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Bioorganic & Medicinal Chemistry Letters 14 (2004) 3049–3052
Bioorganic & Medicinal Chemistry Letters

Synthesis and pharmacological evaluation of piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinoline derivatives as novel specific bradycardic agents

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Received 21 March 2004; revised 12 April 2004; accepted 13 April 2004

Abstract—A series of piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinoline derivatives were synthesized, and their bradycardic activities were investigated in the isolated right atria of guinea pigs and in conscious rats. These efforts identified the achiral compound **2f**, which exhibited potent and long-lasting bradycardic activity with minimal effects on mean blood pressure in conscious rats.

The reduction of sinus heart rate (HR) is of major interest in the treatment of cardiac ischemia. Myocardial ischemia results from an imbalance between oxygen supply and demand. HR reduction can correct this imbalance by improving myocardial perfusion and reducing myocardial oxygen demand.[1,2] A reduction in HR can be achieved by β-adrenoreceptor antagonists[3] and certain calcium-channel blockers.[4] However, these agents can cause concomitant negative inotropic and hypotensive effects, which are potentially deleterious during ischemia.[5] Therefore, agents that reduce HR without negative inotropic and hypotensive effects, namely 'specific bradycardic agents'[6] are predicted to be more beneficial in the treatment of cardiac ischemia.

During the past few decades, two specific bradycardic agents, Zatebradine[7] and the related compound Ivabradine,[8] have been developed and subjected to clinical testing for the treatment of ischemic heart disease (Fig. 1).

In our present program, which aims to search for novel specific bradycardic agents, the 2-(3-piperidino)-1,2,3,4-tetrahydroisoquinoline derivative **1** has been shown to exhibit potent specific bradycardic activities that are comparable with those of Zatebradine.[9] Therefore, to further investigate the structure–activity relationship (SAR) of compound **1**, we designed compound **2a** by opening the existing piperidine ring of **1** and joining the nitrogen to the β-carbon with a three-carbon linker (Fig. 2). Compound **2a** was found to be equipotent to Zatebradine both in vitro and in vivo (Table 1 and Fig. 3). To examine the SAR of compound **2a**, the compounds described by Formula **I** were synthesized and their biological activities were evaluated. The results of the SAR study on this series of piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinoline derivatives are reported here.

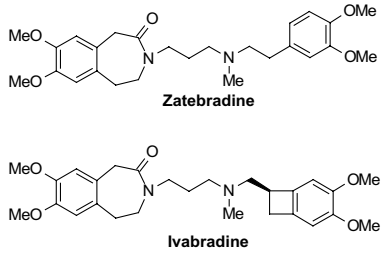

Figure 1.

The preparation of the piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinoline derivatives is outlined in Scheme 1. Condensation of 3-pyridylethanol (**3**) with sesamol, followed by reduction of the pyridine ring, produced **7c**.

Keywords: Cardiac disease; Myocardial ischemia; Bradycardic agent; Zatebradine.
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doi:10.1016/j.bmcl.2004.04.031

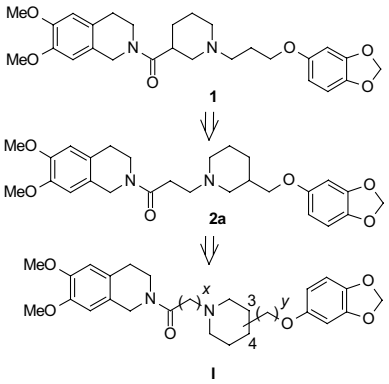


Figure 2.

Alkylation of sesamol with the corresponding pyridylalkylhalides **4a**,**b**, and **4c**, followed by reduction of the pyridine ring, yielded **7a**,**d**, and **7h**, respectively. Condensation of **5a**,**b**, and **5c** with sesamol, followed by deprotection, afforded **7b**,**f**, and **7e**, respectively. Alkylation of sesamol with **6**,[10] followed by deprotection, produced **7g**. Acylation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**) with 2-chloroacetylchloride provided **9a**. Compounds **9b** and **9c** were prepared in an analogous manner to **9a**, except that 2-chloroacetylchloride was replaced with acryloyl chloride and 4-chlorobutyryl chloride, respectively. Compounds **10** and **11** were obtained by alkylation of **7a** with the corresponding alkyl halides **9a** and **9c**, respectively. Compounds **2a**–**h** were accessed by alkylation of **7a**–**h**, respectively, with **9b**.

Evaluation of the bradycardic activity exhibited by the synthesized compounds was performed in vitro in the isolated right atria of guinea pigs. The EC_{30} value, which is defined as the concentration of the compound that produces a 30% reduction in the initial spontaneous beating rate, was determined for each compound using linear regression.[9] The effects on HR of the compounds with high in vitro activities were examined in conscious rats following oral administration.[9]

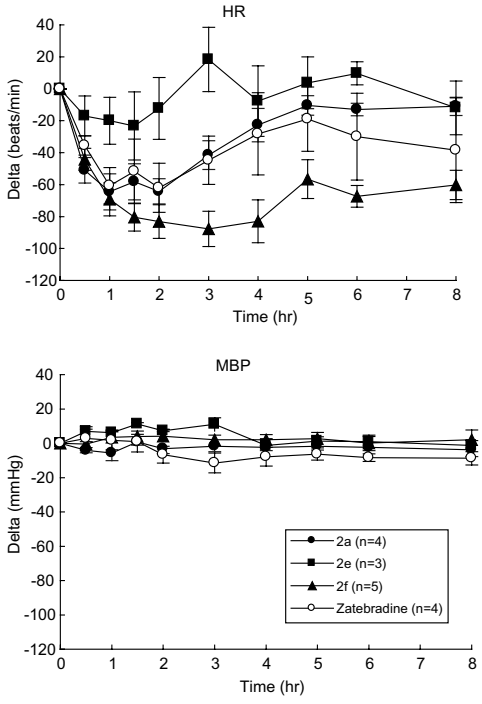
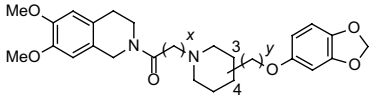


Figure 3. Effects of piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinoline derivatives **2a**,**e**, and **2f** on heart rate (HR) and mean blood pressure (MBP) in consious rats. Compounds were orally administrated at time zero. Each point represents mean ± SEM from three to five experiments.

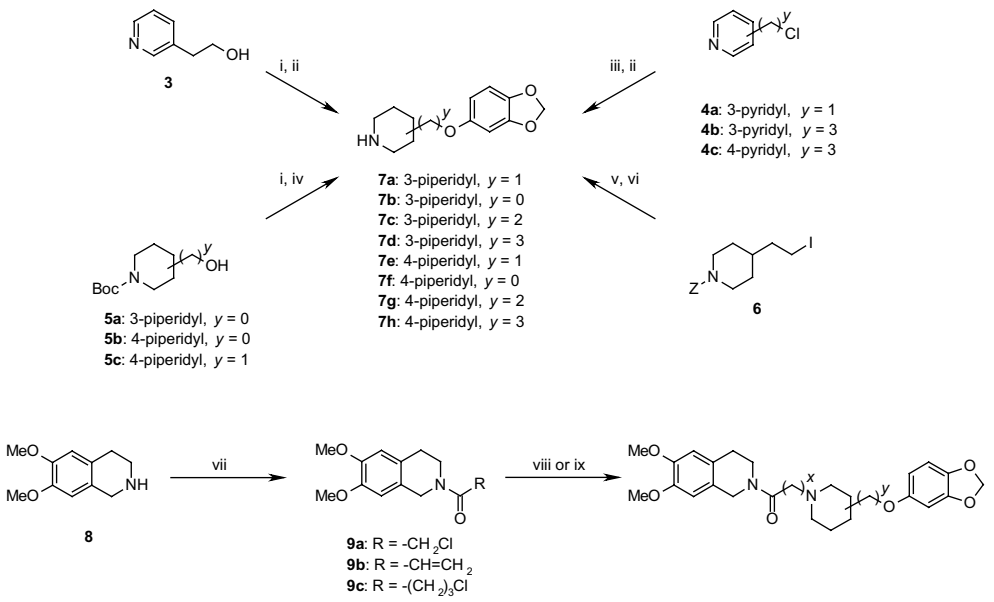
Our previous SAR studies indicated that the 1,2,3,4-tetrahydroisoquinoline ring, the basic nitrogen of the piperidine ring and the terminal phenyl ring are all essential for the production of potent bradycardic activity.[9,11] The SAR study of compound **1** confirmed that the spatial orientation of these three essential components plays a crucial role in bradycardic activity.[9] We therefore designed compound **2a** by opening the existing piperidine ring of **1** and joining the nitrogen to the β-carbon with a three-carbon linker, which maintained the spatial orientation between these three parts.

Table 1. Bradycardic activities of piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinolin derivatives **2a**–**h**, **10**, and **11**



Compounds	*x*	*y*	Position	EC_{30}, μM[a]
1				0.37 ± 0.02 (3)
2a	$-(CH_2)_2-$	$-CH_2-$	3	0.17
10	$-CH_2-$	$-CH_2-$	3	1.17
11	$-(CH_2)_3-$	$-CH_2-$	3	0.85
2b	$-(CH_2)_2-$	Bond	3	3.03
2c	$-(CH_2)_2-$	$-(CH_2)_2-$	3	0.34
2d	$-(CH_2)_2-$	$-(CH_2)_3-$	3	0.39
2e	$-(CH_2)_2-$	$-CH_2-$	4	0.47
2f	$-(CH_2)_2-$	Bond	4	0.44
2g	$-(CH_2)_2-$	$-(CH_2)_2-$	4	0.45
2h	$-(CH_2)_2-$	$-(CH_2)_3-$	4	0.62
Zatebradine				0.26 ± 0.05 (7)

[a] EC_{30} is the concentration required to produce a 30% reduction from the initial beat rates in isolated guinea pigs right atria. EC_{30} values are shown with ± SE (number of determinations) where more than three determinations were made. Otherwise results based on two determinations are given.



Scheme 1. Synthesis of compounds **2a**–**h**, **10**, and **11**. Reagents and conditions: (i) sesamol, PPh_3, DEAD, THF; (ii) H_2, PtO_2, AcOH; (iii) sesamol, K_2CO_3, DMF, Δ; (iv) 4 M HCl/AcOEt; (v) sesamol, K_2CO_3, CH_3CN, Δ; (vi) H_2, 10% Pd/C, AcOH; (vii) RCOCl, Et_3N, THF; (viii) **7**, K_2CO_3, CH_3CN, Δ; (ix) **7**, toluene, Δ.

As a result, the parent compound **2a** exhibited potent bradycardic activity that was comparable to that of Zatebradine both in vitro and in vivo (Table 1 and Fig. 3). Encouraged by these results, further SAR studies of **2a** were conducted in order to establish the effect of the linkers between the piperidine nitrogen atom and the carbonyl moiety (*x*-linker), and between the piperidine C-3 or C-4 position and the oxygen atom (*y*-linker).

In the 3-piperidyl series of analogues with a one-carbon *y*-linker, shortening (**10**) or extending (**11**) the *x*-linker resulted in a fivefold to sevenfold loss of in vitro activity. These results indicated that the optimal composition of the *x*-linker was an ethyl chain. Among the analogues that contained two-carbon *x*-linkers, shortening the *y*-linker alkyl chain drastically reduced the bradycardic activity (**2b**). By contrast, extensions of the *y*-linker alkyl chain of up to three carbon atoms were well tolerated (**2c** and **2d**). These results indicated that there might be sufficient variability for further structural manipulations in the *y*-linker portion.

We investigated achiral analogues in which the *y*-linker was attached to the C-4 position of the piperidine ring because the 3-piperidyl series would confer considerable disadvantages associated with the preparation of a single enantiomer, either by stereoselective synthesis or resolution.

Fortunately, the 4-piperidyl derivative **2e** was equipotent to the corresponding 3-piperidyl derivative **2a**, which was probably the result of the variability of the *y*-linker portion. Encouraged by the potency of compound **2e**, we conducted further SAR studies on the 4-piperidyl derivatives. In contrast to the 3-piperidyl derivatives, shortening of the alkyl chain of the *y*-linker to $y = 0$ (**2f**) was well tolerated. Furthermore, in the 4-piperidyl series of analogues with a two-carbon *x*-linker, chain extensions of up to three carbon atoms were well tolerated (compounds **2g** and **2h**).

On the basis of the potent bradycardic activity displayed in the isolated right atria of guinea pigs, and as a result of their achiral nature, **2e** and **2f** were subjected to further pharmacological evaluation as the representatives in the 4-piperidyl series (**2e**–**h**). These compounds were administrated orally (10 mg/kg) to conscious rats, and the effects on HR and mean blood pressure (MBP) were examined (Fig. 3). Although the 4-piperidyl derivative **2e** was equipotent to the corresponding 3-piperidyl derivative **2a** in vitro, it was significantly less active in vivo. Compound **2e** reduced spontaneous HR by less than -20.0 ± 14.7 beats/min ($-5.28 \pm 2.59\%$ from initial value). By contrast, compound **2f** reduced spontaneous HR by as much as -87.8 ± 11.0 beats/min ($-23.5 \pm 2.64\%$ from initial value) with minimal influence on MBP (2.00 ± 2.73 mmHg, $2.12 \pm 2.68\%$ from initial value). Furthermore, its bradycardic effect was sustained for more than 8 h. These results suggest that **2f** is better absorbed and has increased metabolic stability compared with **2e**. In fact, **2f** showed comparable potency and increased duration of action compared with Zatebradine.

In conclusion, a series of piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinoline derivatives were synthesized and evaluated. These efforts identified the achiral compound **2f**, which showed potent bradycardic activity that was comparable to lead compound **1**. Compound **2f** also showed potent and long-lasting bradycardic activity with a minimal influence on MBP in conscious rats following oral administration. On the basis of its pharmacological properties and structural simplicity (no chiral center), compound **2f** represents a novel lead for

the continuous development of specific bradycardic agents.

Acknowledgements

The authors deeply acknowledge Dr. Minoru Okada for helpful support for preparing this manuscript, and also grateful to the staff of the Division of Analytical Science Laboratories for the elemental analysis and spectral measurement.

References and notes

1. Harron, D. W. G.; Jady, K.; Riddell, J. G.; Shanks, R. G. *J. Cardiovasc. Pharmacol.* **1982**, *4*, 213.
2. Guth, B. D.; Heusch, G.; Seitelberger, R.; Matsuzaki, M.; Ross, J. *Eur. Heart J.* **1987**, *8*, 61.
3. Buckberg, G. D.; Fixler, D. E.; Archie, J. P.; Hoffman, J. I. E. *Circ. Res.* **1972**, *30*, 67.
4. Buckberg, G. D.; Fixler, D. E.; Archie, J. P.; Henney, R. P.; Hoffman, J. I. E. *Cardiovasc. Res.* **1975**, *9*, 1.
5. (a) Opie, L. H. *Cardiovasc. Drugs Ther.* **1989**, *3*, 257; (b) Kern, M. J.; Deligonul, U.; Labovitz, A. *Am. Heart J.* **1989**, *118*, 361.
6. Kobinger, W.; Lillie, C. *Eur. Heart J.* **1987**, *8* (Suppl. L), 7.
7. (a) Reiffen, M.; Eberlein, W.; Muller, P.; Psiorz, M.; Noll, K.; Heider, J.; Lillie, C.; Kobinger, W.; Luger, P. *J. Med. Chem.* **1990**, *33*, 1496; (b) Goethals, M.; Raes, A.; von Bogaert, P. P. *Circulation* **1993**, *88*, 2389.
8. (a) Thollon, C.; Cambarrat, C.; Vian, J.; Prost, J.; Peglion, J. L.; Vilain, J. P. *Br. J. Pharmacol.* **1994**, *112*, 37; (b) Thollon, C.; Bidouard, J.; Cambarrat, C.; Lesage, L.; Reure, H.; Delescluse, I.; Vian, J.; Peglion, J. L.; Vilain, J. P. *Eur. J. Pharmacol.* **1997**, *339*, 43.
9. Kubota, H.; Watanabe, T.; Kakefuda, A.; Masuda, N.; Wada, K.; Ishii, N.; Sakamoto, S.; Tsukamoto, S. *Bioorg. Med. Chem.* **2004**, *12*, 871.
10. Grumel, V.; Merour, J. Y.; Lesur, B.; Giboulot, T.; Frydman, A.; Guillaumet, G. *Eur. J. Med. Chem. Chim. Ther.* **2002**, *37*, 45.
11. (a) Kubota, H.; Watanabe, T.; Kakefuda, A.; Masuda, N.; Wada, K.; Ishii, N.; Sakamoto, S.; Tsukamoto, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2155; (b) Kubota, H.; Kakefuda, A.; Watanabe, T.; Ishii, N.; Wada, K.; Masuda, N.; Sakamoto, S.; Tsukamoto, S. *J. Med. Chem.* **2003**, *46*, 4728.