HETEROCYCLES, Vol. 55, No. 9, pp. 1789 – 1804, Received, 6th April, 2001

SYNTHESIS AND VASORELAXANT POTENCY OF MONAGRA . A CHIRAL 5-(2-METHYL–2,3 –DIHYDRO-7-BENZOFURYL)-PYRAZOLOPYRIMIDONE ANALOG OF VIAGRA®

Nader R. Al-bojuk[a], Mustafa M. El-Abadelah*[a], Salim S. Sabri[b], Alain Michel[c], Wolfgang Voelter[d], Cäcilia M.-Mössmer[e], and Yousef Al-Abed[f]

[a]Chemistry Department, Faculty of Science, Jordan University, Amman, Jordan
[b]Faculty of Arts and Sciences, University of Sharjah, P.O . Box 27272, UAE
[c]Laboratoire de Pharmacologie, Faculte´ de Pharmacie, 15, Avenue Charles Flahaut, 34060-Montpellier, Cedex 2, France
[d]Abteilung für Physikalische Biochemie, Physiologisch-chemisches Institut der Universität Tübingen, Hoppe-Seyler-Straβe 4, D-72076 Tübingen, Germany
[e]Institut für Anorganische Chemie auf der Morgenstelle 18, Universität Tübingen, D-72076 Tübingen, Germany
[f]The Picower Institute for Medical Research, 350 Community Drive, Manhasset NY 11030, USA

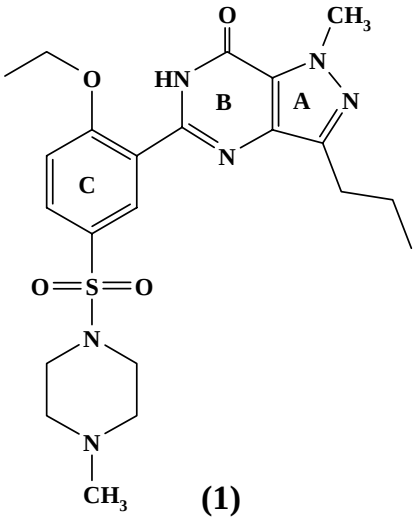
Abstract- Synthesis and properties of a chiral 5-(2-methyl-2,3-dihydro-7-benzofuryl)pyrazolo[4,3-*d*]pyrimidin-7-one (**3**), an analog of Viagra® (**1**) and Biagra (**2**), are described. The key material, (±)-3-methyl-2,3-dihydrobenzofuran-7-carboxylic acid (**8a**) was resolved into the (*S*)-**8b** (95% ee) and (*R*)-**8c** (99% ee) enantiomers using, respectively, (-)-cinchonidine and (+)-cinchonine.The absolute configuration of **8c** was determined as *R* by X-Ray measurements. Preliminary *in vitro* experiments on rat isolated thoracic aorta show that the vasorelaxant potency of **3b,c** is truly higher than that of **1** and **2**.

Introduction

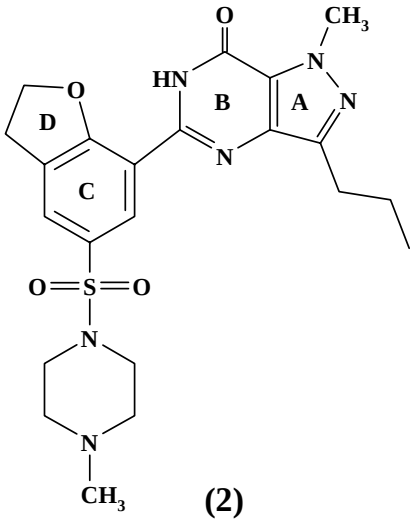
The advent of introducing Viagra® (**1**)[1,2] as a medicament for treatment of impotence has attracted widespread attention. This therapeutic agent potently inhibits cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE 5) isozyme.[1] Sexual arousal causes increased release of nitric oxide

(NO) from non-cholinergic non-adrenergic parasympathetic nerve endings in the walls of the arteries and sinusoids of the penile corpora cavernosa (PCC).[3] Some NO is also released by endothelial cells lining the blood vessels and sinusoids of PCC. Acting as a diffusion signalling molecule, NO stimulates a cytoplasmic guanylyl cyclase to increase cGMP production from guanosine triphosphate (GTP). As a second messenger in the erectile cycle, cGMP triggers the relaxation of smooth muscle cells-such as in the arterial walls of the sinusoids, as well as the sinusoids themselves.[4] This vasodilating event reduces the resistance to the blood flow into the penis, thereby increasing the amount of blood flow into the sinusoids with consequent attainment of penile erection. Thereafter, cGMP is rapidly hydrolyzed into inactive GMP in a substrate-specific manner. Viagra® depends on this NO/cGMP pathway for its erectogenic effect by working as a potent selective PDE-5 inhibitor.[1,5] In this way, Viagra® would block cGMP breakdown and therefore act synergistically with NO to elevate cGMP concentration and cause penile smooth muscle relaxation-erection interplay.

Quite recently, we have reported on the synthesis and properties of *biagra* (**2**),[6] a 5-(2,3-dihydro-7-benzofuryl)pyrazolo[4,3-*d*]pyrimidone derivative which showed *in vitro* vasorelaxant activity on rat isolated thoracic aorta comparable to viagra® (**1**).[7] This result motivated us to design structural modifications on **2** for improvement of the observed potency. We anticipate that introduction of a methyl group at C-2´ of the dihydrofuryl moiety (ring D of *biagra* **2**) would result in compound (**3)** which, from molecular modeling, closely resembles viagra® (**1**). The modified structure (±)-**3a** (we call it *monagra*) also has a stereogenic center and is obtainable in its optically pure (*S*)- and (*R*)-enantiomers (**3b** and **3c**, respectively) that are expected to show enantioselective activity as PDE-V inhibitors and as smooth muscle vasorelaxants. This follows from the fact that enantiomers can elicit vastly different biological responses in living organisms and the biological activity of enantiomers often differ widely. Besides, the



(1)



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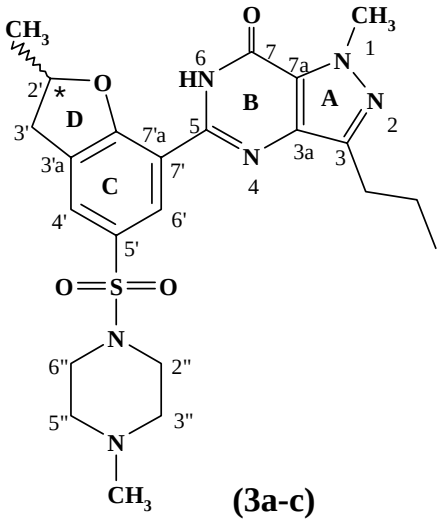


(3a-c)

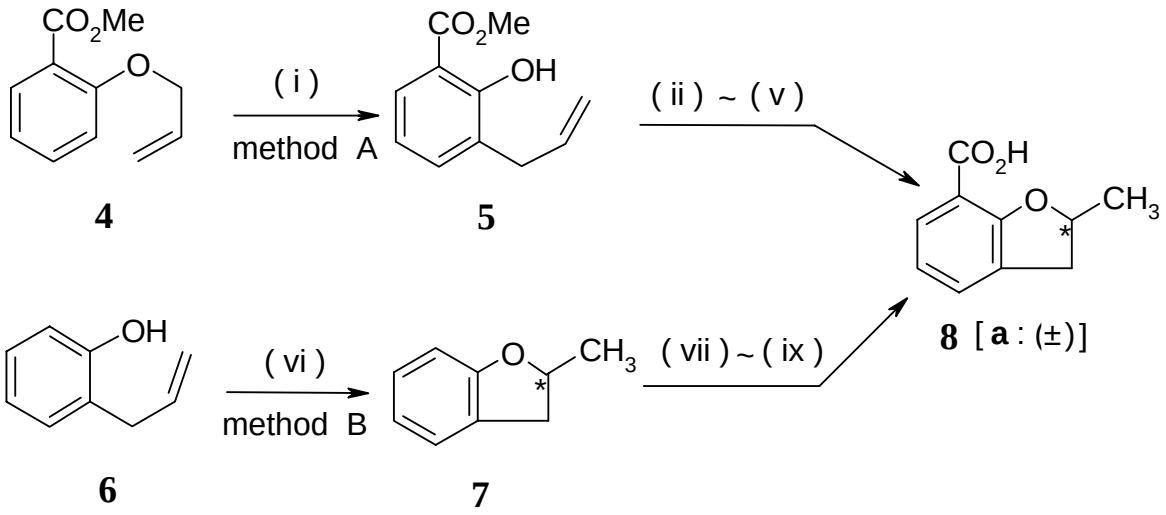
benzofuran entity is known to occur in several biologically interesting natural (and synthetic) products.[8] Accordingly, the present work aims at evaluating the *in vitro* vasorelaxant activity of **3a-c** as compared to **1** and **2**. Herein we describe the synthesis and properties of **3** starting with 2-methyl-2,3-dihydrobenzofuran-7-carboxylic acid **(8)** (Schemes I and II).

Results and Discussion

Synthesis

The requisite racemic acid **(8a)** was prepared according to published procedures [9,10] utilizing methyl *O*-allylsalicylate **(4)**[10] which, upon heating, delivers **5**[9] in a [3,3] sigmatropic Claisen rearrangement. Subsequent cyclization of **5** using mercuric acetate, followed by demercuration with sodium borohydride in alkali, furnished **8a**[9] (method A, Scheme I). An alternative route toward **8a** involves selective lithiation at C-7 of 3-methyl-2,3-dihydrobenzofurn **(7)** (prepared by cyclization of 2-allylphenol **(6)** with zinc chloride and hydrochloric acid),[11] and quenching with dry ice at -78 ^{o}C (method B, Scheme I).

Scheme I



(i) 210-215 ^{o}C under N_2

(ii) $Hg(OAc)_2$, THF, Δ

(iii) $NaBH_4$, 12% NaOH

(iv) 25 % $NaHCO_3$

(v) 15 % KOH, Δ; then 15 % HCl (0 ^{o}C)

(vi) conc. HCl, $ZnCl_2$/AcOH, Δ

(vii) *n*-BuLi in hexane/TMEDA

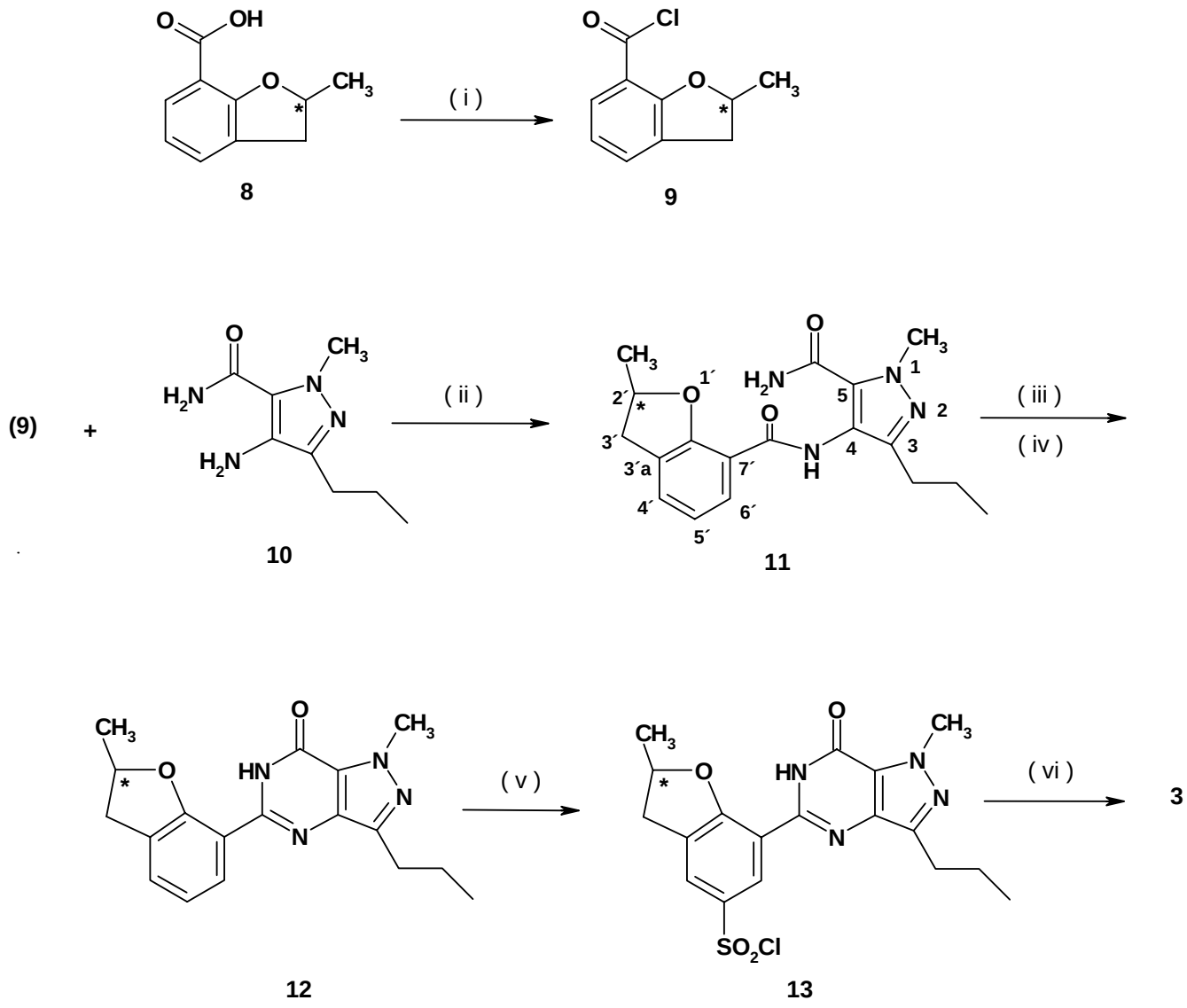
(viii) CO_2(s), -78 ^{o}C

(ix) conc. HCl

The methodology adopted here is essentially similar to that reported for related systems.[6,9] The racemic acid **(8a)** was resolved into its enantiomers (-)-**8b** and (+)-**8c** by fractional crystallization of their (-)-

cinchonidine and (+)-cinchonine diastereomeric salts, respectively, following reported procedures for resolving the 5-chloro[12] and 5-sulfamoyl[13] analogs of **8a**.

Scheme II



(i) $SOCl_2$ / benzene, Δ

(ii) NEt_3 / benzene, Δ

(iii) *tert*–BuO^-K^+ / *tert* –BuOH , Δ

(iv) 3N aq. HCl

(v) $ClSO_3H$ / 65-70 ^{0}C, 2 h

(vi) 1-methylpiperazine, THF / rt

Compounds (**3,8,9** and **11-13)**

a	**b**	**c**
(±)	(*S*)	(*R*)

The optical purity of (+)-**8c** was measured as 99% ee, and the configuration at C-2 of (+)-**8c** was determined as *R* by X-Ray crystallogrpahy (*vide infra*). The general synthetic route to prepare the target compounds(**3a-c**) commenced with the formation of the bis-amides (**11a-c)** *via* coupling of the particular acid chloride (**9a-c)** with 4-amino-1-methyl-3-propylpyrazole-5-carboxamide **(10)** (Scheme II). The latter is obtained from ethyl 2,4-dioxoheptanoate according to established methodology. [1,14] Cyclization of **11a-c** with potassium *tert*-butoxide in refluxing *tert*-butanol yielded the corresponding pyrazolo[4,3-*d*]pyrimidin-7-one derivatives (**12a-c)**. Selective chlorosulfonylation at C-7 of **12a-c** gave the corresponding intermediates (**13a-c)** which, upon treatment with 1-methylpiperazine, furnished the desired products (**3a-c)**.

Spectral Data

The IR, MS and NMR spectral data and microanalyses of the new compounds (**3,11-13)** conform with the suggested structures, and are included in the experimental part. Thus, their MS spectra display the correct M^+ for which the measured high resolution data are in good agreement with the calculated values based on the respective molecular formulas. ^{1}H-Signal assignments to the different protons are straightforward. ^{13}C-Assignments follow from DEPT, HMBC and HMQC experiments.

Crystal Structure Determination of (+)-8c

Colorless block crystals were grown by allowing a solution of **8c** in *iso*propyl ether / dichloromethane solvent system (10:3 v/v) to stand at ambient temperature for 48 h (open flask); crystal dimensions: 0.25 × 0.2 × 0.15 mm. Crystal data for $C_{10}H_{10}O_3$: FW = 178.18, monoclinic, space group $P2_1$ with a = 7.4840 (5), b = 9.3550 (7), c = 12.7760 (7) Å , α = 90°, β = 105.502 (5)°, γ = 90°, V = 861.94 (10) Å^3, Z = 2, d_{calc} = 1.373 g/cm^3. Data collection was made at 213 (2) K , using an ENRAF - NONIUS CAD4 diffractometer operating in the omega scan mode . 3851 Independent reflections were measured within the range θ = 5.94 - 64.92° using Cu-K$_\alpha$ radiation (λ = 1.54184 Å). The unit cell parameters and orientation matrices for the data collection were obtained using the setting angles of 25 reflections (θ = 17.12 - 29.4°). The structure was solved by direct method using the program SHELXS 86.[15] All non - hydrogen atoms were refined anisotropically by full - matrix least - squares procedure based on F^2 using all unique data with SHELXL 97.[16] The hydrogen atoms have been found in the difference Fourier map and were refined isotropically. This resulted in *R*-values R_1/wR_2 = 0.0558 / 0.1396 for all data and 0.0491 / 0.1338 for the 2903 observed reflections and 316 variable parameters ; GOF = 1.066, largest peak and hole in final Fourier difference map were 0.202 and - 0.184 e / Å^3 , respectively .

Selected bond lengths and angles are given in Table 1 for (*R*)-**8c**, and for which the molecular structure is displayed in Figure 1 . The asymmetric unit comprises two half-molecules, thus forming a unit cell with slightly different molecules of the same configuration .

Table 1 . Selected bond lengths (Å) and angles (°) for (*R*) –**8c**

O (1)-C(8)	1.357(3)	C (8)-O(1)-C(2)	108.0 (2)
O (1)-C(2)	1.475(3)	O (1)-C(2)-C(20)	107.9 (2)
C (2)-C(3)	1.533(3)	O (1)-C(2)-C(3)	105.7 (2)
C (3)-C(9)	1.502(3)	C (20)-C(2)-C(3)	115.3 (3)
C (8)-C(9)	1.392(3)	C (9)-C(3)-C(2)	103.0 (2)
C (2)-C(20)	1.496(3)	C (9)-C(8)-C(7)	121.6 (3)
O (2)-C(70)	1.304(3)	C (8)-C(9)-C(3)	108.0 (3)
O (3)-C(70)	1.237(3)	O (3)-O(70)-O(2)	122.1 (3)

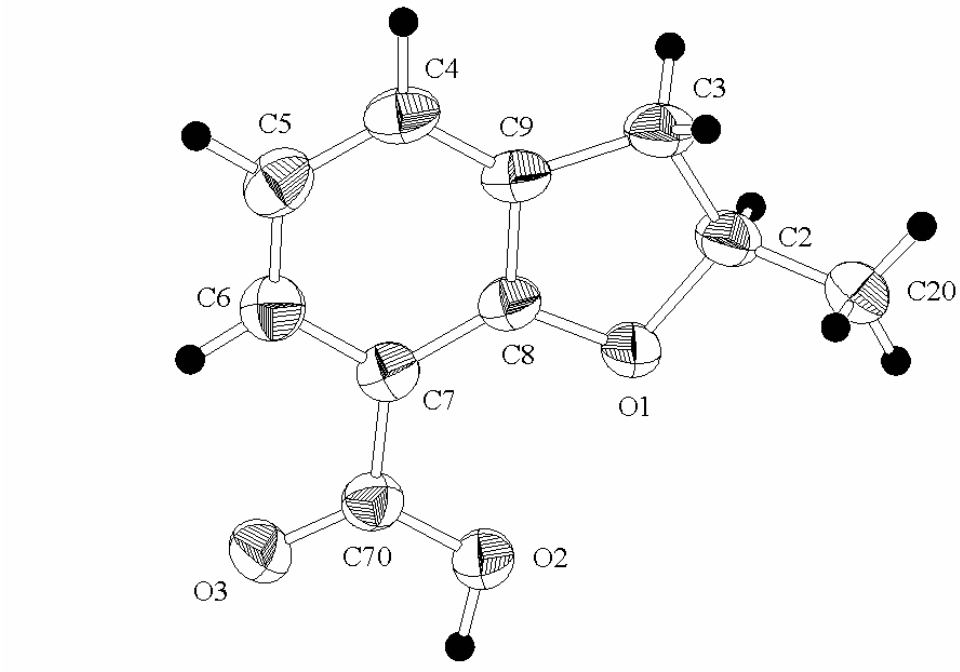


Figure 1. ORTEP plot of the molecular structure of (*R*)-**8c**

Calculations based on SHELXL 97[16] using Fiedel pairs led to a Flack parameter of 0.1233. This value indicates *R*-configuration for (+)-**8c**. Further information of the crystal structure data can be ordered from the Cambridge Crystallographic Data Center under the depository number CCDC 161090 .

Preliminary Pharmacological Results

Viagra® (**1**) and Biagra (**2**) were previously noted to induce relaxation of the artery with almost the same potency.[7] In the present work, the *in vitro* vasorelaxant activity of the enantiomers (**3b**) and (**3c**) has been evaluated on rat isolated thoracic aorta precontracted with 40 mM KCl (that induced stable contraction for 90 min) in the presence of endothelium. It can be seen from the preliminary results, as presented in Figure 2, that the vasorelaxant potencies of (*R*)-**3b** and (*S*)-**3c** are very close, but clearly higher than that of Biagra (**2**) and, by inference, Viagra® (**1**).

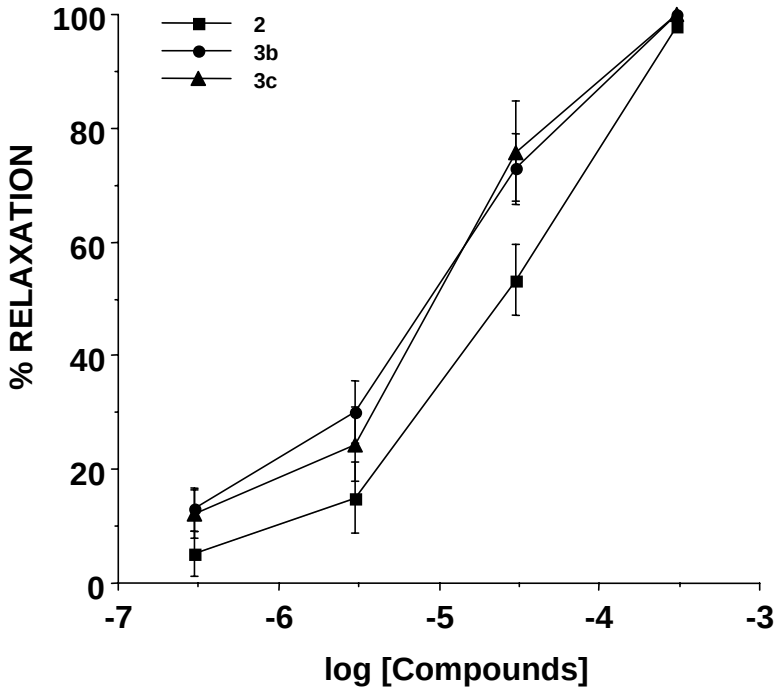


Figure 2 . Vasorelaxant activity of **2** and **3b**,**c**

We envisage that **2** and **3** operate as vasodilating agents by two different, albeit complementary, mechanisms: (i) Direct inhibition of cellular smooth muscle PDE-V, in a relatively rapid mode of action. (ii) Stimulation of NO Synthase with ultimate increase in NO levels, perhaps *via* a comparatively slower and indirect process. The latter hypothesis is currently the subject of experimental investigation, and additional bio-studies with this series of molecules will be reported in due course.

EXPERIMENTAL

2-Allylphenol, *N, N, N,′N ′*-tetramethylethylenediamine (TMEDA), *n*-butyllithium solution (2.5M, in *n*-hexane), (+)-cinchonine and (-)-cinchonidine were purchased from *ACROS* Organics . Melting points (uncorrected) were determined on an electrothermal Mel-Temp. Apparatus. ^{1}H- and ^{13}C-NMR spectra

were measured on a Bruker WM-400 and a Bruker DPX-300 instruments with TMS as internal reference. EIMS spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV; ion source temperature = 200 °C. IR spectra were recorded as KBr discs on a Burker IFS 48. Microanalysis was preformed at the Microanalytical Laboratory-Inorganic Chemistry Department, Morgenstelle 18
(Tübingen Universität , Germany).

Enantioselective Gas -Chromatographic Analysis

Enantioselective analysis was performed on a gas chromatograph (Carlo Erba instrumentation, Milan, Italy) equipped with a flame ionization detector (FID). The chiral stationary phase , Chirasil β. Dex with 11 spacer Permethylated-β-cyclodextrin, 40%(w/w) was dissolved in PDMS+SI-H(Gelest,ABCR GmbH & Co, Karlsruhe, Germany) and coated on 20 m × 0.25 mm fused silica capillary column (0.25 μm film thickness). The analysis conditions were: Injector temperature = 250 °C, FID temperature = 300 °C, oven temperature = 145 °C during the simultaneous separation of enantiomers of the racemic acid (**8a).** Hydrogen was used as the carrier gas (60 Kpa column head pressure). The retention time of the (*S*)-**8b** and (*R*)-**8c** acids were 57.1 and 59.6 min., respectively. The acid was identified by using GC/MSD-system HP 6890/5973 (Hewlett Packared, Waldbronn,Germany) equipped with an HP 7683 autosampler. The enantiomeric excess (% ee) was found to be 99 % for the (*R*)-compound **(8c)**, and 95 % for the (*S*)-enantiomer **(8b)**.

(±)-2-Methyl-2,3-dihydrobenzofuran-7-carboxylic acid (8a)

Method A : the title compopund was prepared from methyl O-allylsalicylate **(4)**[10] according to a published procedure.[9] Overall yield of **8a** 46% ; mp 128-129 ^{o}C (lit.,[9] mp 127-128 ^{o}C).

Method B : Compound (**8a)** was also prepared according to the following procedure as reported for related analogs[9] : To a solution of (±)-2-methyl-2,3-dihydrobenzofuran (**7)**[11] (9.0 g ; 67 mmol) and TMEDA (17.4 g ; 150 mmol) in anhydrous *n*-hexane (250 mL) was added at rt *n*-butyllitium solution (2.5 M, in *n*-hexane ; 60 mL). The reaction mixture was further stirred at rt for 1 h , cooled to –78 ^{o}C and transferred, *via* a double-ended needle, onto excess dry ice (100 g). The whole operation was conducted under dry argon atmosphere. The resulting mixture was allowed to warm-up to rt, treated with 4 N aqueous NaOH solution (250 mL) and ether (250 mL), and shaken well in a separatory funnel. The aqueous phase was separated, made acidic with 6 N hydrochloric acid and extracted with dichloromethane (2 x 150 mL). The combined organic extracts were dried (Na_2SO_4), dichloromethane was evaporated and the residual solid product was recrystallized from *iso*propyl ether-methanol solvent pair (95:5 v/v). Yield of pure **8a** 8.0 g (67 %) ; mp 129-130 ^{o}C, undepressed upon admixture with an authentic sample of **8a** prepared *via* method A above.

Optical resolution of the acid **((±)-8a)**

Optical resolution of the racemic acid (**8a)** was achieved according to the following procedure which was reported for the (**±)** 5-chloro[12] and 5-sulfamoyl[13] analogs of **8**.

(*S*)-*2-Methyl- 2,3- dihydrobenzofuran -7-carboxylic acid* (8b)

A mixture of (-)-cinchonidine (10.3 g ; 35 mmol) and *iso*propanol (40 mL) was added to a mixture of racemic 2-methyl-2,3-dihydrobenzofuran-7-carboxylic acid (**8a**) (6.2 g; 35 mmol) and *iso*prpanol (40 mL). The resulting mixture was dissolved by warming and was allowed to stand overnight at rt. The precipitated diastereomeric salts were collected by filtration, recrystallized from EtOH / MeOH (20 mL /10 mL), and then recrystallized once more from EtOH / MeOH (15 mL /8 mL) to give 1.4 g of the (-)-cinchonidine salt of (*S*)-**8b**. This salt was suspended in water (15 mL) and acidified by addition of 6 N HCl with stirring. The precipitate was collected by suction filtration and recrystallized from aqueous EtOH to affored pure (*S*)-**8b**. Yield 0.56 g (9%); mp 130-131 °C. $[\alpha]_D^{20}$ = - 6.2 ^{o} (*c*~0.2, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found : C, 67.12; H, 5.48 .

(*R*)-*2-Methyl-2,3-dihydrobenzofuran-7- carboxylic acid* (8c)

A mixture of (+)-cinchonine (10.3 g; 35 mmol) and EtOH (50 mL) was added to a mixture of racemic **8a** (6.2 g; 35 mmol) and EtOH (50 mL). The mixture was dissolved by warming and was allowed to stand overnight at rt. The precipitated diasteriomeric salts were collected by filtration, recrystallized from EtOH (60 mL), and then recrystallized once more from *iso*propanol (50 mL) to give 1.3 g of the cinchonine salt of (*R*)-(**8c**) which was suspended in water (15 mL) and acidified by addition of 6 N HCl with stirring. The white precipitate was collected by suction filtration and recrystallized from aqueous EtOH to affored 0.5 g (8 %) of (*R*)-**8c**; mp 130°-131 °C. $[\alpha]_D^{20}$ = + 6.5 ^{o} (*c*~0.2, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.31; H, 5.43. The (*S*)-and (*R*)-acids (**8b, 8c**), thus obtained, display identical spectral properties (IR, ^{1}H- / ^{13}C - NMR, MS-EI) to those described for the racemic acid (**8a**).

(±) *4-(2-Methyl-2,3-dihydro-7-benzofuroyl)amino-1-methyl-3-propyl-5-pyrazolecarboxamide* (11a)

A mixture of the (**±)**-acid (**8a**) (3.0 g ; 17 mmol) and $SOCl_2$ (12 mL; 165 mmol) in dry benzene (30 mL) was refluxed (oil bath, 85 °C) for 3 h. Excess $SOCl_2$ and benzene were then removed in vaccuo, and the residual acid chloride was treated with a solution of the 4-aminopyrazole derivative (**10)**[14] (3.1 g ; 17 mmol) in anhydrous benzene (25 mL), followed by addition of triethylamine (5 mL; 36 mmol). The resulting mixture was refluxed for 3 h, benzene was then evaporated, the solid residue was soaked in cold water (80 mL), the remaining solid product was collected by suction filtration, washed with water and

recrystallized from aqueous ethanol. Yield 4.6 g (79 %) ; mp 140 – 141 °C. *Anal.* Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36. Found: C, 63.09; H, 6.42; N, 16.25 ; MS-EI *m/z* (% rel. int.): 342 (M^+, 4); HRMS-Calcd: 342.16919. Found: 342.17270), 325(5), 324 (4), 310 (1), 161(100), 133 (8), 105 (4); IR (KBr) : ν /cm^{-1} = 3536(m), 3339 (s), 3270 (m), 2962 (m), 2929 (w), 2870 (w), 1685 (s, amide), 1647 (m), 1609 (w), 1533 (m), 1450 (m), 1290 (s), 1191 (m), 1028 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.56 (d, *J* = 6.3 Hz, 3H, C2′-$C\underline{H}_3$), 1.65 (m_c , 2H , $CH_2C\underline{H}_2CH_3$), 2.55 (t , *J* = 7.6 Hz, 2H, $C\underline{H}_2CH_2CH_3$), 2.95 (dd, J_{AB} = 15.6 Hz, J_{AX} = 7.5 Hz , 1H, C3′-H_A, part of ABX system), 3.45 (dd, J_{BA} = 15.6 Hz , J_{BX} = 8.8 Hz , 1H , C3′-H_B), 5.20 (m_c , 1H , C2′-H , X-portion of the ABX system), 4.06 (s, 3H , N-CH_3), 5.89, 7.96 (two br s, 1H each of $CONH_2$), 7.00 (dd, *J* = 7.9 Hz, *J* = 8.5 Hz, 1H , C5′-H), 7.39 (dd, *J* = 8.5 Hz, *J* = 1.1 Hz,1H, C4′-H), 7.94 (dd, *J* = 7.9 Hz, *J* = 1.1 Hz,1H, C6′-H), 9.04 (s, 1H, NHCO); ^{13}C NMR (75 MHz , $CDCl_3$): δ 13.9 ($CH_2CH_2\underline{C}H_3$), 21.8 (C2′- $\underline{C}H_3$), 22.4 ($CH_2\underline{C}H_2CH_3$), 27.7 ($\underline{C}H_2CH_2CH_3$), 36.3 (C-3′) , 39.3 (N-$\underline{C}H_3$), 82.2 (C-2′), 114.4 (C-7′), 115.7 (C-4), 121.3 (C-5′), 128.2 (C-3′a), 129.5 (C-6′), 129.6 (C-4′), 133.1(C-5), 146.9 (C-3), 157.5 (C-7′a), 161.7 ($CONH_2$), 166.0 (NHCO).

(*S*)-(*4-(2-Methyl-2,3-dihydro-7-benzofuroyl)amino-1-methyl-3-propyl-5-pyrazolecarboxamide* (11b)

This compound was prepared from (*S*)-(**8b**) (0.50 g; 2.8 mmol) and **10** (0.51 g; 2.8 mmol) by following the same procedure described above for obtaining (±)-**11b**. Yield 0.78 g (81 %); mp 141-142 °C. $[\alpha]_D^{20}$ = -17.9 ^{o} (*c*~0.2 , $CHCl_3$). *Anal.* Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36. Found: C, 62.88; H, 6.39; N, 16.37.

(*R*)-*4-(2-Methyl-2,3-dihydro-7-benzofuroyl)amino-1-methyl-3-propyl-5-pyrazolecarboxamide* (11c)

This compound was prepared from (*R*)-**8c** (0.50 g ; 2.8 mmol) and **10** (0.51 g ; 2.8 mmol) by following the same procedure described above for obtaining (±)-**8a**. Yield 0.75 g (78 %); mp 141-142 °C. $[\alpha]_D^{20}$ = +18.8^o (*c*~0.2, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36. Found: C, 62.94; H, 6.42; N, 16.34. The (*S*)- and (*R*)-bisamides (**11b, 11c)**, thus obtained, display identical spectral properties to those listed above for the racemate **(11a)**.

(±)-*5-(2-Methyl-2,3-dihydro-7-benzofuryl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7- one* (12a)

Potassium *t*-butoxide (3.5 g ; 30 mmol) was added to a stirred suspension of the bis-amide ((±)-**11a**) (3.4 g ; 10 mmol) in *t*-butanol (80 mL), and the resulting mixture was heated under reflux for 10 h (oil bath,

95 °C), then allowed to cool to rt . Water (70 mL) was added, the solution was neutralized with 5 % HCl to pH ~ 7, and cooled to about 5-10 °C. The precipitated solid product was collected by suction filtration, washed with cold water and dried. Yield 2 g (86 %) ; mp 176-178 °C. *Anal.* Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.32; H, 6.03; N, 17.10 ; MS-EI *m/z* (% rel. int.): 324 (M^+, 53); HRMS-calcd: 324.15863. Found: 324.16106), 309(27), 296(100), 281(5), 182(14), 153(10), 136(49), 132(10); IR (KBr) : ν /cm^{-1} = 3314 (s), 2962 (m), 2923 (w), 2864 (w), 1693 (s , pyrimidone), 1569 (s), 1440 (m), 1384 (m), 1313 (w), 1206 (m), 1039 (w); ^{1}H NMR (300 MHz , $CDCl_3$) : δ 1.05 (t , J = 7.4 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.60 (d , J = 6.3 Hz , 3H , C2′-$C\underline{H}_3$) , 1.87 (m_c , 2H , $CH_2C\underline{H}_2CH_3$), 2.92 (t , J = 7.5 Hz, 2H, $C\underline{H}_2CH_2CH_3$), 2.90 (dd, J_{AB} = 15.6 Hz , J_{AX} = 7.4 Hz , 1H, C3′-H_A, part of ABX system), 3.39 (dd , J_{BA} = 15.6 Hz , J_{BX} = 8.7 Hz , 1H , C3′-H_B), 5.20 (m_c, 1H, C2′-H, X-portion of the ABX system), 4.25 (s, 3H, N-CH_3), 7.00 (dd, J = 7.3 Hz, J = 7.8 Hz, 1H ,C5′-H), 7.26 (dd , J = 7.3 Hz, J = 1.0 Hz, 1H, C4′-H), 8.23 (dd, J = 7.8 Hz, J = 1.0 Hz, 1H, C6′-H), 10.80 (br *s*, 1H, N6-H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 14.1 ($CH_2CH_2\underline{C}H_3$), 21.9 (C2′-$\underline{C}H_3$), 22.3 ($CH_2\underline{C}H_2CH_3$), 27.8 ($\underline{C}H_2CH_2CH_3$), 36.2 (C-3′), 38.2 (N-$\underline{C}H_3$), 82.0 (C-2′), 114.4 (C-7′), 121.5 (C-5′), 124.4 (C-7a), 127.4 (C-4′), 127.7 (C-6′), 128.4 (C-3′a) , 146.5 (C-3), 147.3 (C-5), 154.1 (C-7), 156.4 (C-7′a) .

(*S*)-*5-(2-Methyl-2,3-dihydro-7-benzofuryl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7- one* (12b)

This compound was prepared from (*S*)-**11b** (0.68 g ; 2.0 mmol) by following the same procedure described above for obtaining (±)-**12a** . Yield 0.52 g (80 %) ; mp 178 - 179° C. $[\alpha]_D^{20}$ = +38.2 ^{o} (*c*~0.3, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.30; H, 6.15; N, 17.08.

(*R*)-*5-(2-Methyl-2,3-dihydro-7-benzofuryl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7- one* (12c)

This compound was prepared from (*R*)-**11c** (0.68 g ; 2.0 mmol) by following the same procedure described above for obtaining (±)-**12a** . Yield 0.54 g (83 %) ; mp 178-179 °C , $[\alpha]_D^{20}$ = -40.2 ^{o} (*c*~0.3, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.42; H, 6.10; N, 17.15. Each of the (*S*)- and (*R*)-enantiomers **(12b,12c)**, thus obtained, displays identical spectral properties to those noted above for the racemate (**12a**).

(±)-*5-(5-Chlorosulfonyl -2-methyl-2,3-dihydro-7-benzofuryl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one* (13a)

Compound ((**±)-12a)** (3.24g ;10 mmol) was added protionwise to chlorosulfonic acid (10 mL; 150 mmol) at 0 °C (ice-salt bath) with stirring. The resulting yellow solution was then allowed to warm to rt, and was then heated slowly to 65-70 °C (oil bath) for 2 h. The reaction mixture was cautiously poured into crushed ice (100g), the white solid (chlorosulfonyl derivative), that has precipitated , was filtered immediately, dried, and used as such in the next step. Yield 3.6 g (85 %); mp 170-172 °C. *Anal.* Calcd for $C_{18}H_{19}N_4O_4ClS$: C, 51.12; H, 4.53; N, 13.25; Cl, 8.38; S, 7.58. Found: C, 50.81; H, 4.74; N, 13.31; Cl, 8.20; S, 7.36; MS-EI *m/z* (% rel. int.): 422(M^+, 54); HRMS-calcd: 422.08156. Found: 422.08396), 407(19), 394(100), 323(22), 294(17), 279(4), 147(11), 136(51), 103(8); IR (KBr): ν /cm^{-1} = 3323 (s, NH) , 2963 (m), 2916 (w), 2848 (w), 1703 (s, pyrimidone), 1636 (w), 1603 (m), 1443 (m), 1374 (s), 1217 (s , 1073 (w); ^{1}H NMR (400 MHz , $CDCl_3$): δ 1.05 (t , *J* = 7.4 Hz , 3H, $CH_2CH_2C\underline{H}_3$), 1.70 (d , *J* = 6.3 Hz , 3H , C2′-$C\underline{H}_3$), 1.87 (m_c, 2H, $CH_2C\underline{H}_2CH_3$), 2.95 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2CH_2CH_3$), 3.06 (dd , J_{AB} = 16.2 Hz , J_{AX} = 7.3 Hz , 1H, C3′-H_A , part of ABX system), 3.60 (dd , J_{BA} = 16.2 Hz , J_{BX} = 8.9 Hz, 1H, C3′- H_B), 5.44 (m_c, 1H, C2′-H, X-portion of the ABX system), 4.27 (s, 3H , N-CH_3), 7.90 (d, *J* = 1.8 Hz ,1H , C4′-H), 8.96 (d, *J* = 1.8 Hz,1H, C6′-H), 10.55 (br *s*, 1H , N6-H); ^{13}C NMR (100 MHz , $CDCl_3$): δ 14.0 ($CH_2CH_2\underline{C}H_3$), 21.9 (C2′-$\underline{C}H_3$), 22.4 ($CH_2\underline{C}H_2CH_3$), 27.6 ($\underline{C}H_2CH_2CH_3$), 35.6 (C-3′), 38.3 (N-$\underline{C}H_3$), 84.4 (C-2′), 115.2 (C-7′), 124.5 (C-7a), 125.6 (C-4′), 128.9 (C-6′), 131.3 (C-3′a), 137.7 (C-5′), 138.0 (C-3a), 144.7 (C-5), 147.1 (C-3), 153.6 (C-7), 161.1 (C-7′a).

(*S*)-*5-(5-Chlorosulfonyl -2-methyl-2,3-dihydro-7-benzofuryl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one* (13b)

This compound was prepared from (*S*)-**12b** (0.39 g ; 1.2 mmol) by following the same procedure described above for obtaining (±)-**13a**. Yield 0.42 g (83 %) ; mp 170-171 °C. $[\alpha]_D^{20}$ = +14.9 ^{o} (*c*~0.2, $CHCl_3$ + MeOH (1:1 v/v)). *Anal.* Calcd for $C_{18}H_{19}N_4O_4ClS$: C, 51.12; H, 4.53; N, 13.25; Cl, 8.38; S, 7.58. Found: C, 51.21; H, 4.33; N, 13.18; Cl, 8.31; S, 7.65.

(*R*)-*5-(5-Chlorosulfonyl -2-methyl-2,3-dihydro-7-benzofuryl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one* (13c)

This compound was prepared from (*R*)-**12c** (0.39 g ; 1.2 mmol) by following the same procedure described above for obtaining (±)-**13a**. Yield = 0.41 g (81 %) ; mp 170-171 °C. $[\alpha]_D^{20}$ = - 15.7 ^{o} (*c*~0.2, $CHCl_3$+MeOH (1:1 v/v)). *Anal.* Calcd for $C_{18}H_{19}N_4O_4ClS$: C, 51.12; H, 4.53; N, 13.25; Cl,

8.38; S, 7.58. Found: C, 51.05; H, 4.66; N, 13.12; Cl, 8.20 ; S, 7.44. Each of the (*S*)-**13b** and (*R*)-**13c**, thus obtained, shows identical spectral properties to those noted above for the racemate (**13a**).

(±)*5-[2-Methyl-5-(4-methylpiperazin-1-ylsulfonyl)-2,3-dihydro-7-benzofuryl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7- one* (3a)

The sulfonyl chloride derivative ((±)-**13a**) (3.5 g ; 8.3 mmol) was dissolved in dry THF (35 mL) and treated with a solution of 1-methylpiprazine (2 mL ; 18 mmol) in THF (10 mL). The resulting mixture was stirred at rt for 2.5 h, THF was then removed and the residue was treated with cold water (80 mL). The resulting pale yellow precipitate was filtered under suction, washed with cold water, and recrystallized from aqueous EtOH. Yield 3.4 g (84 %); mp 184 –186 °C. *Anal.* Calcd for $C_{23}H_{30}N_6O_4S$: C,56.77; H, 6.21; N, 17.27; S, 6.59. Found: C, 56.39; H, 5.98; N, 17.07; S, 6.48 ; MS-EI *m/z* (% rel. int.): 486 (M^+, 1); HRMS-calcd: 486.20493. Found: 486.20448), 416 (18), 323 (3), 136(3), 99 (100). IR (KBr) : ν /cm^{-1} = 3326 (s, NH), 2939 (w), 2847 (w), 2798 (m), 1693 (s, pyrimidone), 1605 (m), 1571 (s), 1489 (w), 1447 (m), 1390 (w), 1356 (m), 1287 (m), 1170 (s), 1077 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (t , *J* = 7.4 Hz , 3H, $CH_2CH_2C\underline{H}_3$), 1.65 (d , *J* = 6.3 Hz , 3H , C2′-C$\underline{H}_3$), 1.85 (m_c, 2H, $CH_2C\underline{H}_2CH_3$), 2.28 (s, 3H, N4″-C$\underline{H}_3$), 2.51 (t, *J* = 4.8 Hz, 4H, C-3″-H/C-5″-H), 2.85 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2CH_2CH_3$) , 3.10 (br t, *J* = 4.8Hz, 4H, C-2″-H/C-6″-H), 3.06 (dd, J_{AB} = 16.0 Hz, J_{AX} = 7.3 Hz, 1H, C3′-H_A , part of ABX system), 3.50 (dd, J_{BA} = 16.0 Hz, J_{BX} = 8.9 Hz, 1H , C3′-H_B), 5.35 (m_c, 1H, C-2′H, X-portion of the ABX system), 4.27 (s, 3H , N_1-CH_3), 7.65 (d, *J* = 1.3 Hz ,1H , C4′-H), 8.65 (d, *J* = 1.3 Hz, 1H, C6′-H), 10.60 (br *s*, 1H , N6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 ($CH_2CH_2\underline{C}H_3$), 21.9 (C2′-$\underline{C}H_3$), 22.2 ($CH_2\underline{C}H_2CH_3$), 27.6 ($\underline{C}H_2CH_2CH_3$), 35.8 (C-3′), 38.3 (N_1-$\underline{C}H_3$), 45.7 (N4″-CH_3), 46.0 (C-2″/C-6″), 54.0 (C-3″/C-5″), 83.8 (C-2′), 115.0 (C-7′) , 124.5 (C-7a), 126.5 (C-4′), 128.0 (C-6′), 129.0 (C-3′a), 130.1 (C-5′), 138.2 (C-3a), 145.5 (C-5), 147.0 (C-3), 153.7 (C-7), 159.5 (C-7′a).

(*S*)-*5-[2-Methyl-5-(4-methylpiperazin-1-ylsulfonyl)-2,3-dihydro-7-benzofuryl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7- one* (3b)

This compound was prepared from (*S*)-**13b** (0.42 g; 1.0 mmol) by following the same procedure described above for obtaining (±)-(**3a**). Yield 0.38 g (78 %) ; mp 186-187 °C. $[\alpha]_D^{20}$ = + 15.2 ^{o} (*c* ~ 0.2, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{30}N_6O_4S$: C,56.77; H, 6.21; N, 17.27; S, 6.59. Found: C, 56.48; H, 5.10; N, 17.05; S, 6.36.

(*R*)-*5-[2-Methyl-5-(4-methylpiperazin-1-ylsulfonyl)-2,3-dihydro-7-benzofuryl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7- one* (3c)

This compound was prepared from (*R*)-**13c** (0.42 g; 1.0 mmol) by following the same procedure described above for obtaining ((±)-**3a**)**.** Yield 0.39 g (80 %); mp 186-187 °C . $[\alpha]_D^{20}$ = -16.0 ^{o} (*c*~0.2, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{30}N_6O_4S$: C,56.77; H, 6.21; N, 17.27; S, 6.59. Found: C, 56.42; H, 6.07; N, 17.11; S, 6.42. The (*S*)- and (*R*)- compounds (**3b** and **3c)** display identical spectral properties to those described for the racemic modification (**3a**).

ACKNOWLEDGEMENTS

We wish to thank BMBF, Bonn-Germany, the University of Jordan and the University of Sharjah-UAE for financial support. Our thanks are also due to Professor V. Schurig and Mr. A. Ghanem (Tübingen Universität) for the chiral HPLC measurements .

REFERENCES

(*) Corresponding author, e-mail: mustelab@ju.edu.jo

1. N. K. Terrett, A. S. Bell, D. Brown, and P. Ellis, *Bioorg. Med. Chem. Lett.*, 1996 , **6** , 1819.
2. P. Ellis and N . K. Terrett (Pfizer Ltd., UK; Pfizer Inc.; Pfizer Research and Development Co., N.V./ S.A.). *PCT Int. Appl* **WO 94 28,902** (1994) , 21 pp (*Chem. Abstr.*, 1995, **122** , 187627n).
3. (a) J. Rajfer, W. J. Aronson, P. A. Bush, F. J. Dorey, and L. J. Ignarro, *N. Engl. J. Med.*, 1992, **326,** 90; (b) F. Holmquist, H. Hedlund, and K. E. Anderson, *J. Physiol.* (london), 1992, **449,** 295; (c) A. L. Burnett, C. J. Lowenstein, D. S. Bredt , T. S. Chang , and S. H. Snyder, *Science*, 1992, **257**, 401; (d) G. Wagner and D. Saenz, *Br. Med. J.***,** 1998 , **316**, 678.
4. (a) V. Mirone, A. Palmieri, and G. Nistico, *Acta Urol. Ital. Suppl.*, 1992, **4**, 11; (b) K.–E. Anderson and G. Wanger, *Physiol. Rev.*, 1995, **75**, 191; (c) A. L. Burnett, *J. Urol.*, 1997, **157,** 320; (d) L. J. Ignarro, P. A. Bush, G. M. Buga, K. S. Wood, J. M. Fukuto, and J. Rajfer, *Biochem. Biophys. Res. Commun.*, 1997 , **170**, 843.
5. (a) M. Boolell, M. J. Allen, S. A. Ballard, S. Gepi-Attee, G. J. Muirhead, A. M. Naylor, I. H. Osterloh, and C. Gingell, *Int. J. Impot. Res.*, 1996, **8**, 47; (b) A. G. Carter, S. A. Ballard, and A. M. Naylor, *J. Urol.*, 1998, **160**, 242; (c) A. T. Chuang, J. D. Strauss, R. E. Murphy, and W. D. Steers, *J. Urol,*, 1998, **160**, 257; (d) J. D. Corbin and S. H. Francis, *J. Bioorg. Chem.*, 1999, **274**, 13729, and refernces therein.
6. (a) W. Voelter, M. M. El-Abadelah, S. S. Sabri , and M. A. Khanfar, *Z. Naturforsch.*, 1999, **54b** , 1469; (b) W. Voelter, C. M.-Mössmer, M. A. Khanfar, M. M. El-Abadelah , and S. S. Sabri, *Z. Naturforsch.*, 1999 , **54b**, 1602.

7. R. J. Abdel-Jalil , Y. Al-Abed , M. M. El-Abadelah , M. A. Khanfar , S. S. Sabri , and W. Voelter (The Picower Institute for Medical Research , USA), *PCT Int. Appl* . **WO 01 03 644** (2001) , 37pp (*Chem* . *Abstr*., 2001, **134**, 95497q).
8. G. D. McCallion, *Current Org. Chem.*, 1999 , **3**, 67.
9. P. Stanetty, H. Koller , and G. Pürstinger, *Monatsh. Chem.*, 1990 , **121,** 883.
10. A. I. Meyers, M. Reuman , and R. A. Gabel, *J. Org. Chem.*, 1981 , **46**, 783.
11. J. Entel, H. R. Clarence , and H. C. Howard, *J. Am. Chem. Soc.*, 1951 , **73**, 2365.
12. T. Kuroita, M. Yasumoto, K. Inaba, M. Sakamori, S. Takehara, and T. Kawakita, *Chem. Pharm. Bull.*, 1994 , **42**, 95.
13. S. Murakami, N. Marubayashi , T. Fukuda, S. Takehara , and T. Tahara , *J. Med. Chem* . , 1991 , **34** , 261.
14. M. M. El-Abadelah, S. S. Sabri, M. A. Khanfar, H. A. Yaseen , and W. Voelter, *J. Heterocycl. Chem* . , (submitted).
15. G. M. Sheldrick, *Acta Crystallogr.*, 1990 , **A46** , 467.
16. G. M. Sheldrick, SHELXL 97, 1997, *Fortran Program for Crystal Structure Refinement*, Universität Göttingen, Germany.