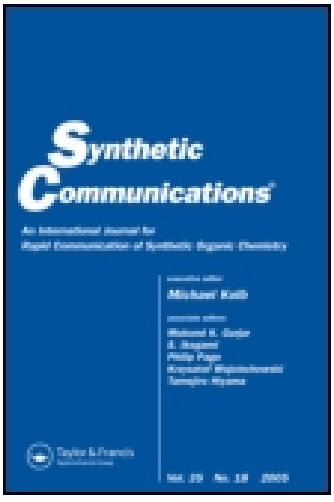
This article was downloaded by: [University of Otago]
On: 25 December 2014, At: 02:11
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of a New Doxazosin-Related Compound

Irina Tsyskovskaia [a], Mustapha Kandil [a] & Yves Beaumier [a]
[a] Pharmascience, Saint-Laurent, Quebec, Canada
Published online: 06 Feb 2007.

To cite this article: Irina Tsyskovskaia, Mustapha Kandil & Yves Beaumier (2007) Synthesis of a New Doxazosin-Related Compound, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:3, 447-450, DOI: 10.1080/00397910601039135

To link to this article: http://dx.doi.org/10.1080/00397910601039135

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Synthetic Communications®, 37: 447–450, 2007
Copyright © Taylor & Francis Group, LLC
ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910601039135

Downloaded by [University of Otago] at 02:11 25 December 2014

Synthesis of a New Doxazosin-Related Compound

Irina Tsyskovskaia, Mustapha Kandil, and Yves Beaumier
Pharmascience, Saint-Laurent, Quebec, Canada

Abstract: A simple procedure for the synthesis of 1-[4-(2,3-dihydro-1, 4-benzodioxin-2-yl) amide-6, 7-dimethoxy-2-quazolinyl]-4-(1,4-bensodioxan-2-yl-carbonyl) piperazine is described.

Keywords: doxazosin, related compounds, synthesis, HPLC

4-Amino-2-[4-(1,4-benzodioxan-2-ylcarbonyl) piperazin-1-yl]-6,7-dimethoxyquin azoline **5** (doxazosin mesylate) is an important new member of the quinazoline family of drugs used for the treatment of hypertension.[1–3] Moreover, the compound has recently attracted more attention because of its efficient treatment of benign prostatic hyperplasia.[4–8] It is believed that doxazosin is a selective blocker of the α-adrenergic receptor.

Several procedures have been developed for the synthesis of doxazosin. The most recent one is based on the conversion of acid **1** to the corresponding acid chloride, followed by the reaction with piperazine to give the benzodioxane **2,** which is coupled with the quinazoline **3** to provide doxazosin hydrochloride **4,** which is then converted into doxazosin mesylate **5** (Figure1).[9]

Two major impurities have been reported in the synthesis of doxazosin mesylate **5**. The first one is the symmetrical bis-amide **6** arising from the bicoupling reaction of the acide chloride with piperazine. The second one was piperazine **8.** Herein, we report the synthesis of compound **8**. Moreover, it can be employed as a reference in the process of controlling the impurities of doxazosin mesylate **5**.

Received in the USA May 18, 2006
Address correspondence to Yves Beaumier, Pharmascience, 6625 Abrams, Saint-Laurent, Quebec, Canada H4S 1X9. E-mail: ybeaumier@pharmascience.com

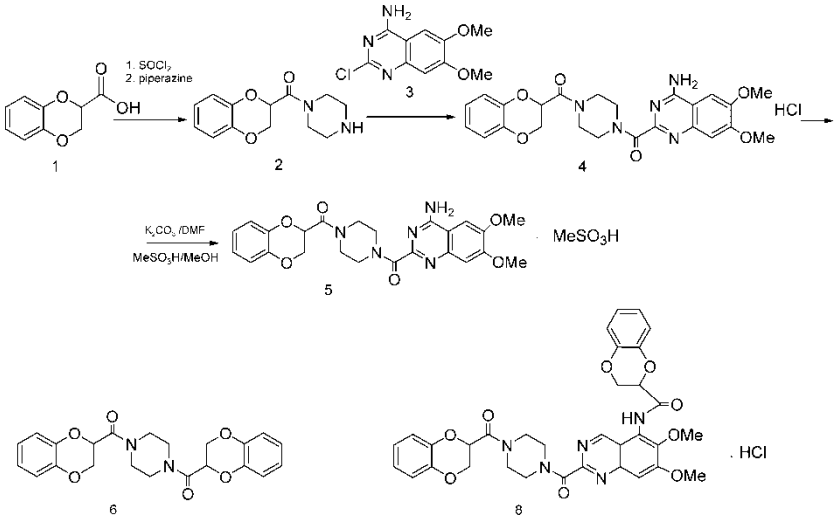


Figure 1. Synthesis of doxazosin mesylate.

Doxazosin mesylate **5** was coupled with 1,4-benzodioxane-2-carbonyl chloride **7** to obtain compound **8** (Fig. 2). The product was obtained in 88% yield after purification by flash chromatography and was characterized by NMR, mass spectrometry (MS) spectroscopy, and analytical high-performance liquid chromatography (HPLC).

EXPERIMENTAL

NMR spectra were recorded on a 400-MHz Bruker instrument. Mass spectra were performed on a Micromass Autospec-TOF spectrometer. Microanalysis was performed on an EA 1108 CHNS model analyzer. For thin-layer chromatography (TLC) of analytical samples, silica-gel $60F_{254}$ precoated aluminum sheets were used (Merck Art. No. 5554).

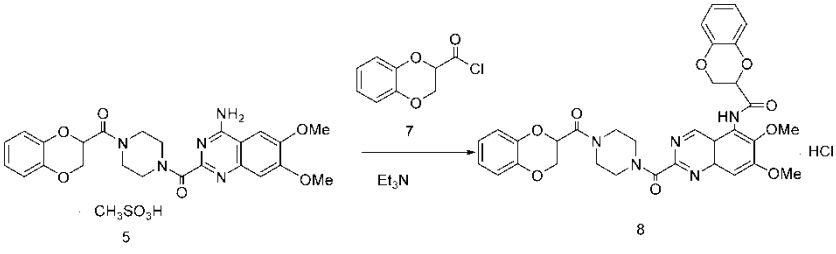


Figure 2. Synthesis of related compound (**8**).

Downloaded by [University of Otago] at 02:11 25 December 2014

Downloaded by [University of Otago] at 02:11 25 December 2014

High-Performance Liquid Chromatography

Liquid chromatography was performed using a HPLC system composed of an Agilent model G1311A pump, equipped with a ternary gradient controller and an Agilent model G1315A diode array detector, wavelength 275 nm. The computer is equipped with Agilent LC3D Chemstation for Analytical program, Revision A:09.03. A 250-mm × 4.6-mm, 5-μm Waters spherisorbs CN column was used for determination of degradation products. A mobile phase consisting of a buffer solution (25 mM $NH_4H_2PO_4$) and acetonitrile was delivered at a rate of 1 mL/min, holding the composition at 95:5 for 20 min, then as a linear gradient to 40:60 in 20 min. A post time of 7.5 min is added.

1,4-Benzodioxan-2-carbonyl Chloride 7

Thionyl chloride (0.49 mL, 6.6 mmol) was added dropwise to a solution of 1,4-benzodioxanecarboxylic acid (1.00 g, 5.5 mmol) in dichloromethane (10 mL). The mixture was stirred for 14 h at room temperature, at which point TLC analysis showed that the reaction was completed. After evaporation of solvent and the excess of thionyl chloride, the crude was employed for the next step without further purification.

1-[4-(2,3-Dihydro-1,4-benzodioxin-2-yl) Amide-6,7-dimethoxy-2-quazolinyl]-4-(1,4-benzodioxan-2-yl-carbonyl) Piperazine 8

Triethylamine (1.4 mL, 10.06 mmol) was added to a stirred suspension of doxazosin mesylate (2.75 g, 5.03 mmol) in dichloromethane (15 mL). Stirring continued at room temperature until a clear solution was obtained. This solution was treated dropwise with a solution of 1,4-benzodioxane-2-carbonyl chloride **7** (1.00 g, 5.03 mmol) in dichloromethane (10 mL).

After 12 h of stirring at room temperature, the reaction mixture was washed with water, dried with anhydrous sodium sulfate (Na_2SO_4), filtered, and evaporated. The solid residue was purified by silica-gel chromatography using chloroform as eluent to give the product as a yellow solid. The yield evaluated by HPLC is 88%, and the purity is 98.6%. Mp: 99–100°C. ^{1}NMR ($CDCl_3$) δ: 8.75 (s, 1H); 7.25 (s, 1H); 7.1 (t, 1H); 6.98–6.84 (m, 8H); 6.76 (s, 1H); 5.05 (t, 1H); 4.9 (dd, 1H); 4.6–4.44 (m, 3H); 4.4–4.37 (m, 1H); 4.19–4.04 (m, 2 H); 3 (s, 3H); 4.01–3.81 (m, 3H); 3.9 (s, 3H); 3.81–3.77 (m, 1H); 3.64–3.57 (m, 2H); 1.61 (s, 2H). (M^+) $M/z = 614$. $C_{32}H_{31}N_5O_8 \cdot HCl \cdot 2.5\ H_2O$ calc. C, 55.9%; H, 4.84%; N, 10.2%; found C, 55.93%; H, 4.71%; N, 9.76%.

REFERENCES

1. Flack, J. M. *Int. J. Clin. Pract.* **2002** (7), 527–530.
2. Joung, R. A.; Brogden, R. N. Drugs **1998**, *35* (5), 525–541.
3. Elliot, H. L.; Meredith, P. A.; Reid, J. L. *Am. J. Cardiol.* **1987**, *59*, 79.
4. Baez, M. A.; Gary, D. C.; Jellad, N. S.; Weidler, D. J.; British, J. *Clin. Pharm.* **1986**, *21*, (Sup. 1), 63S–67S.
5. Kirby, R. S.; Andersen, M.; Gratzke, P.; Dahlstrand, C.; Hoye, K. BJU International **2001**, *87* (3), 192–200.
6. Kirby, R. S. *Int. J. Clin. Pract.* **1998**, *52*, 402.
7. Guthrie, R. M.; Siegle, R. L. *Clin. Ther.* **1999**, *21*, 1732–1748.
8. Campbell, S. F.; Davey, M. J.; Hardstone, D.; Levis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49–57.
9. Fang, Q. K.; Grover, P.; Han, Z.; McConvill, F. X.; Rossi, R. F.; Olsson, D. J.; Kessler, W.; Wald, S. A.; Senanayake, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2169–2174.

Downloaded by [University of Otago] at 02:11 25 December 2014