Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 2705–2707

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Determination of the Relative and Absolute Stereochemistry of a Potent and α_{1A}-Selective Adrenoceptor Antagonist

Bharat Lagu,[a,*] John M. Wetzel,[a] Carlos Forray,[b] Michael A. Patane[c] and Mark G. Bock[c]

[a]*Department of Chemistry, Synaptic Pharmaceutical Corporation, 215 College Road, Paramus, NJ 07652, USA*
[b]*Department of Pharmacology, Synaptic Pharmaceutical Corporation, 215 College Road, Paramus, NJ 07652, USA*
[c]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*

Received 8 June 2000; accepted 5 September 2000

Abstract—The binding affinities and selectivities of antagonists **1**–**4** for the α_{1A}-adrenoceptor are dependent on the stereochemical orientation of the groups at the C-4 and C-5 positions of the oxazolidinone ring. The unambiguous assignment of the relative and absolute configurations of the diastereomers of SNAP 7915 (**1**) is reported. © 2000 Elsevier Science Ltd. All rights reserved.

We have recently reported the discovery of the structurally novel, orally bioavailable α_{1A}-adrenoceptor antagonist **1** (SNAP 7915) as a potential treatment for benign prostatic hyperplasia (BPH).[1] Of the four possible diastereomers with this structure (viz. **1**–**4**, Fig. 1), one of them (**1**) binds the α_{1A}-adrenoceptor with the highest affinity and selectivity in radioligand binding assays[2] as summarized in Table 1. We therefore sought to unambiguously assign the relative and absolute configurations of compounds **1**–**4**.

Two workable synthetic routes were devised to access the oxazolidinone ring system. The first approach (Scheme 1, eq 1) involved the addition of imine **5** to acetaldehyde, affording intermediate **6**, which after deprotection provided amino alcohol **7**.[3] Compound **7** was then converted to oxazolidinone **8** via a two-step sequence of *N*-acylation and cyclization with base.[1]

In the alternative route (Scheme 1, eq 2), the dianion of commercially available 3,4-difluorophenylacetic acid **9** was treated with acetaldehyde to obtain the β-hydroxy acid **10** as a 1:1 mixture of *cis* (*erythro*) and *trans* (*threo*) isomers. The crude product was then transformed into the corresponding oxazolidinones **8a**–**b** in excellent yield via Curtius rearrangement.[4] The *cis* and *trans* diastereomers (**8a** and **8b**) were separated by flash column chromatography or preparative thin-layer chromatography (first isomer, **8b**: R_f 0.6, second isomer, **8a**: R_f 0.5; hexane:EtOAc 3:1). The separation of the enantiomers was accomplished by preparative chiral HPLC.[5]

The relative configurations (*cis*/*trans*) of **8a** and **8b** were assigned on the basis of ^{1}H NMR analysis of the respective *p*-nitrophenyloxycarbonyl derivatives **11a** and **11b** (Scheme 1, eq 2), as shown in Figure 2. For compound **11b**, an NOE was observed between the protons of the C-5 methyl group and the proton at C-4. No NOE was observed between the protons at the C-4 and C-5 positions of this isomer, which was thus assigned *trans* stereochemistry. For oxazolidinone **11a**, no NOE was observed between the protons of the C-5 methyl group and the proton at C-4. However, an NOE was observed between the protons at the C-4 and C-5 positions, leading us to assign this isomer *cis* stereochemistry. The vicinal coupling constants of the C-4 protons of **11a** ($J = 7.8$ Hz) and **11b** ($J = 5.1$ Hz) are also consistent with the values reported for similar oxazolidinones, and were thus helpful in making the stereochemical assignments.[6]

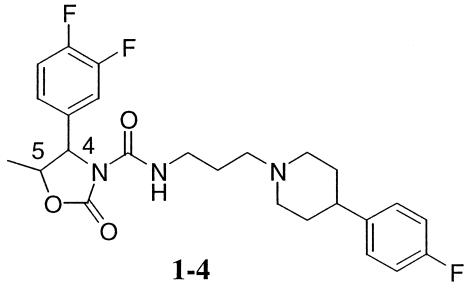
In order to assign the absolute configurations at the stereogenic centers of the oxazolidinone rings, a new synthetic route (Scheme 2) was designed which employed an enantiomerically pure substrate derived from the chiral pool. Commercially available (*S*)-(+)-methyl lactate was converted into amide **13** according to the method of Martin et al.[7] Treatment of compound **13** with 3,4-difluorophenyllithium yielded ketone **14** as the sole product, which was then converted to oxime **15**.

*Corresponding author at present address: R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ, USA. Tel.: +1-908-704-4291; fax: +1-908-526-6469; e-mail: blagu@prius.jnj.com

0960-894X/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(00)00524-2

Reduction of the oxime with $LiAlH_4$, *N*-acylation, and base induced cyclization provided oxazolidinone isomers **17** and **18**, which were separated by flash column chromatography. The enantiomeric purity of these isomers was confirmed by chiral HPLC analysis and their relative configurations were assigned by comparison of their ^1H NMR spectra with those of the racemic isomers **8a** and **8b**. To complete the analysis, oxazolidinones **17** and **18** were converted into products **1** and **4**, respectively. As the absolute configuration at C-5 is (*S*), the C-4 center in *trans* compounds **1** and **17** also has the (*S*) configuration. Accordingly, the absolute configurations for the stereogenic centers in the *cis* compounds **4** and **18** are assigned as (4*R*,5*S*). Compounds **2** and **3**, the enantiomers of **1** and **4**, thus have the (4*R*,5*R*) and (4*S*,5*R*) stereochemistry, respectively.

Among the four diastereomers in Figure 1, compound **1** clearly stood out on the basis of its high binding affinity and selectivity for the cloned human α_{1A}-adrenoceptor. This compound was also found to be a potent antagonist in a number of in vitro and in vivo functional assays, and exhibited a long plasma half-life (6 h in rat and >12 h in dog) and good oral bioavailability (25% in rat and 74% in dog).[1] The present study has provided an unambiguous stereochemical assignment of **1** and its isomers, and three methods for its synthesis. These results will facilitate the further study of **1** and its analogues as potential therapeutics for BPH.



1-4

Figure 1.

^1H NMR data for selected compounds. Spectra were recorded at 300 MHz in $CDCl_3$. Chemical shifts are referenced to TMS.

8a (*cis*): δ 0.96 (d, $J=6.6$ Hz, 3H), 4.91 (d, $J=8.1$ Hz, 1H), 4.99 (dq, $J=6.6$, 8.1 Hz, 1H), 6.63 (br s, 1H), 7.08–7.28 (m, 3H).

8b (*trans*): δ 1.49 (d, $J=6.0$ Hz, 3H), 4.37 (dq, $J=6.0$, 7.2 Hz, 1H), 4.45 (d, $J=7.2$ Hz, 1H), 6.63 (br s, 1H), 7.08–7.28 (m, 3H).

11a (*cis*): δ 1.10 (d, $J=6.6$ Hz, 3H, C-5 $C\underline{H}_3$), 5.09 (dq, $J=6.6$, 7.8 Hz, 1H, C-5$\underline{H}$), 5.39 (d, $J=7.8$ Hz, 1H, C-4$\underline{H}$), 7.00–7.30 (m, 3H), 7.22 (d, $J=8.7$ Hz, 2H), 8.21 (d, $J=8.7$ Hz, 2H).

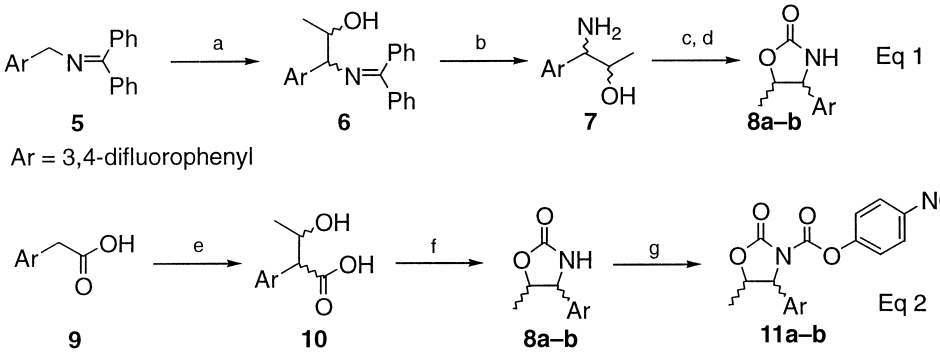
11b (*trans*): δ 1.61 (d, $J=6.3$, 3H, C-5 $C\underline{H}_3$), 4.56 (dq, $J=5.1$, 6.3 Hz, 1H, C-5$\underline{H}$), 4.89 (d, $J=5.1$ Hz, 1H, C-4$\underline{H}$), 7.10–7.30 (m, 3H), 7.24 (d, $J=9.3$, 2H), 8.23 (d, $J=9.3$, 2H).

4 (*cis*): δ 1.03 (d, $J=6.6$ Hz, 3H), 1.70–1.85 (m, 6H), 1.97–2.09 (m, 2H), 2.42 (t, $J=6.9$ Hz, 2H), 2.39–2.51

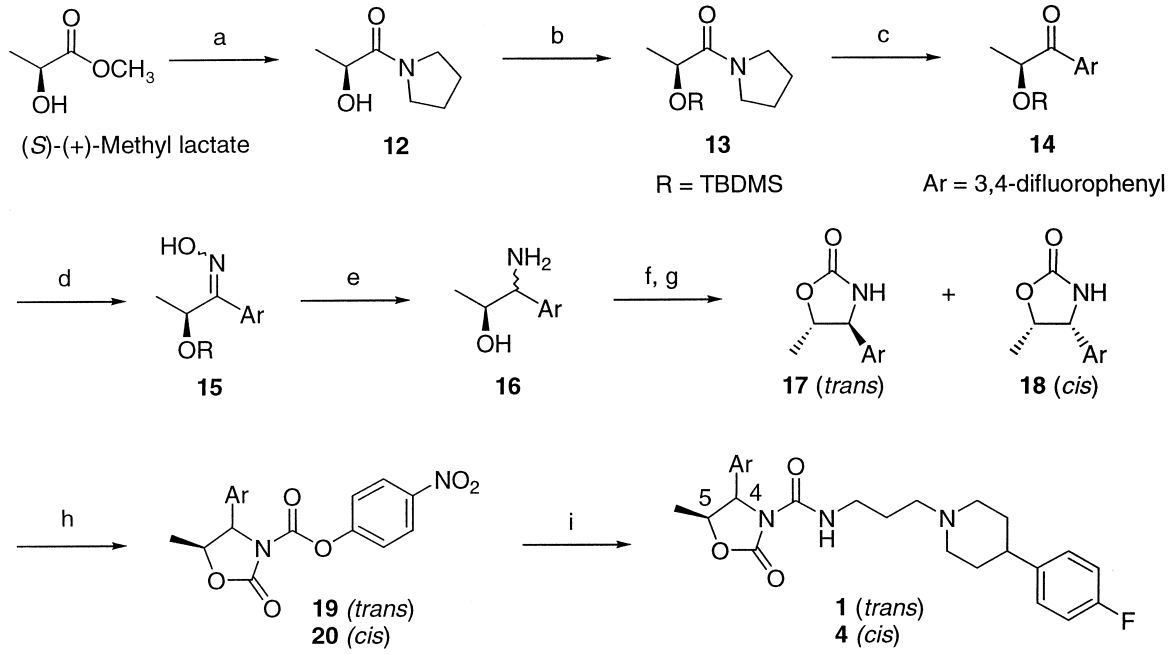
Table 1. Binding affinities of compounds **1**–**4** for the recombinant human α_1-adrenoceptors[2]

Compound	Relative stereochemistry	K_i (nM)[a]			Selectivity $K_i\ \alpha_{1B,1D}/K_i\ \alpha_{1A}$
		α_{1A}	α_{1B}	α_{1D}	
1	(+)-*trans*	0.17±0.03	119±24	122±6	>500
2	(−)-*trans*	13±0.6	74±16	193±15	<10
3	(+)-*cis*	0.9±0.3	48±11	92±5	<60
4	(−)-*cis*	30±5	76±9	253±49	<10

[a]K_i values were obtained using [^{125}I]-HEAT in competition binding assays with recombinant human receptors.



Scheme 1. (a) *tert*-BuLi, THF, then CH_3CHO; (b) $MeONH_2{\cdot}HCl$, MeOH, 68% for two steps; (c) Boc_2O, $CHCl_3$, 91%; (d) NaH, THF, 80%; (e) LDA, then CH_3CHO; (f) $NaHCO_3$, diphenylphosphorylazide, DMF, 60 °C, 96% over three steps. (g) NaH, THF followed by inverse addition to 4-nitrophenyl chloroformate in THF, 79–84%.



Scheme 2. (a) Pyrrolidine (neat), rt; (b) TBDMSCl, imidazole, DMAP, DMF, 86% for two steps; (c) *n*-BuLi, 1-bromo-3,4-difluorobenzene, THF, 78% (96% based on recovered **13**); (d) $H_2NOH{\cdot}HCl$, NaOAc, MeOH, 94%; (e) $LiAlH_4$, Et_2O, reflux, 92%; (f) Boc_2O, $CHCl_3$, 91%; (g) NaH, THF, 80%; (h) NaH, *p*-nitrophenylchloroformate; (i) 3-[4-(4-fluorophenyl)piperidin-1-yl]propylamine, THF, 80%.

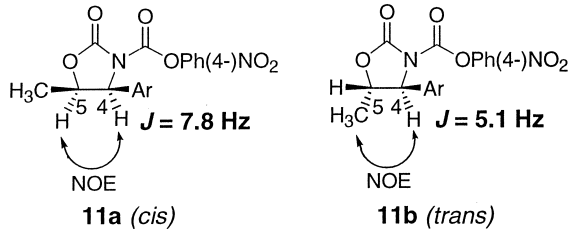


Figure 2.

(m, 1H), 3.06 (br d, $J = 11.4$ Hz, 2H), 3.26–3.41 (m, 2H), 4.99 (dq, $J = 6.6$, 7.8 Hz, 1H), 5.35 (d, $J = 7.8$ Hz, 1H), 6.90–7.03 (m, 4H), 7.15–7.27 (m, 3H), 8.14 (t, $J = 5.4$ Hz, 1H).

1 (*trans*): δ 1.54 (d, $J = 6.3$ Hz, 3H), 1.68–1.82 (m, 6H), 1.95–2.03 (m, 2H), 2.40 (t, $J = 6.9$ Hz, 2H), 2.41–2.52 (m, 1H), 3.01 (br d, $J = 11.4$ Hz, 2H), 3.33 (q, $J = 6.3$ Hz, 2H), 4.47 (dq, $J = 4.5$, 6.3 Hz, 1H), 4.91 (d, $J = 4.5$ Hz, 1H), 6.97–7.21 (m, 7H), 8.12 (t, $J = 5.4$ Hz, 1H).

Acknowledgements

We thank Ms. Yong Zheng, Mr. Boshan Li, and Mr. Vincent Jorgensen for conducting the biological assays, and Mr. Jim Peng for technical assistance. We also thank Dr. Charles Gluchowski for his encouragement.

References and Notes

1. Lagu, B.; Tian, D.; Jeon, Y.; Li, C.; Nagarathnam, D.; Shen, Q.; Wetzel, J.; Gluchowski, C.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Ransom, R. W.; Rodrigues, D.; Kassahun, K.; Pettibone, D. J.; Freidinger, R. M. *J. Med. Chem.* **2000**, *43*, 2775.
2. Patane, M. A.; Scott, A. L.; Broten, T. P.; Chang, R. S. L.; Ransom, R. W.; DiSalvo, J.; Forray, C.; Bock, M. G. *J. Med. Chem.* **1998**, *41*, 1205.
3. Ding, C. Z. *Tetrahedron Lett.* **1996**, *37*, 945.
4. A similar procedure has recently been reported. Takacs, J. M.; Jaber, M. R.; Vellekoop, A. S. *J. Org. Chem.* **1998**, *63*, 2742.
5. A Chiralcel OD column (20×250 mm) was used with isocratic 80% hexane/20% ^{i}PrOH/0.1% Et_2NH as the eluting system (12 mL/min, UV 254 nm). The retention times for the enantiomers of the *trans* oxazolidinone were 12.1 min {$[\alpha]_D$ +36° (*c* 0.25, acetone)} and 15.6 min {$[\alpha]_D$ −31° (*c* 0.20, acetone)}, respectively. The retention times for the enantiomers of the *cis* oxazolidinone were 13.7 min {$[\alpha]_D$ +65.8° (*c* 0.92, acetone)} and 19.9 min {$[\alpha]_D$ −65.0° (*c* 0.74, acetone)}, respectively.
6. Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181.
7. Martin, R.; Pascual, O.; Romea, P.; Rovira, R.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1997**, *38*, 1633.