Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 327–332

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Novel Series of O-Substituted 8-Quinolines and 4-Benzothiazoles as Potent Antagonists of the Bradykinin B_2 Receptors

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Received 16 October 1998; accepted 9 December 1998

Abstract: The synthesis and the SAR study of novel O-substituted 8-quinolines and 4-benzothiazoles as highly potent non-peptide bradykinin B_2 receptor antagonists are described. Several members of this series of antagonists efficiently inhibited the BK-induced vasoconstriction on different isolated organ preparations. © 1999 Elsevier Science Ltd. All rights reserved.

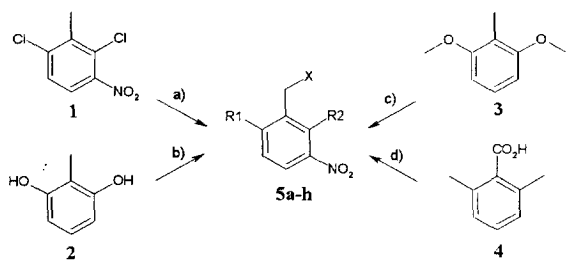
It is now well established that bradykinin (BK) participates in the pathophysiology of various diseases like inflammation, pain, asthma, allergic rhinitis, arthritis, shock, and acute pancreatitis.[1-4] Its involvement in the avid sodium retention of liver cirrhosis has also been demonstrated recently.[5]

The major part of the acute pathophysiological actions of BK is mediated by the B_2 receptor.[6] In the past decade, antagonism of this receptor was restricted to BK-derived peptides like the "second generation" antagonists icatibant (HOE 140)[7] and bradycor (CP0127).[8] Recently, researchers from Fujisawa delineated the first "third generation" of B_2 receptor antagonists, which were orally active non-peptide antagonists of this BK receptor subtype.[9] Prototypes of this new class of antagonists are FR 167 344 and FR 173 657.[9,10,11]

Herein we report the synthesis and SAR study of novel series of O-substituted quinolin-8-ols and benzothiazol-4-ols with particular emphasis on the influence of the 2,6-substituents of their central 3-*N*-methylamidobenzyl moiety on the affinity towards the BK B_2 receptor. Most of this compounds exhibit high affinity to the BK B_2 receptor on guinea pig ileum membranes and have a pronounced inhibitory action on the BK-induced vasoconstriction in different isolated organ preparations.

The BK receptor antagonists **8a-o** and **13a-h** of the quinoline and the benzothiazole series described here are shown in Table 1 and 2 and their synthetic access is outlined in the Schemes 1-3.

Scheme 1:



	R1	R2	X
5a	Cl	Cl	Br
5b	Cl	CN	Br
5c	OCH_3	CN	Br
5d	Cl	OCH_3	Br
5e	OCH_3	Cl	Br
5f	OCH_3	OC_3H_7	Br
5g	OCH_3	OCH_3	Br
5h	CH_3	CH_3	OMs

I. *X=H*: a) *1.* CuCN, DMF, 150 °C, 10 h; *2.* MeOH, Na, reflux, 2 h or MeOH, NaH, DMF, rt, 2h, separation; b)*1.* $NaNO_2$, H_2SO_4, H_2O, 0 °C, 30 min.; *2.* HNO_3, 5 °C, 30 min.; *3.* $(CH_3O)_2SO_2$, K_2CO_3, acetone, rt, 15 h; *4.* C_3H_7Br, NaH, DMF, 70 °C, 7 h; c) HNO_3, 0 °C, 15 min.; II. *X=Br*: 1,3-dibromo-5,5-dimethylhydantoin, $(PhCO)_2O$, PhCl, reflux, 12 h; d) *1.* HNO_3, H_2SO_4, 0 °C, 1 h; *2.* $(CH_3)_3SiCl$, $BzNEt_3BH_4$, CH_2Cl_2, 0 °C, 2 h; *3.* MsCl, NEt_3, CH_2Cl_2, rt, 30 min.

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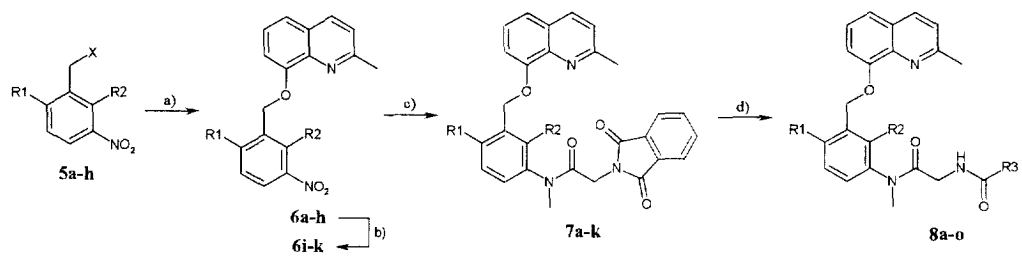
PII: S0960-894X(98)00736-7

The first step in the synthesis of these B_2 receptor antagonists is the preparation of the 2,6-disubstituted nitrobenzylbromides **5a-f** and nitrobenzylmesylate **5g** as outlined in Scheme 1.

The benzylbromides **5a-e** are prepared by bromination of their appropriate toluene precursors along with selective nucleophilic substitution of chloride in **1** by copper(I) cyanide[12] and sodium methoxide. The 2,6-dialkoxy substituted benzylbromide **5f** is obtained by nitrosation of 2,6-dihydroxytoluene **2**, oxidation of the nitroso intermediate, regioselective alkylation of the 6-hydroxy group with dimethoxysulfate[13], alkylation of the hydroxyl in position 2 by treatment with propylbromide followed by benzylic bromination. The dimethoxy derivative **5g** results from 2,6-dimethoxytoluene **3** by nitration[14] and successive bromination. The benzylmesylate **5h** derives from 2,6-dimethylbenzoic acid **4** by nitration, selective reduction of the carboxyl group with benzyltriethylammonium borohydride-chlorotrimethyl-silane[15] and subsequent treatment of the benzylalcohol intermediate with methanesulphonyl chloride.

As shown in Scheme 2 the synthesis proceeds[9] with the alkylation of 8-hydroxyquinaldine with benzyl-bromides **5a-g** and benzylmesylate **5h** to afford benzyloxy-substituted quinolines **6a-h**. The methylthio-ethers **6i-k** derived from successive selective displacement of the appropriate chloro substituents by treatment with sodium methanethiolate. Subsequent reduction of the nitro group of **6a-k** with $SnCl_2$ dihydrate gives the intermediate amines, which are coupled with the acid chloride of phthaloylglycine. Subsequent N-alkylation of the amide nitrogen with methyl iodide affords the corresponding N-methylacetamides **7a-k**. Deprotection of **7a-k** with hydrazine monohydrate and acylation with appropriate acylating agents provides the desired quinolines **8a-o** listed in Table 2.

Scheme 2:

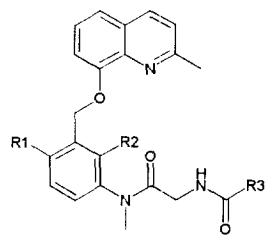


a) 8-hydroxyquinaldine, K_2CO_3, DMF, rt, 2 h; b) MeSNa, DMF, rt, 12 h; c) *1.* $SnCl_2$ x $2H_2O$, EE, reflux, 1 h; *2.* $PhthCH_2COCl$, DMAP, pyridine, 50 °C, 2 h; *3.* CH_3I, NaH, DMF, 50 °C, 4 h; d) *1.* H_2NNH_2 x H_2O, CH_2Cl_2, EtOH, reflux, 2 h; *2.* R3COCl, NEt_3, CH_2Cl_2, reflux, 1h *or* R3NCO, DMF, rt, 2h *or* $R3NH_2$, $(ImCO)_2O$, $EtN(iPr)_2$, DMF, rt, 4h.

As revealed in Table 2, the synthesized antagonists **8a-o** in the quinoline series exhibited nanomolar or better affinity towards the BK B_2 receptors on guinea pig ileum membranes. The antagonistic properties of **8a-o** could also be confirmed functionally by their high efficacy in the inhibition of the BK-induced contraction of isolated organ preparations from the guinea pig ileum and the rabbit jugular vein. From the

modifications of R1, R2 and R3 described here, those of R1 and R2 were more important for the potency of the antagonists than changes in R3. The best antagonists **8b**, **8d** and **8e** had two electron-withdrawing substituents R1 and R2 in the 2,6-position of the benzyloxy moiety of the quinolines, and had IC_{50}-values of 0.9, 0.7 and 1.2 nM, respectively. The exchange of one of these two R1/R2 substituents by an electron-donating group like methoxy, thiomethoxy or methyl[9c] in **8f-o** is associated with a significant loss in activity of one to two orders of magnitude. The least potent B_2 antagonist in the quinoline series is **8m**, having a methoxy group in position 2 and a thiomethoxy group in position 6. The affinity of **8i**, with a 2-propoxy group, is only slightly lower in comparison to **8e** or **8g** which suggests that in contrast to this electrostatic interaction, steric features seems to be of minor importance. Nevertheless, the only moderate B_2 receptor binding affinity of **8m** indicates that steric requirements for position 6 are more influential than those for position 2.

Table 1: *Quinolines*



	R1	R2	R3	B_2 [a]		EC_{50} or % inhibition [b]	
				IC_{50} [*nM*]	K_i [*nM*]	GPI [*M*]	RJV [*M*]
8a	-Cl	-CN	-NH-CH_2-CH_3	64.8	8.3	2.9×10^{-7}	10^{-5}: 66 %
8b	-Cl	-CN	-NH-$(CH_2)_4$-NH_2	0.9	0.1	3.5×10^{-7}	10^{-5}: 72 %
8c	-Cl	-CN	-NH-$(CH_2)_3$-CO_2H	25.7	2.9	4.0×10^{-7}	10^{-5}: 80 %
8d	-Cl	-CN	-CH=CH-C_6H_5-(*m*-OCH_3)	0.7	0.1	4.1×10^{-9}	10^{-5}: 78 %
8e	-Cl	-CN	-CH=CH-C_6H_5-(*p*-CF_3)	1.2	0.3	5.6×10^{-8}	10^{-5}: 82 %
8f	-OCH_3	-CN	-NH-CH_2-CH_3	53.8	6.0	4.5×10^{-7}	10^{-5}: 59 %
8g	-Cl	-OCH_3	-CH=CH-C_6H_5-(*p*-CF_3)	21.9	2.5	5.5×10^{-8}	2.8×10^{-8}
8h	-OCH_3	-Cl	-CH=CH-C_6H_5-(*p*-CF_3)	11.5	1.3	1.3×10^{-7}	2.6×10^{-7}
8i	-OCH_3	-OC_3H_7	-CH=CH-C_6H_5-(*p*-CF_3)	32.9	3.9	2.2×10^{-7}	10^{-5}: 82 %
8j	-OCH_3	-OCH_3	-CH=CH-C_6H_5-(*m*-CH_3)	81.3	9.2	*n.d.* [c]	10^{-5}: 68 %
8k	-OCH_3	-SCH_3	-CH=CH-3-Pyridyl-(6-NHAc)	5.2	0.6	5.9×10^{-8}	10^{-5}: 95 %
8l	-OCH_3	-SCH_3	-$(CH_2)_4$-CO_2CH_3	47.2	5.4	4.8×10^{-7}	10^{-5}: 55 %
8m	-SCH_3	-OCH_3	-CH=CH-C_6H_5-(*p*-CF_3)	393.0	45.4	1.1×10^{-6}	10^{-6}: 41 %
8n	-SCH_3	-SCH_3	-CH=CH-C_6H_5-(*p*-OCH_3)	56.9	6.3	6.6×10^{-7}	8.7×10^{-6}
8o	-CH_3	-CH_3	-CH=CH-C_6H_5-(*p*-CF_3)	11.8	1.3	*n.d.* [c]	10^{-5}: 81 %

a) IC_{50} and K_i for inhibition of specific binding of ^{3}H-BK to guinea pig ileum (GPI) membrane preparations; n = 3-8
b) EC_{50} for inhibition of BK-induced (4×10^{-8} M) contraction of isolated GPI and rabbit jugular vein (RJV); n = 6
c) Not determined

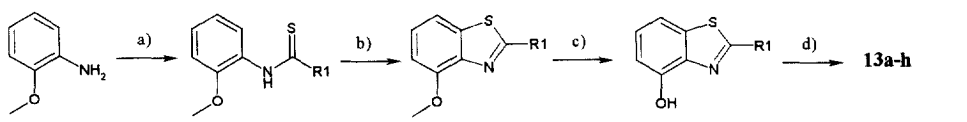
For the terminal group R3 a great variety of acyl substituents are tolerated indicating that this residue interferes with an receptor binding site less important for the affinity of the antagonists. However, the weaker binding affinity of **8a** and **8f** suggests that an ethylamino residue is obviously too small for an optimal interaction of the antagonists with the B_2 receptor. All other terminal residues (i.e. cinnamoyls as in **8d**, **8e**, **8g-j** and **8m-o**, amidobutylamine as in **8b**, and amidobutanoic acid as in **8c**) are well tolerated, indicating that modifications in this position could be used to adjust the physicochemical properties of the antagonists in this series towards the desired route of application without concomitant loss in binding affinity.

Accordingly to the recently published SAR studies of closely related series of antagonist on human B_2 receptors expressed in CHO cells by Fujisawa[9b,c], this high tolerance in the N-substituents of the glycine moiety seems to be restricted only to the guinea pig ileum B_2 receptor. They discovered that in this series of antagonists only compounds with an extended basic framework incorporating an N-terminal cinnamamide residue on the glycine moiety overcome the species differences in affinity between BK B_2 receptors in guinea pig ileums and humans resulting in highly potent antagonist of the human B_2 receptor.

Various attempts to modify the 3-N-methylamidobenzyloxy moiety[9] failed to produce antagonists of the BK B_2 receptor with an binding affinity comparable to this of the reported quinolines or the benzothiazoles listed in Table 2. This basic skeleton seems to be an essential structural requirement of antagonists to adopt the appropriate bioactive conformation.

The synthetic route to obtain the antagonists **13a-h** of the benzothiazole series is shown in Scheme 3. The 2-methyl- and 2-phenyl-substituted 4-hydroxybenzothiazole moieties **12a-b** are synthesized from 2-methoxy-aniline **9** in a 5-step procedure.[16] In the first step of this procedure, amine **9** is acylated and the resulting amides are converted to the corresponding thioamides **10a-b**. Radical-induced cyclization of **10a-b** with potassium hexacyanoferrate(III) gave the 4-methoxy-substituted benzothiazoles **11a-b**. Ether cleavage of intermediates **11a-b** gave the desired 4-hydroxybenzothiazoles **12a-b** suitable for further modifications. The 4-hydroxybenzothiazole **12c** without a substituent in position 2 was synthesized according to a procedure known from the literature.[17] These three 4-hydroxybenzothiazoles are then used for further conversions towards the antagonists **13a-h** listed in Table 2 analogously to the procedures described for the antagonists of the quinoline series (Scheme 2).

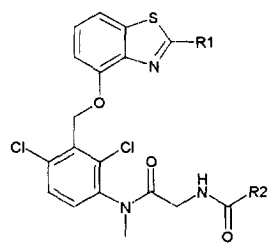
Scheme 3:



a) *1.* CH_3COCl or PhCOCl, NEt_3, CH_2Cl_2, 0-10 °C, 2h; *2.* P_2S_{10}, n-butyl acetate, reflux, 5 h; b) $K_3Fe(CN)_6$, EtOH, NaOH, H_2O, 90 °C, 5 h; c) HI, P_{red}, CH_3CO_2H, reflux, 10 h; d) see Scheme 2.

As shown in Table 2, very potent BK B_2 receptor antagonists derived also in the benzothiazole series. In comparison to the quinoline series, both the binding affinity towards the B2 receptor as well as the functional response for the 2-methyl benzothiazoles **13b-g**, are only slightly decreased. Like for the quinoline antagonists a large variety of terminal R3-substituents are tolerated in the benzothiazole series, too. However, a dramatic drop in binding affinity and in the functional response is observed for **13a** in which the 2-methyl benzothiazole moiety of **13b-g** is replaced by a benzothiazole unsubstituted in position 2. The replacement of the 2-methyl substituted benzothiazole moiety of **13b-g** by a 2-phenyl substituted benzothiazole as in **13h** results in a total loss in binding affinity. These findings substantiate that a 2-methyl group is an essential requirement for highly efficient antagonism of the BK B_2 receptor in the benzothiazole series.

Table 2: *Benzothiazoles:*



	R1	R2	B_2 [a]		EC_{50} or % inhibition [b]	
			IC_{50} [*nM*]	K_i [*nM*]	GPI [*M*]	RJV [*M*]
13a	-H	-CH=CH-C_6H_5-(*p*-CH_3)	1350	160	1.3×10^{-6}	10^{-5}: 17 %
13b	-CH_3	-CH=CH-C_6H_5-(*p*-CH_3)	14.2	1.8	2.3×10^{-8}	6.6×10^{-8}
13c	-CH_3	-CH=CH-C_6H_5-(*p*-CF_3)	23.0	2.8	1.0×10^{-7}	7.6×10^{-8}
13d	-CH_3	-CH=CH-C_6H_5-(*m*-OCH_3)	10.3	1.3	5.4×10^{-8}	1.8×10^{-7}
13e	-CH_3	-CH=CH-(2-furyl)	29.8	3.4	*n.d.* [c]	7.8×10^{-7}
13f	-CH_3	-CH=CH-CH=CH_2	26.2	3.1	2.6×10^{-7}	5.2×10^{-6}
13g	-CH_3	-O-CH_2-C_6H_5	77.8	9.1	*n.d.* [c]	10^{-5}: 75 %
13h	-C_6H_5	-CH=CH-C_6H_5-(*p*-CH_3)	11000	1300	2.0×10^{-5}	10^{-5}: 15 %

a) - c): see legend of table 1

In summary, novel series of O-substituted 8-quinolines and 4-benzothiazoles as potent non-peptide antagonists of the BK B_2 receptor based on lead structures delineated by Fujisawa were discovered. The potency of the quinolines were found to be slightly superior to those found for the corresponding benzothiazoles. The most potent antagonist **8d** is derived from the quinoline series and exhibits an IC_{50}-value of 0.7 nM and an EC_{50}-value of 4.1 nM. The described compounds may serve as valuable tools to further aid in the understanding of the BK B_2 receptor.

Acknowledgement: The authors wish to thank K.-H. Herget, N. Hörl, M. Mollath, and N. Wöllmer for their technical assistance.

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