Synthesis and Properties of Biagra [1].
A 5-(2,3-Dihydro-7-benzofuryl) Analog of Viagra®

Wolfgang Voeltera, Mustafa M. El-Abadelahb, Salim S. Sabrib, and Monther A. Khanfar

a Abteilung für Physikalische Biochemie, Physiologisch-chemisches Institut der Universität Tübingen, Hoppe-Seyler-Straße 4, D-72076 Tübingen, Germany
b Chemistry Department, Faculty of Science, University of Jordan, Amman, Jordan
c Institut für Anorganische Chemie, der Universität Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen, Germany

Reprint requests to Prof. Dr. Dr. h.c. W. Voelter.
E-mail: wolfgang.voelter@uni-tuebingen.de or to Prof. Dr. M. El-Abadelah

Z. Naturforsch. 54b, 1469–1473 (1999); received May 10, 1999

Dihydrobezofuryl-pyrazolo[4,3-d]pyrimidin-7-one, Viagra® Analog, Erectogenic Activity

The synthesis and spectral properties (IR, MS, NMR) of a substituted 5-(2,3-dihydro-7-benzofuryl)pyrazolo[4,3-d]pyrimidin-7-one (2), an analog of Viagra® (1), are described. The generally applicable route involves interaction of 2,3-dihydro-7-benzofuranoyl chloride (3) with 4-amino-1-methyl-3-propyl-5-pyrazolecarboxamide (4), and the resulting bis-amide (5) is cyclized to the corresponding substituted pyrazolo[4,3-d]pyrimidin-7-one (6). Chlorosulfonylation of 6, followed by treatment with 1-methylpiperazine, furnished the title compound 2 (named Biagra). Preliminary experiments “associated with the erectile process” on rats lend evidence of greater potency of Biagra (2) as compared to Viagra® (1).

Introduction

Viagra® (1) is commanding international interest following its approval in 1998 as a therapeutic drug for the oral treatment of male erectile dysfunction (MED) [2]. The physiology of the erectile cycle has been widely investigated over the past years [3]. Nitric oxide (NO), a messenger molecule released in response to sexual arousal, activates the enzyme guanyl cyclase which converts guanosine triphosphate into cyclic guanosine monophosphate (cGMP) [3,4]. This key second messenger in the cycle is a vasodilator that induces relaxation of the corpus cavernosal smooth muscle (CCSM), thereby allowing blood to flow more strongly leading to pressure filling of the corpora and consequent erection [4]. However, cGMP is quickly hydrolysed by phosphodiesterase-type 5 enzyme (PDE-5), to inactive GMP. Viagra® (1) works by blocking part of the cycle. It selectively inhibits the PDE-5 enzyme, thence preventing the breakdown of cGMP. This allows cGMP to accumulate in CCSM and prolong the vasodilation effect [2,5].
There is a need in the art to design new vasodilating agents with improved pharmacokinetics. Structural modifications on Viagra® (1) with the concept of replacing the substituted phenyl ring on the 5-position (ring C) by selected biophoric heteroaryls is hitherto undescribed. This approach, retaining the pyrazolo[4,3-b]pyrimidone moiety unaltered, appears attractive and might produce a genus of compounds with improved erectogenic potency. Consequently, and as part of an ongoing project aimed at investigating improvements on Viagra®, we sought to prepare compound 2 that incorporates a substituted 2,3-dihydro-7-benzofuryl moiety at carbon-5. Thus, compound 2 (we call it Biagra) bears very close resemblance to Viagra. Herein, we describe the synthesis and properties of 5-[2,3-dihydro-5-(4-methylpiperazin-1-ylsulfonyl)-7-benzofuryl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (2).

**Results and Discussion**

**Chemistry**

The general synthetic route employed to prepare the title compound Biagra commenced with the two key intermediates 3 and 4 as depicted in Scheme 1. 2,3-Dihydro-7-benzofurancarboxylic acid [6] is converted to the respective acid chloride synthon 3 by heating with thionyl chloride. Construction of the substituted pyrazolo intermediate 4 was accomplished from ethyl 3-oxoheptanoate [7] by a series of straightforward reactions according to a literature methodology [2a]. Direct interaction between the acid chloride 3 and the 4-aminopyrazole derivatives 4 afforded the respective bis-amide 5 which was cyclized to the corresponding substituted pyrazolo[4,3-d]pyrimidin-7-one 6 under the action of potassium tert-butoxide in refluxing tert-butanol. Chlorosulfonylation of compound 6 proceeded smoothly and selectively at position 5 of the 2',3'-dihydrobenzofuryl moiety to afford compound 7 which, upon coupling with 1-methylpiperazine, furnished the target compound 2.

**Spectral data**

The MS, NMR and IR spectral data and elemental analyses of the new compounds (2, and 5-7) are in accord with the proposed structures, and are listed in the experimental section. Thus, their mass spectra display the correct molecular ions, M⁺, as suggested by the respective molecular formulas. The main IR absorption bands conform with the assigned structures. Assignments of the ¹H NMR signals are straightforward. Carbon-13 assignments are based on DEPT, HMBC and HMQC experiments [8].

It is worth mentioning that the two bicyclic heteroaryls in 2 (rings A B and C' D') retain coplanarity by virtue of a strong intramolecular hydrogen bond between the pyrimidone -NH and the oxygen lone pair of the 2',3'-dihydrobenzofuryl moiety as evidenced from X-ray crystal structure [9]. A similar structural feature was reported for 1.

---

Scheme 1. Conditions: (i) NEt₃, benzene/ Δ; (ii) t-BuOK/ t-BuOH; Δ; (iii) ClSO₂H/ 65-70 °C, 1 h; (iv) THF, 1-methylpiperazine/ r.t., 1 h.
and related compounds (confirmed by X-ray crystal structure) [2a].

Preliminary biological tests

Compound 2 was tested in a rat model predictive of therapeutic activity in ED using a laser doppler probe to record blood flow rates following administration of 2. There has been evidence of greater potency of 2 over Viagra® which was used as a positive control in the test. The quantitative data and other related bio-results will be communicated separately.

Experimental

2,3-Dihydrobenzofuran, N,N,N',N'-tetramethyl-ethylenediamine (TMEDA) and n-butyllithium solution in hexane (2.4 m) were purchased from Aldrich. Melting points were determined on an electrotherm Melting Temperature apparatus and are uncorrected. NMR Spectra were measured on Bruker WM-400 and DPX-300 MHz spectrometers with TMS as internal reference. Mass spectra (EI) were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV. IR spectra were recorded as KBr discs on a Nicolet impact-400 FT-IR instrument.

2,3-Dihydro-7-benzofurancarboxylic acid

This compound was prepared by direct lithiation of 2,3-dihydrobenzofuran (using n-butyllithium and TMEDA in cyclohexane at r.t.), followed by treatment with solid CO₂ at -78 °C under argon throughout the whole operation. The methodology adopted here is analogous to a reported procedure [6] with slight modification. The crude product (76%) was recrystallized from methanol. Yield of pure product = 62%; m.p = 172-173 °C (Lit. [6] data: yield = 55%; m.p = 170.5-171 °C).

4-Amino-1-methyl-3-propyl-5-pyrazolecarboxamide (4)

This compound is prepared according to a reported methodology [2a] whereby the pyrazole ring is constructed from ethyl 3-oxoheptanoate [7] and hydrazine, followed by regioselective N-methylation and subsequent hydrolysis. Nitrification of the resultant 1-methyl-3-propyl-5-pyrazolecarboxylic acid, followed by carboxamide formation and nitro group reduction furnished the substituted pyrazole 4.

A mixture of 2,3-dihydrobenzofuran-7-carboxylic acid (1.5 g, 0.0091 mole) and SOCl₂ (8 ml) was refluxed (oil bath) for 3 h. Excess SOCl₂ was removed in vacuo, and the residual acid chloride (3) was treated with a suspension of compound 4 (1.4 g; 0.0077 mole) in anhydrous benzene (25 ml), followed by addition of triethylamine (3 ml). The resulting mixture was refluxed for 3 h, and benzene was then evaporated in vacuo. The solid residue was soaked in cold water (40 ml), and the remaining solid product was collected by suction filtration, drained, washed with water (2 x 20 ml), diethyl ether (2 x 10 ml), and dried. Yield of pure product = 2.3 g (91%). m.p. = 173-174 °C.

Analysis for C₁₇H₂₉N₄O₃ (328.37)

Calcd C 62.18 H 6.14 N 17.06%,
Found C 61.95 H 6.07 N 17.11%.

MS m/z (rel. int.): 328.15364 (M⁺, 5%, requires: 328.15354), 311 (6%), 296 (3%), 182 (4%), 164 (2%), 147 (100%), 91 (22%).

IR (KBr): 3396, 3335, 3302, 2957, 2868, 1676, 1644, 1611, 1540, 1477, 1212 cm⁻¹.

¹H NMR (CDCl₃): δ 0.86 (t, J = 7.4 Hz, 3H, CH₃CH₂CH₂), 1.56 (m, 2H, CH₂CH₂CH₃), 2.46 (t, J = 7.6 Hz, 2H, CH₂CH₂CH₂), 3.27 (t, J = 8.5 Hz, 2H, C3'-H), 3.97 (s, 3H, N-C//3), 4.73 (t, J = 8.5 Hz, 2H, C2'-H), 6.94 (dd, J = 7.2; 8.1 Hz, 1H, C5'-H), 7.34 (d, J = 7.2 Hz, 1H, C4'-H), 6.26, 7.72 (two br s, 1H each of CONH₂) 7.86 (d, J = 8.1 Hz, 1H, C6'-H), 8.88 (br s, 1H, N/CO).

¹³C NMR (CDCl₃): δ 13.7 (CH₂CH₂CH₃), 22.2 (CH₂CH₂CH₂), 27.5 (CH₂CH₂CH₂), 28.9 (C-3'), 39.1 (N(CH₃)), 72.8 (C-2'), 114.5 (C-3), 115.6 (C-7'), 121.4 (C-5'), 128.0 (C-3'a), 129.3 (C-4'), 129.4 (C-6'), 132.1 (C-4), 147.0 (C-5), 157.9 (C-7'a), 161.7 (NHCO), 165.8 (CONH₂).

5-(2,3-Dihydro-7-benzofuryl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidine-7-one (6)

Potassium t-butoxide (0.5 g; 0.0045 mole) was added to a stirred suspension of compound 5 (1.1 g; 0.0034 mole), in t-butanol (20 ml) and the resulting mixture was heated under reflux for 8 h (oil bath), then allowed to cool to room temperature. Water (14 ml) was added and then the solution was neutralized with dilute HCl (4%; 13 ml) to pH ~ 7, cooled to about 5-10 °C, collected by suction filtration, washed with cold water (2 x
10 ml), crystallized from ethanol and dried. Yield = 1.0 g (96%). m.p. = 174-175 °C.

Analysis for C_{17}H_{16}N_{4}O_{5} (310.36)

Caled C 65.79 H 5.85 N 18.05%
Found C 65.72 H 5.91 N 17.93%

MS m/z (rel. int.): 310.14370 (M\(^+\), 52%, requires: 310.14298), 295 (29%), 282 (100%), 267 (8%), 136 (41%), 126 (14%), 91 (10%).

IR (KBr): 3336, 3086, 2963, 2871, 1697, 1602, 1570, 1492, 1446, 1374, 1210, 1173 cm\(^{-1}\).

\[ \text{IR (KBr): 3325, 3079, 2960, 2853, 2802, 1701, 1604, 1572, 1436, 1360, 1285, 1169 cm}^{-1}. \]

Acknowledgement
We wish to thank the BMBF, Bonn, Germany for financial support.

Compounds 15-23 were prepared by the general method of portionwise to chlorosulfonic acid. The resulting mixture was stirred at room temperature for 1 h. THF was then removed under vacuum and the residue treated with cold water (50 ml). The resulting white precipitate was filtered, washed with water (2 x 10 ml), drained and recrystallized from 90% ethanol. Yield of pure product = 1.2 g (83%), m.p. = 194–195 °C.

Analysis for C_{18}H_{22}N_{2}O_{5} (472.57)

Caled C 55.92 H 5.97 N 17.78 S 6.79%
Found C 56.00 H 6.09 N 17.51 S 6.73%

Analysis for C_{17}H_{16}N_{4}O_{5} (408.86)

Caled C 49.94 H 4.19 C 18.67 N 13.70 S 7.84%
Found C 49.73 H 4.08 C 18.61 N 13.56 S 7.68%

MS m/z (rel. int.): 472.19036 (M\(^+\), 5%, requires: 472.18927), 408 (4%), 402 (84%), 352 (3%), 136 (2%), 126 (3%), 99 (100%), 70 (6%).

IR (KBr): 3325, 3079, 2960, 2853, 2802, 1701, 1604, 1572, 1436, 1360, 1285, 1169 cm\(^{-1}\).

\[ \text{IR (KBr): 3325, 3079, 2960, 2853, 2802, 1701, 1604, 1572, 1436, 1360, 1285, 1169 cm}^{-1}. \]

Acknowledgement
We wish to thank the BMBF, Bonn, Germany for financial support.
[1] IUPAC Name: 5-[2,3-Dihydro-5-(4-methylpiperazin-1-ylsulfonyl)-7-benzofuryl]-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]-pyrimidin-7-one.


c) A. L. Burnett, Biol. Reprod. 52, 485 (1995);
d) A. L. Burnett, J. Urol. 157, 320 (1997);


b) D. Libermann, N. Rist, F. Grumbach, S. Cals, M. Moyeux, A. Rouaix, Bull. Soc. Chim. Fr. 687 (1958);
c) C. A. 52, 20147 g (1958);
d) F. L. Breusch, H. Keskin, Enzymologia 11, 356 (1945); C. A. 40, 57029 a (1946).
