Non-Peptide Bradykinin B_2 Receptor Antagonists. 1. Construction of the Basic Framework. *J. Med. Chem.* **1998**, *41*, 564−578.

(21) (a) Inamura, N.; Asano, M.; Hatori, C.; Sawai, H.; Hirosumi, J.; Fujiwara, T.; Kayakiri, H.; Satoh, S.; Abe, Y.; Inoue, T.; Sawada, Y.; Oku, T.; Nakahara, K. Pharmacological Characterization of a Novel, Orally active, Nonpeptide Bradykinin B_2 Receptor Antagonist, FR167344. *Eur. J. Pharmacol.* **1997**, *333*, 79−86. (b) Aramori, I.; Zenkoh, J.; Morikawa, N.; O'Donnell, N.; Asano, M.; Nakamura, K.; Iwami, M.; Kojo, H.; Notsu, Y. Novel Subtype-Selective Nonpeptide Bradykinin Receptor Antagonists FR167344 and FR173657. *Mol. Pharmacol.* **1997**, *51*, 171−176.

(22) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Inamura, N.; Asano, M.; Hatori, C.; Sawai, H.; Oku, T.; Tanaka, H. A Novel Class of Orally Active Non-Peptide Bradykinin B_2 Receptor Antagonists. 2. Overcoming the Species Difference between Guinea Pig and Man. *J. Med. Chem.* **1998**, *41*, 4053−4061.

(23) (a) 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. (b) Rizzi, A.; Gobeil, F.; Calò, G.; Inamura, N.; Regoli, D. FR173657: A New, Potent, Nonpeptide Kinin B_2 Receptor Antagonist. *Hypertension* **1997**, *29*, 951−956. (c) Griesbacher, T.; Legat, F. J. Effects of FR173657, a Non-Peptide B_2 Antagonist, on Kinin-Induced Hypotension, Visceral and Peripheral Oedema Formation and Bronchoconstriction. *Br. J. Pharmacol.* **1997**, *120*, 933−939. (d) Griesbacher, T.; Sametz, W.; Legat, F. J.; Diethart, S.; Hammer, S.; Juan, H. Effects of the Non-peptide B_2 Antagonist FR173657 on Kinin-induced Smooth Muscle Contraction and Relaxation, Vasoconstriction and Prostaglandin Release. *Br. J. Pharmacol.* **1997**, *121*, 469−476.

(24) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Inamura, N.; Asano, M.; Aramori, I.; Hatori, C.; Sawai, H.; Oku, T.; Tanaka, H. A Novel Class of Orally Active Non-Peptide Bradykinin B_2 Receptor Antagonists. 3. Discovering Bioisosteres of the Imidazo[1,2-*a*]pyridine Moiety. *J. Med. Chem.* **1998**, *41*, 4062−4079.

(25) 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.

(26) Konzett, H.; Rössler, R. Versuchsanordnung zu Untersuchungen an der Bronchialmuskulatur. *Naunyn-Schmiedeberg's Arch. Exp. Path. Pharmak.* **1940**, *195*, 71−74.

(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.

JM980330I