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(±)-2-(3-Piperidyl)-1,2,3,4-tetrahydroisoquinolines as a New Class of Specific Bradycardic Agents

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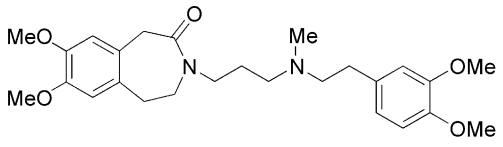
Abstract—A series of (±)-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinolines were prepared and their bradycardic activities were examined in isolated guinea-pigs' right atria and in anesthetized rats. Modifications on the benzyl moiety of the parent compound, **1**, led to the identification of compound **11e** as a potent and specific bradycardic agent.

Introduction

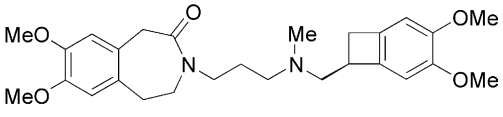
Myocardial ischemia always results from an imbalance between supply and demand of oxygen. Since heart rate (HR) is a major determinant of myocardial oxygen consumption,[1] reduction in HR is useful in treating ischemic heart diseases.[2] Reduction in HR can be achieved by β-adrenoreceptor antagonists[3] or certain calcium channel blockers.[4] However, these agents may cause concomitant negative inotropic and hypotensive effects which are potentially deleterious during ischemia.[5] Therefore, agents which reduce HR without negative inotropic and hypotensive effects, namely 'specific bradycardic agents'[6] are expected to be more beneficial in treating ischemic heart diseases.

Recent research efforts have yielded two specific bradycardic agents, Zatebradine[7] and its related compound, Ivabradine[8] (Fig. 1). They have undergone clinical testing in ischemic heart diseases patients.

In our program searching for novel specific bradycardic agent, (±)-2-(1-benzyl-3-piperidyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1**, Fig. 1) was found to show good bradycardic activities.[9] To improve its potency, we attempted modification of the benzyl moiety of **1** and examined its effects on the analogues' bradycardic activities in isolated guinea-pigs' right atria and in anesthetized rats. This provided the novel compound **11e** showing a potent and specific bradycardic activity.



Zatebradine



Ivabradine

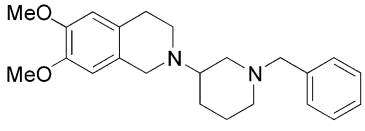


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Figure 1.

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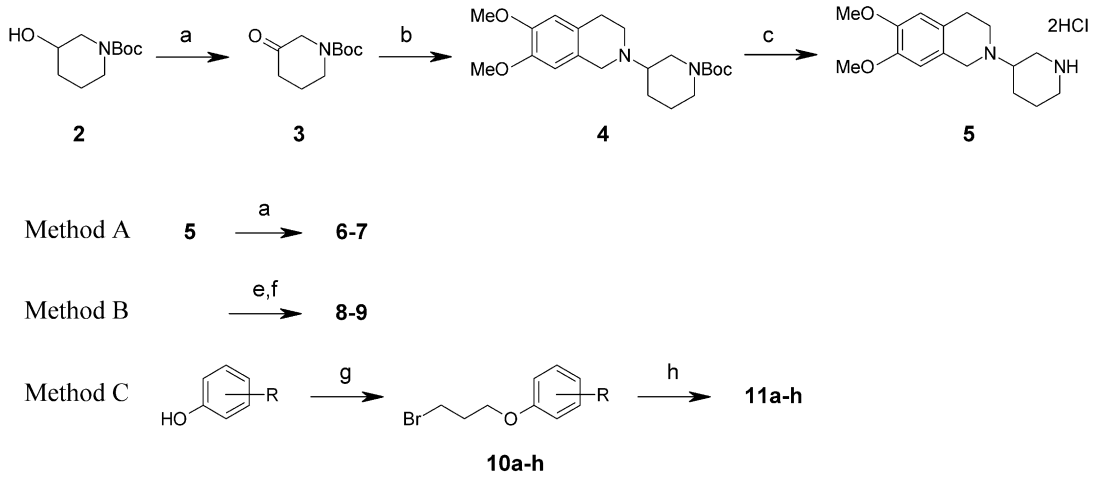


Scheme 1. Conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −70 °C; (b) 6,7-dimethoxy-1,2,3,4- tetrahydroisoquinoline, $NaBH(OAc)_3$, AcOH, THF (82% from **2**); (c) 4 N HCl (g) /AcOEt, MeOH (50%); (d) 2-phenylacetaldehyde or 3-phenylpropionaldehyde, $NaBH(OAc)_3$, AcOH, $Cl(CH_2)_2Cl$ (12 and 61%); (e) 4-phenylbutyric acid or 5-phenylvaleric acid, EDC·HCl, HOBt, $Cl(CH_2)_2Cl$; (f) $LiAlH_4$, THF, reflux (53 and 66% from **5**); (g) 1,3-dibromopropane, K_2CO_3, CH_3CN, 80 °C (62–90%); (h) **5**, K_2CO_3, CH_3CN, 80 °C (11–73%).

Chemistry

The target compounds were prepared by coupling of amine, **5**, which was obtained from **2** in three steps, with arylalkyl or aryloxyalkyl components by three general methods, Method A, B, and C shown in Scheme 1.[10] Compounds **6–9** were synthesized by reductive alkylation of **5** with aldehydes (Method A), or by acylation of **5** with carboxylic acids followed by reduction with $LiAlH_4$ (Method B). Compounds **11a–h** were prepared by alkylation of **5** with various 3-arylokypropyl bromides, **10a–h**,[11] which were obtained from the corresponding phenols by treating with excess 1,3-dibromopropane (Method C).

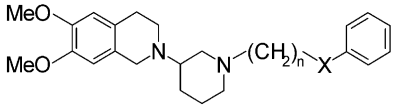
Results and Discussion

The bradycardic activities of synthesized compounds were assessed in isolated guinea-pigs' right atria (in vitro),[12] and in urethane-anesthetized rats (in vivo).

Initially, we examined the effects of modifying the tether linking between the piperidine ring and the terminal aromatic ring of **1** (Table 1). Among the phenylalkyl derivatives **6–9** ($n = 1$–4; $X = CH_2$), the butylene analogue **8** ($n = 3$) showed the most potent in vitro activity, and it was more potent than **1**. Substitution of the benzylic methylene of **8** by an oxygen atom (the 3-oxypropyl analogue **11a**) maintained in vitro activity. In anesthetized rats, compound **11a** reduced HR by 40%, which was potent than the benzyl analogue **1**, whereas compound **8** reduced HR by only 23%. Because of good activities of **11a** both in vitro and in vivo, we next studied the effects of modifying the terminal aromatic ring of **11a** (Table 2).

Both of the 4-methoxy analogue **11b** and the 3,4-dimethoxy analogue **11c** showed similar in vitro activity and equivalent or improved in vivo activity compared to **11a**. The 3,4,5-trimethoxy analogue **11d** exhibited weaker activity than **11a**. The 3,4-methylenedioxy analogue **11e** showed more potent activities than **11a** both

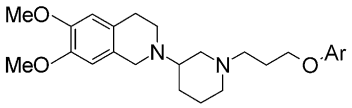
Table 1. The bradycardic activities of (±)-6,7-dimethoxy-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinolines (**6–9** and **11a**)

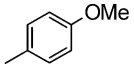
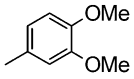
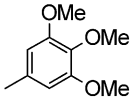
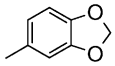
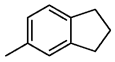
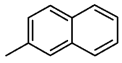
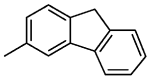


Compd	*n*	X	Right atria EC_{30},[a] μM	Anesthetized rats % change in HR[b] at 3 mg/kg iv	Method	Formula
1	0	CH_2	0.83	−33	A	$C_{23}H_{30}N_2O_2{\cdot}2HCl{\cdot}0.5H_2O$
6	1	CH_2	2.2	N.T.[c]	A	$C_{24}H_{32}N_2O_2{\cdot}2HCl{\cdot}1.8H_2O$
7	2	CH_2	1.2	N.T.[c]	A	$C_{25}H_{34}N_2O_2{\cdot}2(CO_2H)_2{\cdot}H_2O$
8	3	CH_2	0.54	−23	B	$C_{26}H_{36}N_2O_2{\cdot}2(CO_2H)_2{\cdot}H_2O$
9	4	CH_2	1.3	N.T.[c]	B	$C_{27}H_{38}N_2O_2{\cdot}2(CO_2H)_2$
11a	3	O	0.43	−40	C	$C_{25}H_{34}N_2O_3{\cdot}2(CO_2H)_2{\cdot}H_2O$
Zatebradine			0.26	−47		

[a]The concentration required to produce a 30% reduction from the initial spontaneous beat rates in isolated guinea-pigs' right atria as mean from at least two experiments.
[b]Percentage change from the initial value in urethane-anesthetized rats as mean from at least two experiments.
[c]Not tested.

Table 2. The bradycardic activities of (±)-6,7-dimethoxy-2-[1-(3-aryloxypropyl)-3-piperidyl]-1,2,3,4- tetrahydroisoquinolines (**11b–h**)



Compd	Ar	Right atria EC_{30},[a] μM	Anesthetized rats % change in HR[b] at 3 mg/kg iv	Method	Formula
11a	Ph	0.43	−40		
11b		0.39	−40	C	$C_{26}H_{36}N_2O_4 \cdot 2(CO_2H)_2 \cdot H_2O$
11c		0.38	−47	C	$C_{27}H_{38}N_2O_5 \cdot 2HCl \cdot 0.6H_2O$
11d		1.5	N.T.[c]	C	$C_{28}H_{40}N_2O_6 \cdot 2(CO_2H)_2 \cdot H_2O$
11e		0.25	−47	C	$C_{26}H_{34}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$
11f		0.66	−38	C	$C_{28}H_{38}N_2O_3 \cdot 2HCl \cdot 0.6H_2O$
11g		0.84	−23	C	$C_{29}H_{36}N_2O_3 \cdot 2HCl \cdot 0.6H_2O$
11h		4.1	N.T.[c]	C	$C_{32}H_{38}N_2O_3 \cdot 1.5HCl \cdot 0.5H_2O$

[a]See the corresponding footnotes of Table 1.
[b]See the corresponding footnotes of Table 1.
[c]See the corresponding footnotes of Table 1.

in vitro and in vivo, with an EC_{30} value of 0.25 μM and a HR reduction by 47%, being comparable to Zatebradine. In contrast, the indane analogue **11f** and the naphthalene analogue **11g** had 3-4-fold less in vitro potency than **11e**. The fluorene analogue **11h** showed considerably poor activity.

In anesthetized rats, compound **11e**, which was one of the most potent bradycardic agents in this series, had minimal influence on mean blood pressure even at a dose of 10 mg/kg iv (5.5% decrease from the initial value). This result proved that **11e** was a specific bradycardic agent. Further characterization on electrophysiological studies in guinea-pigs' sino-atrial node revealed that **11e** significantly decreased the rate of Phase 4 slow depolarization (dV/dt4; 56.6% decrease from control at 1 μM) without change in the maximal diastolic potential (MDP) at the same concentration. Since the I_f channels are thought to be the channels responsible for Phase 4 depolarization,[13] the bradycardic effects of **11e** may be reffered to its effect on the I_f channels.

Conclusion

We have discovered that (±)-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinolines have good bradycardic activities. Among them, compound **11e** showed potent bradycardic activities with minimal influence on mean blood pressure in anesthetized rats. Compound **11e** is a novel specific bradycardic agent which would be beneficial in treating ischemic heart diseases.

Acknowledgements

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References and Notes

1. (a) Laurent, D.; Bolene-Williams, C.; Williams, F. L.; Katz, N. L. *Am. J. Physiol.* **1956**, *185*, 355. (b) Sonnenblick, F. H.; Ross, J.; Braunwald, E. *Am. J. Cardiol.* **1968**, *32*, 328.
2. Kendall, M. J.; Lynch, K. P.; Hjalmarson, A.; Kjekshus, J. *Ann. Intern. Med.* **1995**, *123*, 358.
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. Kakefuda, A.; Watanabe, T.; Taguchi, Y.; Masuda, N.; Tanaka, A.; Yanagisawa, I. *Chem. Pharm. Bull.* **2003**, *51*, 390.
10. Satisfactory analytical data were obtained for all the target compounds. Example, **11e:** colorless powder; mp 167–169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.84–2.01 (2H, m), 2.23–2.33 (2H, m), 2.94 (2H, brs), 3.25–3.53 (8H, m), 3.70–3.73 (1H, m), 3.73 (3H, s), 3.74 (3H, s), 3.91–4.02 (4H, m), 4.33–4.43 (2H, m), 5.96 (2H, s), 6.44 (1H, dd, $J = 8.8$, 2.4 Hz), 6.65 (1H, d, $J = 2.4$ Hz), 6.76–6.83 (3H, m), 11.69–12.00 (2H, m); MS (FAB) m/z 455 (MH^+); Anal. calcd for $C_{26}H_{34}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$: C 58.21, H 6.95, N 5.22, Cl 13.22; found: C 58.18, H 7.06, N 5.20, Cl 13.03.
11. For example, see: (a) Katakami, T.; Yokoyama, T.; Miyamoto, M.; Mori, H.; Kawauchi, N.; Nobori, T.; Sannohe, K.; Kaiho, T. *J. Med. Chem.* **1992**, *35*, 3325. (b) Lunney, E. A.; Hagen, S. E.; Domagala, J. M.; Humblet, C.; Kosinski, J.; Tait, B. D.; Warmus, J. S.; Wilson, M.; Ferguson, D.; Hupe, D.; Tummino, P. J.; Baldwin, E. T.; Bhat, T. N.; Liu, B.; Erickson, J. W. *ibid* **1994**, *37*, 2667. (c) Dodic, N.; Dumaitre, B.; Daugan, A.; Pianetti, P. *ibid* **1995**, *38*, 2418.
12. Perez, O.; Gay, P.; Franqueza, L.; Carron, R.; Valenzuela, C.; Delpon, E.; Tamargo, J. *Br. J. Pharmacol.* **1995**, *115*, 787.
13. (a) DiFrancesco, D. *J. Physiol.* **1991**, *434*, 23. (b) DiFrancesco, D. *Ann. Rev. Physiol.* **1993**, *55*, 451.