Published in final edited form as:

Tetrahedron Lett. 2006 June 5; 47(23): 3953–3955.

Synthesis of oxazolidinedione derived bicalutamide analogs

Vipin A. Nair^a, Suni M. Mustafa^a, Michael L. Mohler^a, James T. Dalton^b, and Duane D. Miller^{a*}

^aDepartment of Pharmaceutical Sciences, University of Tennessee, 847 Monroe Avenue, RM 227 C, Memphis, TN 38163, USA

^bDepartment of Pharmaceutics and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, OH, USA

Abstract

The synthesis of chiral oxazolidinedione derived bicalutamide analogs has been discussed.

Keywords

Oxazolidinedione; Bicalutamide; Enantiomers; Androgen; Receptor

In our earlier investigations, we developed a series of second generation androgen receptor binding ligands **1b** (Fig. 1), which were analogous to bicalutamide **1a** in structure.^{1–4} Biological testing of these compounds exhibited high binding affinities and biological activities.^{5–8} Based on the results obtained and homology modeling, we had earlier reported the binding interactions between the androgen receptor and the ligands.^{9–11} Examination of torsional strain parameters and hydrogen bonding interactions revealed that the molecule adopts a conformation similar to **1c**. The hydroxyl group α to the carbonyl undergoes positioning in such a manner that it enters into hydrogen bonding interaction with Asparagine705 of the receptor. The amino group forms a weak hydrogen bond with the back bone oxygen of Leucine704. The computational predictions made were in agreement with the results obtained from the binding assays. However, to convincingly establish the aforesaid interactions and the conformation adopted by the molecules, it was highly imperative to have a suitable molecular model, which did not have free hydroxyl and amide protons and above all was conformationally restricted to a structure similar to **1c**. Accordingly, we decided to interlock the amide nitrogen and the hydroxyl oxygen by a carbonyl functionality, which led to the design of structure **1d**, an oxazolidinedione derivative. As of this day, no literature reports are available on the synthesis of chiral oxazolidinedione derived bicalutamide analogs and hence we devised and attempted a stereoselective synthesis of this molecule, the details of which form the subject matter of the present letter.

Pyrrolidine-2-carboxylic acid **2** was acylated by Schotten Baumann reaction to obtain methacryloyl pyrrolidine-2-carboxylic acid **3**, which was subsequently lactonized to obtain bromolactone **4**, according to the procedure that we reported recently.^{12,13} Nucleophilic substitution of compound **4** with 4'-fluorobenzenethiol under alkaline conditions in 2-propanol medium afforded compound **5**. However, hydrolysis of compound **5** under acidic conditions did not afford the desired chiral hydroxy acid **6**. Since our initial attempt failed to give **6**, we decided to reinvestigate the synthesis of chiral hydroxy acid **6** (Scheme 1), as we knew from our earlier experiments that the hydrolysis of bromolactone **4** using HBr solution under reflux conditions would give 3-bromo-2-hydroxy-2-methylpropanoic acid **7** in excellent yields.¹²

Corresponding author. Tel.: +1 901 448 6026; fax: +1 901 448 3446; e-mail:dmiller@utmem.edu.

The hydroxy and carboxyl groups of compound **7** were then protected with tribromoacetaldehyde under acidic conditions to obtain compound **8**.¹⁴ which was coupled with 4'-fluorobenzenethiol. Acidification of the reaction mixture with concd HCl followed by workup and isolation afforded chiral hydroxy acid **6** in good yields.¹⁴ Unlike intermediate **5**, in this case, the hydrolysis of the protecting group was easily achieved upon acidification.

4-Nitro-3-trifluoromethylaniline **9** was converted to the corresponding isothiocyanate **10**. Cyclocondensation of isothiocyanate **10** with chiral hydroxy acid **6** afforded oxazolidinedione **12** as a yellow oil, which was characterized by spectral and elemental analyses.¹⁴ The formation of oxazolidinedione must have occurred through the nucleophilic displacement of silver sulfide from the imino carbon by the hydroxy group followed by a concerted cyclic rearrangement as illustrated by intermediate structures **11a** and **11b** depicted in Scheme 2; a mechanism identical to that established by Shibuya et al.¹⁵ HPLC analysis of this product on a π acceptor/donor (*R,R*)-Whelk-O1 chiral column exhibited two peaks in the ratio 70:30 corresponding to the two enantiomers, with an enantiomeric excess of 40%. Efforts are ongoing to extend the excellent separation of the enantiomers obtained in the aforesaid analytical chiral column to the corresponding preparative column in order to obtain quantitative yields of the enantiomers and thereby determine their absolute configurations with exciton coupled vibrational circular dichroism and infrared spectroscopy along with the aid of Gaussian empirical calculations. Studies will also be carried out in determining the binding affinities between the ligand and the androgen receptor, and also the structure activity relationships. Future investigations will be aimed at replacing the oxygen atom of the heterocyclic ring system by an amino group so as to obtain enantiomeric hydantoin analogs of bicalutamide, which would then provide an additional site for hydrogen bonding interaction with the receptor.

Acknowledgments

Financial supports in the form of grants from the Department of Defense (DOD) (Grant No: DAMD17-01-1-0103), the National Institute of Health (NIH) (Grant No: DK 065227), GTx Inc., and a pre-doctoral fellowship for Michael L. Mohler from the American Chemical Society (Division of Medicinal Chemistry) are gratefully acknowledged.

References and notes

1. Dalton JT, Mukherjee A, Zhu Z, Kirkovsky L, Miller DD. Biochem. Biophys. Res. Commun 1998;244:1. [PubMed: 9514878]
2. Mukherjee A, Kirkovsky LI, Kimura Y, Marvel MM, Miller DD, Dalton JT. Biochem. Pharmacol 1999;58:1259. [PubMed: 10487527]
3. Kirkovsky L, Mukherjee A, Yin D, Dalton JT, Miller DD. J. Med. Chem 2000;43:581. [PubMed: 10691684]
4. Marhefka CA, Moore BM II, Bishop TC, Kirkovsky LI, Mukherjee A, Dalton JT, Miller DD. J. Med. Chem 2001;44:1729. [PubMed: 11356108]
5. Yin D, Gao W, Kearbey JD, Xu H, Chung K, He Y, Marhefka CA, Veverka KA, Miller DD, Dalton JT. J. Pharmacol. Exp. Ther 2003;304:1334. [PubMed: 12604714]
6. Yin D, Xu H, He Y, Kirkovsky LI, Miller DD, Dalton JT. J. Pharmacol. Exp. Ther 2003;304:1323. [PubMed: 12604713]
7. Gao W, Kearbey JD, Nair VA, Chung K, Parlow AF, Miller DD, Dalton JT. Endocrinology 2004;145:5420. [PubMed: 15308613]
8. Chen J, Hwang DJ, Bohl CE, Miller DD, Dalton JT. J. Pharmacol. Exp. Ther 2005;312:546. [PubMed: 15347734]
9. Marhefka CA, Gao W, Chung K, Kim J, He Y, Yin D, Bohl C, Dalton JT, Miller DD. J. Med. Chem 2004;47:993. [PubMed: 14761201]
10. Bohl CE, Chang C, Mohler ML, Chen J, Miller DD, Swaan PW, Dalton JT. J. Med. Chem 2004;47:3765. [PubMed: 15239655]

11. Bohl CE, Gao W, Miller DD, Bell CE, Dalton JT. *Proc. Natl. Acad. Sci* 2005;102:6201. [PubMed: 15833816]
12. Nair VA, Mustafa SM, Mohler ML, Fisher SJ, Dalton JT, Miller DD. *Tetrahedron Lett* 2004;45:9475.
13. Nair VA, Mustafa SM, Mohler ML, Yang J, Kirkovsky LI, Dalton JT, Miller DD. *Tetrahedron Lett* 2005;46:4821.
14. Preparation of compound **8**: Tribromoacetaldehyde (26.0 mmol, 2.8 mL) and compound **7** (22.0 mmol, 4.0 g) were cooled to 0 °C under argon atmosphere, and concd sulfuric acid (10 mL) was added drop-wise with stirring. After 2 h the solution turned dark; the ice bath was removed and the reaction mixture was stirred overnight at room temperature. The solution was diluted with ice and extracted with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated to obtain compound **8**, which appeared as white crystals upon recrystallization from ethyl acetate–hexane. The compound was characterized by spectral and elemental analyses. Yield: 89%; mp 97 °C; NMR (¹H, 300 MHz, CDCl₃): 1.8 (s, 3H, CH₃), 3.7 (s, 2H, CH₂), 5.8 (s, 1H, CH); C₆H₆Br₄O₃ Calcd: C, 16.17; H, 1.36. Found: C, 16.08; H, 1.25. Preparation of compound **6**: Compound **8** (4.8 mmol, 2.1 g), dissolved in a 1:1 mixture of 2-propanol and 1M NaOH, was stirred at room temperature. After 3 h, when no starting material was detectable by TLC, 4'-fluorobenzenethiol (4.8 mmol, 0.6 g) was added and the reaction mixture was stirred overnight. The reaction mixture was then adjusted to pH 1 with concd HCl, extracted with ethyl acetate, and dried over anhydrous sodium sulfate. The organic layer was concentrated to obtain an oil. Flash column chromatography of the reaction mixture in hexane–ethyl acetate–acetic acid mixture followed by recrystallization in ethyl acetate–hexane afforded compound **6** as colorless needle shaped crystals. The product was characterized by spectral and elemental analyses. Yield: 65%; mp 54 °C; [α]_D²⁵ + 24.85 (c 1.0, MeOH); NMR (¹H, 300 MHz, CDCl₃): 1.5 (s, 3H, CH₃), 3.2 (d, 1H, CH), 3.4 (d, 1H, CH), 7.0 (m, 2H, Ar, *J* = 2.0, 8.9 Hz), 7.5 (m, 2H, Ar, *J* = 2.0, 8.9 Hz); MS: No parent ion peak; C₁₀H₁₁FO₃S Calcd: C, 52.16; H, 4.82. Found: C, 52.05; H, 4.76. Preparation of compound **12**: 4-Nitro-3-trifluoromethylaniline **9** (23.0 mmol, 4.7 g) was converted to the corresponding isothiocyanate **10** by adding thiophosgene (25 mmol, 1.9 mL) and excess sodium bicarbonate in chloroform medium at 0 °C, followed by overnight stirring at room temperature. The reaction mixture was concentrated, extracted into ethyl acetate and purified by flash column chromatography using hexane–ethyl acetate mixture to afford compound **10**, which appeared as an yellow oil. To the mixture of hydroxy acid **6** (4.1 mmol, 0.9 g) and 4-nitro-3-trifluoromethylphenylisothiocyanate **10** (3.9 mmol, 0.9 g) in acetonitrile, silver trifluoroacetate (8.2 mmol, 1.8 g), and triethyl amine (12.3 mmol, 1.8 mL) were added with stirring and the reaction mixture was heated to reflux for 1 h. After removal of silver sulfide by filtration and evaporation of the solvent under reduced pressure, the resulting residue was washed with water, extracted into ethyl acetate, and concentrated. The desired product, isolated by flash column chromatography using a hexane–ethyl acetate mixture, appeared as an yellow oil. The compound was identified on the basis of spectral and analytical data. Yield : 52%; [α]_D²⁵ + 39.7 (c 1.0, MeOH); NMR (¹H, 500 MHz, CDCl₃): 1.8 (s, 3H, CH₃), 3.2 (s, 1H, CH), 3.3 (s, 1H, CH), 6.9 (m, 2H, Ar, *J* = 2.0, 8.9 Hz), 7.2 (m, 2H, Ar, *J* = 2.0, 8.9 Hz), 7.9 (m, 1H, Ar, *J* = 2.1, 9.0 Hz), 8.0 (m, 1H, Ar, *J* = 0.5, 2.1 Hz), 8.1 (m, 1H, Ar, *J* = 0.5, 9.0 Hz); NMR (¹³C, 500 MHz, CDCl₃): 22.8, 43.4, 86.7, 117.0, 117.3, 124.4, 124.5, 124.6, 125.0, 126.8, 129.3, 134.2, 134.3, 135.3, 164.9, 172.8; MS: No parent ion peak; C₁₈H₁₂F₄N₂O₅S Calcd: C, 48.65; H, 2.72; N, 6.30. Found: C, 48.59; H, 2.70; N, 6.31.
15. Shibuya I, Goto M, Shimizu M, Yanagisawa M, Gama Y. *Heterocycles* 1999;51:2667.

Figure 1.

Reagents: R₁ = NO₂, CN; R₂ = CF₃, Cl, I; R₃ = F, Cl, Br, I; X = O, NH, S, SO₂, CH₂.

Scheme 1.

Reagents: (a) methacryloyl chloride, NaOH, acetone; (b) NBS, DMF; (c) NaOH, 4'-fluorobenzenethiol, 2-propanol; (d) concd HCl; (e) 24% HBr; (f) tribromoacetaldehyde, concd H₂SO₄; (g) (1) NaOH, 4'-fluorobenzenethiol, 2-propanol, (2) concd HCl.

Scheme 2.

Reagents: (h) thiophosgene, chloroform, NaHCO₃; (i) silver trifluoroacetate, triethylamine, acetonitrile.