Synthesis and Properties of *iso*Viagra [1]. A 2-Methyl-2*H*-pyrazolo[4,3-*d*]pyrimidin-7-one Isomer of Viagra®

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The synthesis and spectral properties (ir, ms, nmr) of a substituted 2-methyl-*2H*-pyrazolo[4,3-*d*]-pyrimidin-7-one (**3**), an isomer of Viagra®, are described. The key synthon, 4-amino-1-methyl-5-propyl-3-pyrazolecarboxamide (**7**), is prepared *via* the reaction of ethyl 2,4-dioxoheptanoate with methylhydrazine, followed by cyclization, nitration, amidation, and nitro group reduction. Interaction of **7** with 2-ethoxybenzoyl chloride yielded the respective bis-amide (**8**) which was cyclized in polyphosphoric acid to the corresponding pyrazolo[4,3-*d*]pyrimidin-7-one derivative **9**. Chlorosulfonylation of **9**, and subsequent treatment with 1-methylpiperazine furnished *iso*Viagra (**3**).

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Introduction.

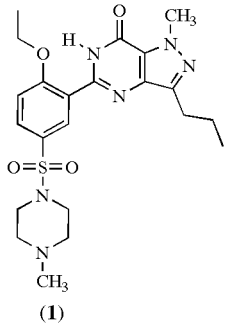
Viagra® (Sildenafil citrate) (**1**), originally conceived as a drug for the treatment of cardiovascular disease, turned out to be effective for male erectile dysfunction (MED) [2]. The process of erection involves release of nitric oxide (NO), a signaling molecule that activates the cytosolic guanylate cyclase enzyme to produce cyclic guanylmonophosphate (*c*GMP) which, in turn, triggers the relaxation of smooth muscle cells – such as in the walls of the blood vessels supplying the penis [3]. Viagra® depends on this NO/*c*GMP pathway for its erectogenic effect by selectively inhibiting type 5 phosphodiesterase (PDE-5) isozyme that hydrolyses *c*GMP, thereby preventing breakdown of the vasodilator *c*GMP to inactive GMP [4]. So, Viagra® can be administered orally to raise the concentration of *c*GMP in the *corpus cavernosum* and cure cases of impotence caused by inadequate production of NO.

Quite recently, we have reported on the synthesis and properties of Biagra (**2**), a 5-(2,3-dihydro-7-benzofuryl) analog of Viagra® (**1**), that exhibits erectogenic and vasorelaxant properties comparable to **1** [5]. In a previous communication, an X-ray crystal structure determination of **3**, the isomeric 2*H*-2-methylpyrazolo[4,3-*d*]pyrimidine-5-one derivative (we call it *iso*Viagra), revealed non-coplanarity between the 2'-ethoxyphenyl and the pyrazolopyrimidone ring systems [6]. The present work describes the synthesis and spectral characterization of *iso*Viagra (**3**), and of the intermediate synthons shown in Scheme 1. Biotesting experiments on **3** are in progress, and the results will be reported separately.

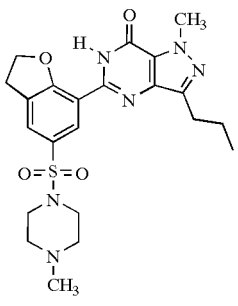
Results and Discussion.

Chemistry.

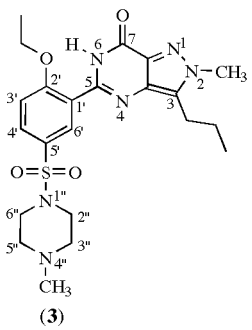
The synthesis of the title compound 2-methyl-2*H*-pyrazolo[4,3-*d*]pyrimidin-7-one derivative (*iso*Viagra) (**3**) is accomplished by the reactions depicted in Schemes 1 and 2. In Scheme 1, 1-methyl-1*H*-5-propylpyrazole-3-carboxylic acid (**4**) is prepared from the reaction between ethyl 2,4-dioxoheptanoate (**A**) [7] and methylhydrazine at 0 - 10 °C, followed by heating of the resultant methylhydrazone in concentrated sulfuric acid at 85 - 90 °C. Nitration of **4** yielded the corresponding 4-nitropyrazole



(**1**)



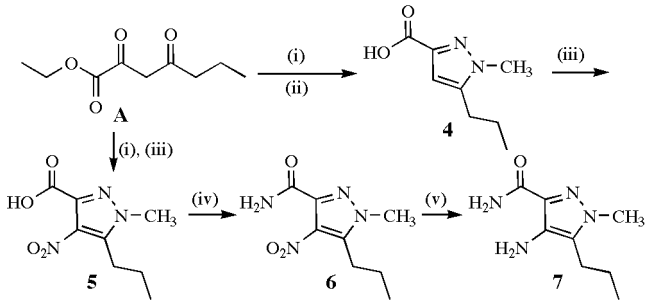
(**2**)



(**3**)

derivative **5** which was also obtained directly by heating the methylhydrazone of **A** in a mixture of concentrated HNO_3 and concentrated H_2SO_4 at 90 – 95 °C for 5 hours. Compound **5** was then converted to the respective 4-nitropyrazole-3-carboxamide (**6**) by heating with thionyl chloride and subsequent work up in concentrated ammonium hydroxide. Stannous(II) chloride reduction of **6** furnished the 4-aminopyrazole-3-carboxamide **7** as the key synthon.

Scheme 1



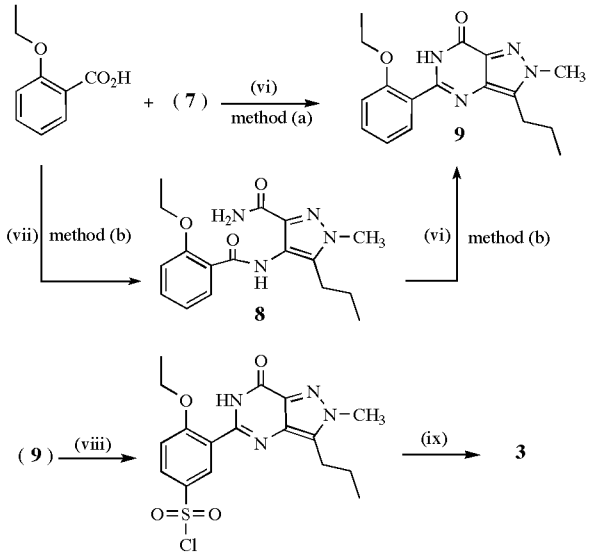
(i) NH_2NHMe; (ii) conc. H_2SO_4, 85 - 90 ºC; (iii) conc. HNO_3/conc. H_2SO_4, 90 - 95 ºC
(iv) $SOCl_2$, Δ/then 30 % aq. NH_3 ; (v) $SnCl_2$/conc. HCl/then NaOH.

In Scheme 2, the pyrazoloamino amide (**7**) is cyclized to the respective 2-methylpyrazolo[4,3-*d*]pyrimidin-7-one (**9**) by stirring with 2-ethoxybenzoic acid in polyphosphoric acid (PPA) at 130 – 140 °C (method (a)). The overall yield of **9** is improved by employing a two-step procedure in which the bis-amide **8** is first preformed from **6** and 2-ethoxybenzoyl chloride, and the isolated product **8** is subsequently cyclized in PPA (method (b)). Comparable PPA-induced cyclocondensation of the related 1,3-dimethylpyrazoloamino amide with various substituted benzoic acids (and of preformed bisamides thereof) to the respective pyrazolopyrimidones is described in the literature [8]. Chlorosulfonation of **9** proceeds selectively at the 5'-position of the 2'-ethoxyphenyl ring to give compound **10** which, upon coupling with 1-methylpiperazine, furnished the target compound *iso*Viagra (**3**). Yields (%), recrystallization solvents, melting points, and microanalyses of the new compounds (**3** – **9**) are included in the experimental part.

Spectral Data.

The spectral data (ms, nmr, and ir) and microanalyses of compounds (**3** - **9**) are in agreement with the proposed structures, and are listed in the experimental part. Thus, their mass spectra display the correct molecular ions, $M^{+\cdot}$, as suggested by the respective molecular formulas. Assignments of the main ir absorption bands, and of the ^1H nmr signals are straightforward.

Scheme 2



(vi) PPA, 130 - 140 °C; (vii) $SOCl_2$, Δ/then (**7**), DMAP, NEt_3, benzene/Δ
(viii) $ClSO_3H$/65 - 70 °C ; (ix) THF, 1-methylpiperazine/20 °C

Distinction of compounds **4** – **7** from their isomeric analogs **4v** – **7v** [2a,c] (Viagra® synthons/Chart 1) follows from the chemical shift values of the *N*-CH_3 proton signals. These protons in the former series resonate at δ-values minor by *ca.* 0.2 ppm, when compared to those of the respective isomers **4v - 7v**, due to the deshielding effect of the adjacent carbonyl moiety in the latter series. Comparable *N*-CH_3 spectral differences and the associated deshielding effect have been reported for related pyrazole-3-(and 5-) carboxylic acids, esters and carboxamides [9]. This *N*-CH_3 spectral trend is also observed and documented in the present study for *iso*Viagra (**3**) and the precursors **8**, **9**, differentiating them from Viagra® (**1**) and its respective precursors. Carbon 13 assignments are based on DEPT and HMBC experiments [10].

EXPERIMENTAL

Diethyl oxalate and 2-pentanone, used in the preparation of ethyl 2,4-dioxoheptanoate (**A**) [6], were purchased from Aldrich. Methylhydrazine, *N*-methylpiperazine, 2-ethoxybenzoic acid, 4-(dimethylamino)pyridine (DMAP) and polyphophoric acid (PPA) were purchased from Acros.

Melting points (uncorrected) were determined on an electrothermal Mel-Temp. apparatus. ^1H and ^{13}C nmr spectra were measured on a Bruker WM-400 spectrometer at (400.14 MHz ^1H, and 100.62 MHz for ^{13}C) with TMS as internal reference. Electron impact (ei) ms spectra were obtained using a Finnigan MAT 731 spectrometer at 70 eV; ion source temperature = 200 °C. Ir spectra were recorded, as potassium bromide discs, on a Nicolet Impact-400 FT-IR instrument. Elemental analyses were performed at the Microanalytical Lab. of Chemistry Department, Al-Najah National University, West Bank.

1-Methyl-5-propyl-3-pyrazolecarboxylic Acid (**4**).

Methylhydrazine (10.1 g; 220 mmol) in methanol (30 ml) was added dropwise to a stirred solution of ethyl 2,4-dioxoheptanoate (**A**) [7] (37.2 g; 200 mmol) in methanol (400 ml) at 0 -5 °C (ice-salt bath). The ice bath was then removed and the resulting mixture was stirred at room temperature overnight. The solvent was then removed *in vacuo* at room temperature, the oily residue was added portionwise to concentrated H_2SO_4 (50 ml) preheated at 75 - 80 °C wherein, an effervescence occurred during the addition (30 - 40 minutes). The reaction mixture was further heated at 85 - 90 °C for 1 - 2 hours, cooled to room temperature and poured onto ice (200 g). The precipitated solid product was collected by suction filtration, washed with ice-cold water (2 × 20 ml) and dried. The title compound **4** was purified by soaking of the crude product in diethyl ether, filtration of the ether-insoluble solid, followed by additional washings with diethyl ether (3 × 40 ml). Yield 10.8 g (36 %); mp 125 - 126 °C. Comparable results were obtained when absolute ethanol was used as a solvent medium in place of methanol; ir (potassium bromide): ν 3449, 3343, 3235, 2970, 2934, 2878, 1681, 1497, 1382, 1244 cm^{-1}; ms: m/z (%): 168 ($M^{+\cdot}$, 42), 151 (10), 139 (100), 122 (22), 111 (5), 95 (21); hrms: Calcd. For $C_8H_{12}N_2O_2$: 168.08987. Found: 168.08567; ^{1}H nmr (400.14 MHz, deuteriodimethylsulfoxide): δ 0.90 (t, J = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.57 (m, 2H, $CH_2CH_2CH_3$), 2.56 (t, J = 7.6 Hz, 2H, $CH_2CH_2CH_3$), 3.76 (s, 3H, N-CH_3), 6.44 (s, 1H, C4-H); ^{13}C nmr (100.62 MHz, deuteriodimethylsulfoxide): δ 13.4 ($CH_2CH_2CH_3$), 20.9 ($CH_2CH_2CH_3$), 26.5 ($CH_2CH_2CH_3$), 36.5 (N-CH_3), 106.6 (C-4), 141.7 (C-5), 144.3 (C-3), 163.2 (CO_2H).

Anal. Calcd. for $C_8H_{12}N_2O_2$ (168.20): C, 57.13; H, 7.19; N, 16.66. Found: C, 56.92; H, 7.13; N, 16.51.

1-Methyl-4-nitro-5-propyl-3-pyrazolecarboxylic acid (**5**).

Method (a).

The following procedure is essentially similar to that reported for the nitration of 1,3-dimethyl-5-pyrazolcarboxylic acid [8]: Compound **4** (16.8 g; 100 mmol) was added, portionwise to a mixture of concentrated H_2SO_4 (40 ml) and concentrated HNO_3 (20 ml), preheated at 75 - 80 °C (oil bath). The mixture was heated at 90 - 95 °C for 3 - 4 hours, then cooled (ice-bath) and poured into ice (200 g). The precipitated white solid product **5** was collected with suction filtration, washed with little ice-cold water (2 × 20 ml) and dried. Yield 16.6 g (78%); mp 116 - 117 °C; ir (potassium bromide): ν 3565, 3415, 2956, 2930, 2872, 1717, 1554, 1489, 1360, 1243 cm^{-1}; ms: m/z (%): 213 ($M^{+\cdot}$, 29), 196 (23), 180 (63), 166 (50), 151 (83), 139 (51), 109 (26), 82 (49), 68 (56), 55 (43), 42 (100); hrms: Calcd. For $C_8H_{11}N_3O_4$: 213.07496. Found: 213.07429; ^{1}H nmr (400.14 MHz, deuteriochloroform): δ 0.99 (t, J = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.65 (m, 2H, $CH_2CH_2CH_3$), 2.91 (t, J = 7.4 Hz, 2H, $CH_2CH_2CH_3$), 3.90 (s, 3H, N-CH_3), 8.33 (br s, 1H, CO_2H); ^{13}C nmr (100.62 MHz, deuteriochloroform): δ 13.7 ($CH_2CH_2CH_3$), 21.2 ($CH_2CH_2CH_3$), 27.7 ($CH_2CH_2CH_3$), 37.8 (N-CH_3), 131.4 (C-4), 137.2 (C-3), 145.1 (C-5), 162.0 (CO_2H).

Anal. Calcd. for $C_8H_{11}N_3O_4$ (213.19): C, 45.07; H, 5.20; N, 19.71. Found: C, 45.12; H, 5.12; N, 19.55.

Method (b).

The oily product, obtained from the treatment of compound **A** (Scheme 1, 200 mmol) with methylhydrazine, was added portionwise to a mixture of concentrated H_2SO_4 (50 ml) and concentrated HNO_3 (30 ml), preheated to 70 – 75 °C. The reaction mixture was then heated at 90 – 95 °C for 4 – 5 hours, and worked up as described in method (a) above. Yield of pure product 13.6 g (32 %); mp 116 –117 °C.

1-Methyl-4-nitro-5-propyl-3-pyrazolecarboxamide (**6**).

Compound **5** (6.4 g; 31 mmol) is refluxed in $SOCl_2$ (20 ml) for 3 hours (oil bath). Excess $SOCl_2$ is distilled off *in vacuo* and the crude acid chloride is added slowly, under stirring, to a cooled (~ 0 °C) aqueous NH_4OH (40 ml, 25 %). Stirring was continued for 3 hours at room temperature. Cold water (50 ml) was then added, and the white solid product **6** was collected by suction filtration and dried. Yield of pure product 5.5 g (86%); mp 149 –150 °C; ir (potassium bromide): ν 3307, 3145, 2966, 2876, 1655, 1557, 1497, 1378, 1333 cm^{-1}; ms: m/z (%): 212 ($M^{+\cdot}$, 40), 197 (22), 183 (34), 168 (80), 151 (100), 138 (31), 84 (54), 79 (33), 42 (31); hrms: Calcd. For $C_8H_{12}N_4O_3$: 212.09094. Found: 212.09140; ^{1}H nmr (400.14 MHz, deuteriodimethylsulfoxide): δ 0.93 (t, J = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.60 (m, 2H, $CH_2CH_2CH_3$), 2.94 (t, J = 7.7 Hz, 2H, $CH_2CH_2CH_3$), 3.84 (s, 3H, N-CH_3), 7.64, 7.93 (two br s, 1H each of NH_2); ^{13}C nmr (100.62 MHz, deuteriodimethylsulfoxide): δ 13.5 ($CH_2CH_2CH_3$), 20.7 ($CH_2CH_2CH_3$), 25.7 ($CH_2CH_2CH_3$), 37.2 (N-CH_3), 129.5 (C-4), 142.9 (C-3), 143.3 (C-5), 162.3 ($CONH_2$).

Anal. Calcd. for $C_8H_{12}N_4O_3$ (212.21): C, 45.28; H, 5.70; N, 26.40. Found: C, 45.06; H, 5.58; N, 26.22.

4-Amino-1-methyl-5-propyl-3-pyrazolecarboxamide (**7**).

The following reaction conditions are essentially similar to those adopted for the reduction of *o*-nitro-anilines [11] and of 3-nitro-4-oxothienopyridines [12]: To a stirred solution of compound **6** (5.3 g; 25 mmol) in concentrated HCl (112 ml) was added portionwise, $SnCl_2$ (26.5 g; 5 equivalents by weight) at room temperature (CAUTION: H_2 was evolved). A white solid salt is formed after 5 - 10 minutes, and stirring was continued for 0.5 h. Water was then added until all the solid salt has dissolved and the mixture became a clear solution (~ 70 ml). Stirring was continued for additional 40 minutes, and the mixture was then placed in an ice bath and made alkaline by slow addition of aqueous NaOH (10 *N*). The resulting solution is cooled to 15 °C, and extracted with CH_2Cl_2 (3 × 200 ml). The combined organic extracts were dried, and the solvent was evaporated *in vacuo* leaving a pure solid product **7**. Yield 4.1 g (90 %); mp 176 - 177 °C; ir (potassium bromide): ν 3332, 3186, 2956, 2934, 2871, 1678, 1656, 1600, 1380, 1314 cm^{-1}; ms: m/z (%): ($M^{+\cdot}$, 100), 164 (8), 153 (56), 136 (98), 125 (8), 108 (5), 84 (41), 42 (17 %); hrms: Calcd. for $C_8H_{14}N_4O$ 182.11676. Found: 182.11601; ^{1}H nmr (400.14 MHz, deuteriodimethylsulfoxide): δ 0.88 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.47 (m, 2H, $CH_2CH_2CH_3$), 2.51 (t, J = 7.6 Hz, 2H, $CH_2CH_2CH_3$), 3.67 (s, 3H, N-CH_3), 4.42 (br s, 2H, NH_2), 6.93, 7.07 (two br s, 1H each, $CONH_2$); ^{13}C nmr (100.62 MHz, deuterio- dimethylsulfoxide): δ 13.5 ($CH_2CH_2CH_3$), 21.1 ($CH_2CH_2CH_3$), 24.4 ($CH_2CH_2CH_3$), 36.7 (N-CH_3), 128.3 (C-3), 130.1 (C-4), 130.7 (C-5), 165.9 ($CONH_2$).

Anal. Calcd. for $C_8H_{14}N_4O$ (182.23): C, 52.73; H, 7.74; N, 30.75. Found: C, 52.48; H, 7.64; N, 30.62.

4-(2-Ethoxybenzoyl)amino-1-methyl-5-propyl-3-pyrazolecarboxamide (**8**).

A mixture of 2-ethoxybenzoic acid (1.6 g; 10 mmol) and $SOCl_2$ (8 ml) was refluxed (oil bath) for 3 hours. Excess $SOCl_2$

was removed *in vacuo*, and the residual acid chloride was treated with a solution of compound **7** (1.8 g; 10 mmol) in anhydrous benzene (25 ml), followed by addition of triethylamine (3 ml) or 4-(dimethylamino)pyridine (DMAP, 2 g). The resulting mixture was refluxed for 3 hours, and benzene was then evaporated *in vacuo*. The solid residue was soaked in cold water (40 ml), and the remaining solid product **8** was collected by suction filtration, and dried. Yield of pure product 2.9 g (88 %); mp 200 - 201 °C; ir (potassium bromide): ν 3463, 3404, 3278, 3212, 2931, 2871, 1675, 1598, 1481, 1294, 1239 cm^{-1}; ms: m/z (%): 330 ($M^{+\cdot}$, 22), 313 (14), 298 (10), 182 (23), 164 (14), 149 (100), 121 (95), 93 (17), 65 (12), 42 (7); hrms: Calcd. for $C_{17}H_{22}N_4O_3$: 330.16919. Found: 330.17168; ^{1}H nmr (400.14 MHz, deuteriodimethylsulfoxide): δ 0.84 (t, J = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.42 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.52 (m, 2H, $CH_2CH_2CH_3$), 2.76 (t, J = 7.6 Hz, 2H, $CH_2CH_2CH_3$), 3.82 (s, 3H, N-CH_3), 4.25 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 7.06 (t, J = 7.6 Hz, 1H, C5'-H), 7.17 (d, J = 8.1 Hz, 1H, C3'-H), 7.25, 7.41 (two br s, 1H each of $CONH_2$), 7.50 (ddd, J = 8.1, 7.6, 1.8 Hz; 1H, C4'-H), 7.96 (dd, J = 7.6, 1.8 Hz, 1H, C6'-H), 10.22 (br s, 1H, N*H*CO); ^{13}C nmr (100.62 MHz, deuteriodimethylsulfoxide): δ 13.7 ($CH_2CH_2CH_3$), 14.2 (OCH_2CH_3), 20.5 ($CH_2CH_2CH_3$), 26.8 ($CH_2CH_2CH_3$), 37.2 (N-CH_3), 64.5 (OCH_2CH_3), 113.1 (C-3'), 118.4 (C-5), 120.6 (C-5'), 121.8 (C-1'), 131.2 (C-6'), 133.0 (C-4'), 135.9 (C-3), 138.1 (C-4), 156.5 (C-2'), 162.5 (NH*C*O), 164.1 ($CONH_2$).

Anal. Calcd. for $C_{17}H_{22}N_4O_3$ (330.39): C, 61.80; H, 6.71; N, 16.96. Found: C, 61.72; H, 6.63; N, 16.84.

5-(2-Ethoxyphenyl)-2-methyl-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (**9**).

Method (a).

A mixture of compound **7** (3.6 g; 20 mmol), 2-ethoxybenzoic acid (3.6 g; 22 mmol) and polyphosphoric acid (22 g) was slowly heated (oil bath) with agitation at 100 - 120 °C (20 minutes) and finally at 130 - 140 °C (40 minutes). The reaction mixture was cooled to about 60 - 70 °C, treated with ice-cold water (100 ml), made slightly alkaline (pH ~ 8) by addition of 2 *N* NaOH and extracted (the aqueous solution and the precipitated solid product) with ethyl acetate. Evaporation of the organic solvent gave a crude product, which upon soaking in ethanol gave pure white solid of compound **9**. Yield 1.90 g (30 %); mp 153 - 154 °C; ir (potassium bromide): ν 3318, 2963, 2934, 2871, 1688, 1594, 1445, 1387, 1301, 1263, 1126, 1032 cm^{-1}; ms: m/z (%): 312 ($M^{+\cdot}$, 100), 297 (19), 284 (51), 279 (24), 255 (17), 239 (27), 166 (62) 136 (81) 91 (11), 84 (41), 42 (20); hrms: Calcd for $C_{17}H_{20}N_4O_2$: 312.15863. Found: 312.15684; ^{1}H nmr (400.14 MHz, deuteriodimethylsulfoxide): δ 0.92 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.32 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.69 (m, 2H, $CH_2CH_2CH_3$), 2.89 (t, J = 7.4 Hz, 2H, $CH_2CH_2CH_3$), 4.01 (s, 3H, N-CH_3), 4.11 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 7.04 (ddd, J = 7.6, 7.6, 0.9 Hz, 1H, C5'-H), 7.12 (d, J = 8.1 Hz, 1H, C3'-H), 7.43 (ddd, J = 8.1, 7.6, 1.8 Hz, 1H, C4'-H), 7.67 (d, J = 7.6 Hz, 1H, C6'-H) 11.53 (br s, 1H, N6-*H*); ^{13}C nmr (100.62 MHz, deuteriodimethylsulfoxide): δ 13.6 ($CH_2CH_2CH_3$), 14.5 (OCH_2CH_3), 21.2 ($CH_2CH_2CH_3$), 25.0 ($CH_2CH_2CH_3$), 38.0 (N-CH_3), 64.1 (OCH_2CH_3), 112.8 (C-3'), 120.4 (C-5'), 122.7 (C-1'), 130.3 (C-6'), 131.7 (C-4'), 133.4 (C-3), 135.9 (C-7a), 137.0 (C-3a), 149.1 (C-5), 156.4 (C-2'), 156.5 (C-7).

Anal. Calcd for $C_{17}H_{20}N_4O_2$ (312.37): C, 65.37; H, 6.45; N, 17.94. Found: C, 65.18; H, 6.33; N, 17.68.

Method (b).

A mixture of compound **8** (1.0 g; 3 mmol) and polyphosphoric acid (6 g) was heated as described in method (a) above. Work-up of the reaction mixture, as noted in method (a) above, gave 0.32 g (34 %) of **9** (purified using TLC plates, silica gel; elution with CH_2Cl_2:CH_3OH (95:5 v/v); mp 153 - 154 °C.

5-(5-Chlorosulfonyl-2-ethoxyphenyl)-2-methyl-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (**10**).

Compound **9** (0.95 g, 3 mmol) was added, portionwise to chlorosulfonic acid (2 ml) cooled to 0 °C (ice-bath) under stirring. The resulting yellow solution was then allowed to warm to room temperature and was then heated to 65 - 70 °C (oil bath) for 1 hour. The reaction mixture was slowly poured into crushed ice (25 g), and the white solid that has precipitated immediately, was collected by filration, and dried. Yield 1.13 g (92 %); mp 170 - 172 °C. This crude product was used directly for the next step.

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-2-methyl-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (**3**).

The sulfonyl chloride derivative **10** (1.23 g, 3 mmol) was dissolved in THF (10 ml) and treated with a solution of 1-methylpiperazine (0.9 g, 3 mmol) in THF (10 ml). The resulting mixture was stirred at room temperature for 1 hour. THF was then removed *in vacuo* and the residue was treated with cold water (50 ml). The resulting white precipitate of **3** was collected by filtration under suction, washed with cold water (2 × 10 ml), drained and recrystallized from ethanol. Yield of pure product 1.2 g (83 %); mp 124 -126 °C; ir (potassium bromide): ν 3212, 3160, 3100, 2978, 2936, 2804, 1690, 1599, 1472, 1350, 1288, 1172 cm^{-1}; ms: m/z (%): 474 ($M^{+\cdot}$, 1), 432 (2), 404 (7), 381 (1), 113 (9), 99 (100), 72 (7), 56 (14); hrms: Calcd. for $C_{22}H_{30}N_6O_4S$: 474.20494. Found: 474.20473; ^{1}H nmr (400.14 MHz, deuteriochloroform): δ 0.93 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$),1.56 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.74 (m, 2H, $CH_2CH_2CH_3$), 2.19 (s, 3H, N4"-H), 2.42 (t, J = 4.8 Hz, 4H, C3"-H/C5"-H), 2.89 (t, J = 7.4 Hz, 2H, $CH_2CH_2CH_3$), 3.00 (br s, 4H, C2"-H/C6"-H), 3.98 (s, 3H, N2-CH_3), 4.23 (q, J = 7.0 Hz, 2H, OCH_2CH_3),7.07 (d, J = 8.8 Hz, 1H, C3'-H), 7.69 (dd, J = 8.8, 2.4 Hz, 1H, C4'-H), 8.62 (d, J = 2.4 Hz, 1H, C6'-H), 10.61 (br s, 1H, N6-*H*); ^{13}C nmr (100.62 MHz, deuteriochloroform): δ 13.7 ($CH_2CH_2CH_3$), 14.4 (OCH_2CH_3), 21.4 ($CH_2CH_2CH_3$), 25.8 ($CH_2CH_2CH_3$), 38.1 (N2-CH_3), 45.5 (N4"-CH_3), 45.7 (C-2"/6"), 53.9 (C-3"/5"), 65.9 (OCH_2CH_3), 113.1 (C-3'), 121.3 (C-1'), 128.4 (C-5'), 130.0 (C-6'), 131.3 (C-4'), 133.8 (C-3), 135.9 (C-7a), 138.0 (C-3a),146.3 (C-5), 156.6 (C-7), 159.4 (C-2').

Anal. Calcd. for $C_{22}H_{30}N_6O_4S$ (474.58): C, 55.68; H, 6.37; N, 17.71; S, 6.76. Found: C, 56.02; H, 6.46; N, 17.88; S, 6.89.

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[1] IUPAC Name: 5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-2-methyl-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrim-

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