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SYNTHESIS AND PROPERTIES OF α-THIAGRA.[1] A SUBSTITUTED 5-(2-THIENYL)PYRAZOLO[4,3-*d*]PYRIMIDIN-7-ONE BIOISOSTERE OF VIAGRA®

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Abstract- For structure-activity manipulations, the compound *α-thiagra* **(3)**, a thiophene bioisostere of viagra®, has been prepared and its X-Ray structure determined. The crystallographic data show that the thiophene and pyrazolo[4,3-*d*]-pyrimidone hetero-ring systems are nearly coplanar by virtue of an adequate intramolecular hydrogen-bond between the pyrimidone NH and the oxygen lone pair of the 3'-ethoxy group.

INTRODUCTION

Viagra® **(1)** is an approved therapeutic drug for the treatment of male erectile dysfunction (MED).[2] The erectogenic process is mediated by nitric oxide (NO)[3] with ultimate production of adequate concentration of cyclic guanosine monophosphate (cGMP), a vasodilator that enhances relaxation of the corpus cavernosal smooth muscle (CCSM).[4] Intracellular levels of cGMP are controlled by NO-activation of guanyl cyclase[3] and breakdown by type-V phosphodiesterase (PDE V) into inactive GMP.[5] Viagra®

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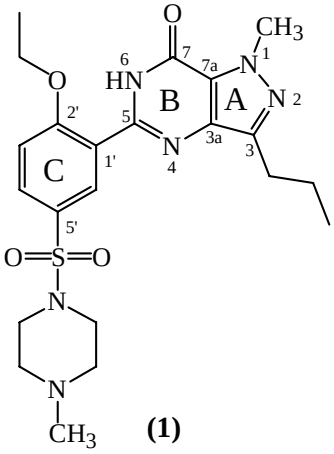
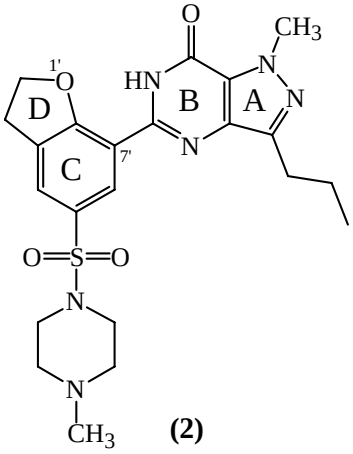
improves erection by selectively inhibiting PDE V, thence preventing the breakdown of cGMP.[5] As a consequence, viagra® leads to the increase in intracellular cGMP concentration, thereby prolonging the vasodilation effect and has utility for the treatment of MED (impotence).[2,5]

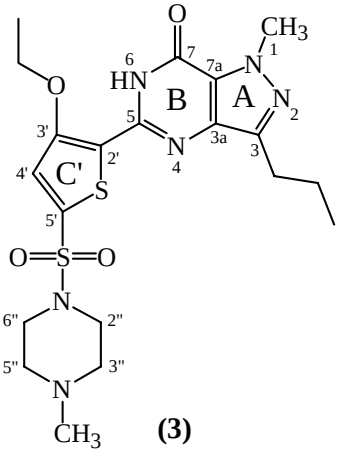
As part of an ongoing research program oriented toward preparing new vasodilating agents with high erectogenic potency, we envisage in the first place to undertake structural modifications of the Viagra® molecule **(1)** for structure-activity relationship (SAR) studies. Our initial focus of the investigation was centered on the aryl moiety (ring C) of **1**. In a preceding communication we have reported on the synthesis and X-Ray structure of *biagra* **(2)**,an analog of viagra® in which the 2'-ethoxyphenyl ring (C) is replaced by 7'-benzofuryl unit.[6] In continuation, and from the standpoint of bioisosterism we sought to prepare an isostere of viagra® with the concept of replacing the benzene moiety (ring C) of viagra® by thiophene, a known bioisostere in other fields of medicinal chemistry.[7] In particular, we wish to prepare a substituted 5-(2-thienyl)pyrazolo[4,3-*d*]pyrimidin-7-one (we call it *α-thiagra*) which from molecular models mimics viagra® **(1)**. Herein we describe the synthesis and properties of *α-thiagra* **(3)**, and of the appropriate intermediates thereof (Schemes I and II).



(1)



(2)



(3)

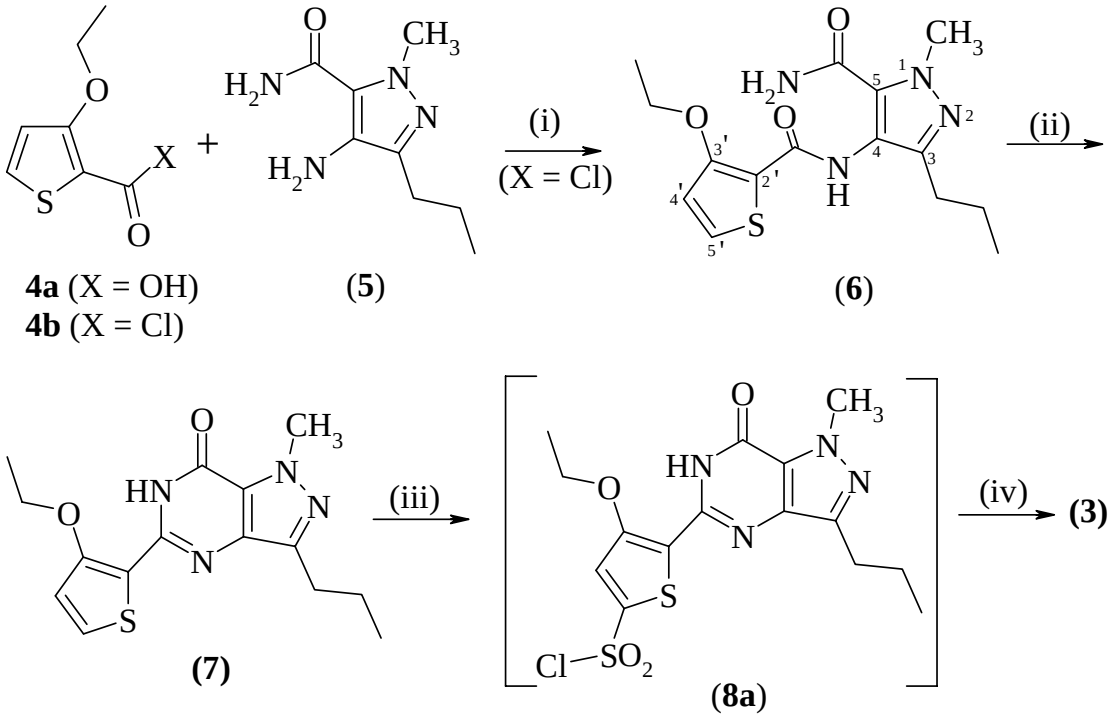
RESULTS AND DISCUSSION

SYNTHESIS

Our synthetic approach follows the generally applicable route which involves direct amidation of the synthon 4-amino-1-methyl-3-propyl-5-pyrazolecarboxamide **(5)**[2,6] with 3-ethoxythiophene-2-carbonyl chloride **(4b)**,[8] accessible from the corresponding acid **(4a)**[8] by the action of thionyl chloride (Scheme 1). Cyclization of the resulting bisamide **(6)** was best accomplished in refluxing *tert*-butanol in the presence of potassium *tert*-butoxide, and the corresponding pyrazolo[4,3-*d*]pyrimidin-7-one product **(7)** was then reacted with chlorosulfonic acid. The crude intermediate 5'-chlorosulfonyl derivative **(8a)**, thus obtained, was reacted directly with a solution of *N*-methylpiperazine in tetahydrofuran to afford the target

compound **(3)**. Lower yields of **7** were, however, obtained when the cyclization step of **6** was performed in polyphosphoric acid (PPA), or alternatively by way of direct interaction between **4a** and **5** in PPA at 140 °C (Scheme II).

Scheme I

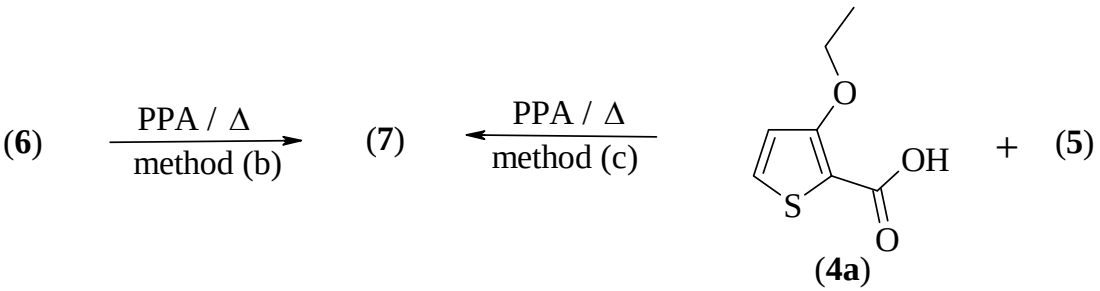


4a (X = OH)
4b (X = Cl)
(**5**)
(**6**)
(**7**)
(**8a**)

Reagents and conditions:

(i) NEt_3 / Benzene, Δ
(ii) *tert*-$BuO^- K^+$ / *tert*-BuOH, Δ
(iii) $ClSO_3H$ / 90-95 °C, 7 h
(iv) 1-methylpiperazine, THF / rt

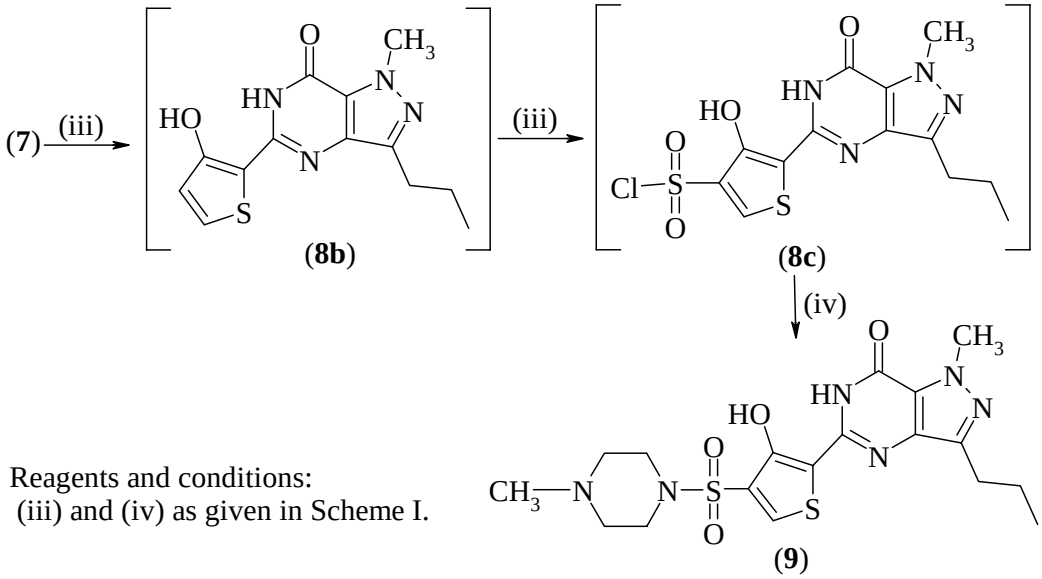
Scheme II



(**4a**)

A by-product namely, 5-[3-hydroxy-5-(4-methylpiperazin-1-yl)-2-thienyl]-1-methyl-3-propyl-6,7-dihydro-*1H*-pyrazolo[4,3-*d*]pyrimidin-7-one **(9)** was isolated from the crude product of **3** in the successive chlorosulfonylation-piperazinylation steps (Scheme III). The production of **9** presumably implies the intermediate formation of its precursors (**8b** and **8c**) which were, however, not isolated.

Scheme III



Reagents and conditions:
(iii) and (iv) as given in Scheme I.

X-Ray Crystallographic Data

The molecular structure of **3** is displayed in Figure 1,and selected bond lengths and angles are given in Table 1. The crystallographic data reveal that the pyrazolopyrimidone and thienyl heteroaryl systems

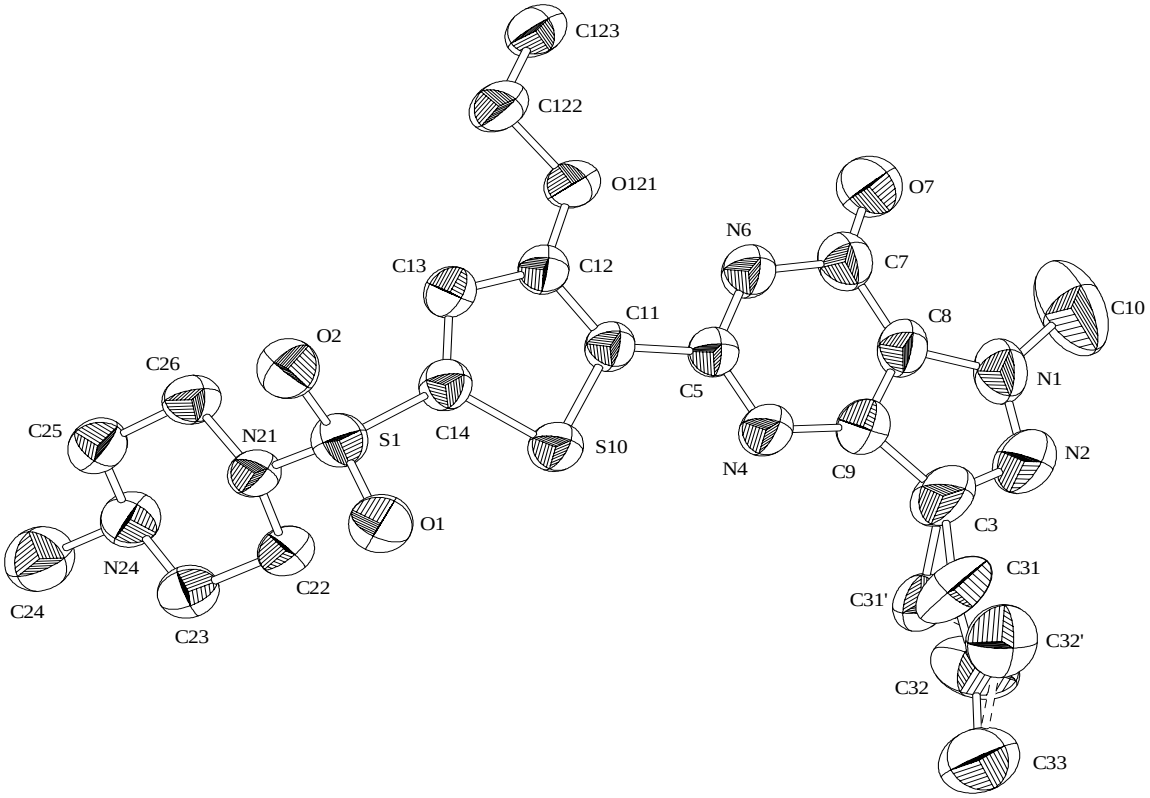


Figure 1. ORTEP plot of the molecular structure of **3**

Table 1. Selected bond lengths and angles for **3**

Bond lengths (Å)

S (10) - C (11)	1.714 (4)	N (2) – N (1) - C (8)	110.1 (4)
O (7) - C (7)	1.221 (5)	C (5) – N (4) - C (9)	114.1 (3)
O (121) - C (12)	1.356 (4)	C (5) – N (6) - C (7)	125.8 (4)
O (121) - H (6)	1.990 (5)	N (4) – C (5) - N (6)	124.1 (3)
N (2) - C (3)	1.327 (7)	N (4) – C (5) - C (11)	119.2 (3)
N (2) - N (1)	1.349 (6)	N (6) – C (5) - C (11)	116.7 (3)
N (1) - C (8)	1.368 (5)	O (7) – C (7) - N (6)	121.0 (4)
N (4) - C (5)	1.290 (5)	O (7) – C (7) - C (8)	129.4 (4)
N (4) - C (9)	1.387 (5)	N (6) – C (7) - C (8)	109.6 (4)
N (6) - C (5)	1.375 (5)	N (1) – C (8) C - (9)	107.2 (4)
N (6) - C (7)	1.396 (5)	N (1) – C (8) - C (7)	130.6 (4)
C (5) - C (11)	1.466 (5)	C (9) – C (8) - C (7)	122.2 (4)
C (7) - C (8)	1.426 (6)	C (8) – C (9) - N (4)	124.3 (4)
C (8) - C (9)	1.373 (6)	C (8) – C (9) - C (3)	105.5 (4)
C (9) - C (3)	1.409 (6)	N (4) – C (9) - C (3)	130.1 (4)
C (11) - C (12)	1.383 (5)	C (12) - C (11) - C (5)	129.2 (3)
C (12) - C (13)	1.409 (5)	C (12) - C (11) - S (10)	111.5 (3)
C (13) - C (14)	1.357 (5)	C (5) - C (11) - S (10)	119.3 (3)
		C (121) - C (12) - C (11)	119.9 (3)
		O (121) - C (12) - C (13)	127.4 (3)

Bond angles (°)

C (11) - S (10) - C (14)	91.0 (2)	C (11) - C (12) - C (13)	112.7 (3)
C (12) - O (121) - (122)	118.4 (3)	C (14) - C (13) - C (12)	111.9 (4)
C (12) - O (121) - H (6)	100.3 (13)	C (13) - C (14) - S (10)	112.9 (3)
C (122) - O (121) - H (6)	140.9 (13)	C (13) - C (14) - S (1)	125.2 (3)
C (3) - N (2) - N (1)	107.3 (4)	S (10) - C (14) - S (1)	121. 9 (2)

(rings AB and C') acquire coplanarity by virtue of intramolecular hydrogen bonding between the pyrimidone -NH and the 3'-ethoxy oxygen lone pair. The interplanar angle, determined as 4.59° [across their joint C(5)-C(11) axis] conforms to the associated coplanarity between the two biophoric ring systems. The spatial interatomic distance, determined for N(6)–O(121) as 1.99 Å, shows them situated in such close proximity that allows for an adequate intra-hydrogen bridge involving N(6)-H and O(121) lone pair. A comparable planar topography, as established between the heteroaryl and 2'-ethoxyaryl systems (rings AB and C) of viagra® **(1)**, was suggested to be a key feature for high affinity binding to PDE-5 receptor cite, and hence the associated selective inhibitory effect.[2]

Preliminary biological tests

Compound **(3)** was tested in a rat model predictive of therapeutic activity in erectile dysfunction using a laser doplar probe to record blood flow rates following administration of **3**. There has been evidence that **3** showed potency comparable to that of viagra® **(1)** which was used as a positive control in the test. For comparative study, the *in vitro* relaxant activity of **1** and **2** has been evaluated on rat isolated thoracic aorta precontracted with phenylephrine, and in the presence or absence of endothelium. The test compounds induce relaxation of the artery with almost the same potency which seems to be endothelium dependent. However, viagra® appears to be more potent than **2** at low concentrations.

EXPERIMENTAL

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 [400 MHz (^{1}H), 100 MHz (^{13}C)] and a Bruker DPX-300 [300 MHz (^{1}H), 75 MHz (^{13}C)] spectrometers 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 KBr discs, on Nicolet impact-400 FT-IR instrument. Elemental analysis was performed at the Microanalytical Lab. of the Chemistry Department, Al-Najah National University, West Bank.

4-(3-Ethoxy-2-thenoyl)amino-1-methyl-3-propyl-5-pyrazolecarboxamide (6)

A mixture of 3-ethoxythiophene-2-carboxylic acid (**4a)** (3.45 g, 20 mmol) and $SOCl_2$ (20 mL, 274 mmol) was refluxed (oil bath) for 3 h. Excess $SOCl_2$ was removed *in vacuo*, and the residual acid chloride **(4b)** was treated with a solution of compound **(5)** (3.65 g, 20 mmol) in anhydrous benzene (50 mL), followed by addition of triethylamine (5 mL, 36 mmol). 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 **(6)** was collected by suction filtration, dried, and recrystallized from ethanol. Yield of pure product 6.2 g (92%). mp 109 – 110 °C. Anal. Calcd for $C_{15}H_{20}N_4O_3S$: C, 53.55; H, 5.99; N, 16.65; S, 9.53. Found: C, 53.28; H, 5.85; N, 16.42; S, 9.36. IR (KBr): ν/cm^{-1} = 3352(m), 3277(s), 3069(w), 3959(w), 1682(s), 1656(s), 1632(s), 1537(s), 1466(s), 1426(m), 1382(m), 1296(m), 1227(m), 1070(s). MS m/z (%): 336.125497 ($M^{+\cdot}$, 25, requires: 336.125581), 319 (17), 304(6), 208(2), 181(2), 155(100), 127(60), 99(6), 86(25), 84(37), 69(15), 42(24). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.44 (t, *J* = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.59 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.48 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2CH_2CH_3$), 3.98 (s, 3H, N–$C\underline{H}_3$), 4.27 (q, *J* = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 6.86 (d, *J* = 5.6 Hz, 1H, 4'-H), 7.46 (d, *J* = 5.6 Hz, 1H, 5'-H), 6.02, 7.88 (two br s, 1H, each of $CON\underline{H}_2$), 8.52 (br s, 1H, N*H*CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 ($CH_2CH_2\underline{C}H_3$), 14.9 ($OCH_2\underline{C}H_3$), 22.2 ($CH_2\underline{C}H_2CH_3$), 27.5 ($\underline{C}H_2CH_2CH_3$), 39.1 (N–$\underline{C}H_3$), 68.1 ($O\underline{C}H_2CH_3$), 115.1 (C-4), 115.2 (C-2'), 115.9 (C-4'), 130.8 (C-5'), 133.2 (C-5), 146.7 (C-3), 157.0 (C-3'), 161.6 ($\underline{C}ONH_2$), 162.9 (NH$\underline{C}$O).

5-(3-Ethoxy-2-thienyl)-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (7)

Method (a): Potassium *tert*-butoxide (1.34 g, 12 mmol) was added to a stirred suspension of compound **(6)** (3.36 g, 10 mmol), in *tert*-butanol (30 mL) and the resulting mixture was heated under reflux for 8 h (oil bath), then allowed to cool to rt. Water (30 mL) was added and the resulting solution was then neutralized with dilute HCl (4%) to pH ~ 7, and cooled to about 5 – 10 °C. The precipitated solid product was collected by suction filtration, washed with ice-cold water (2 × 10 mL), dried, and recrystallized from ethanol. Yield 2.90 g (91%). mp 153 – 155 °C. Anal. Calcd for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60; S, 10.07. Found: C, 56.70; H, 5.62; N, 17.43; S, 9.88. IR (KBr): ν/cm^{-1} = 3321(s), 3088(w), 2953(w), 2868(w), 1697(s), 1583(s), 1482(w), 1385(w), 1317(w), 1232(w), 1223(m), 1072(s). MS m/z (%): 318.116509 ($M^{+\cdot}$, 100, requires: 318.115021), 303(30), 290(41), 285(24), 275(26), 361(22), 246(14), 192(8), 136(28), 108(8), 69(19), 42(11). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.49 (t, *J* = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.76 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.82 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2CH_2CH_3$), 4.18 (s, 3H, N–$C\underline{H}_3$), 4.27 (q, *J* = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 6.80 (d, *J* = 5.6 Hz, 1H, 4'-H), 7.31 (d, *J* = 5.6 Hz, 1H, 5'-H), 10.38 (br s, 1H, N6-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 ($CH_2CH_2\underline{C}H_3$), 14.9 ($OCH_2\underline{C}H_3$), 22.1 ($CH_2\underline{C}H_2CH_3$), 27.6 ($\underline{C}H_2CH_2CH_3$), 38.1 (N–$\underline{C}H_3$), 68.2 ($O\underline{C}H_2CH_3$), 114.2 (C-2'), 116.3 (C-4'), 124.0 (C-7a), 128.6 (C-5'), 138.4 (C-3a), 145.4 (C-3), 145.9 (C-5), 153.5 (C-7), 155.6 (C-3').

Method (b): A mixture of compound **(5)** (0.55 g, 3 mmol), 3-ethoxythiophene-2-carboxylic acid **(4a)** (0.52 g, 3 mmol), and polyphosphoric acid (4.0 g) was slowly heated (oil bath) with agitation at 100 –

120 °C (20 min), and finally at 130 – 140 °C (40 min). The dark 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 with ethyl acetate. Evaporation of the organic solvent gave a crude product, which upon soaking in ethanol (5 mL) gave pure white solid of compound **(7)**. Yield 0.057 g (6%). mp 152 – 154 °C.

Method (c): A mixture of compound **(6)** (1.0 g, 3 mmol) and polyphosphoric acid (6.0 g) was heated as described in method (b) above. Work-up of the reaction mixture, as noted in method (b) above, gave 0.095 g (10%) of purified **(7)** (TLC plates, silica gel; elution with CH_2Cl_2 : MeOH (95 : 5 v/v). mp 154 – 155 °C.

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

Compound **(7)** (0.64 g, 2 mmol) was added, portionwise to chlorosulfonic acid (2 mL, 30 mmol) cooled to 0 °C under stirring. The resulting yellow solution was then allowed to warm to rt, followed by heating at 93 – 96 °C (oil bath) for 7 h. The reaction mixture was then slowly poured onto crushed ice (25 g), and the yellow solid chlorosulfonyl derivative **(8a)** that was precipitated immediately, filtered, dried, and used as such for the next step.

The sulfonyl chloride derivative **(8a)** was dissolved in THF (10 mL) and treated with a solution of 1-methylpiperazine (0.6 g, 6 mmol) in THF (10 mL). The resulting mixture was stirred at rt for 1 h. THF was then removed *in vacuo* and the residue was treated with cold water (50 mL). The resulting white precipitate was filtered under suction, washed with cold water (5 mL) and cold ethanol (5 mL), and recrystallized from ethanol. Yield of pure product 0.37 g (45%). mp 224 – 226 °C; R_f = 0.6 [silica gel; CH_2Cl_2 / MeOH (95 : 5 v/v)]. Anal. Calcd for $C_{20}H_{28}N_6O_4S_2$: C, 49.98; H, 5.87; N, 17.49; S, 13.34. Found: C, 50.06; H, 5.81; N, 17.25; S, 13.22. IR (KBr): ν/cm^{-1} = 3324(m), 2942(m), 2798(m), 1706(s), 1578(s), 1527(w), 1455(m), 1386(m), 1287(s), 1205(w), 1148(s), 1091(m), 1065(m), 1031(m). MS m/z (%): 480.1605 ($M^{+\cdot}$, 2, requires: 480.1613), 416(4), 318(1), 261(2), 111(4), 99(100), 70(7), 56(19), 42(4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.52 (t, *J* = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.75 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.25 (s, 3H, N4"–$C\underline{H}_3$), 2.46 (t, *J* = 4.9 Hz, 4H, 3"-H/5"-H), 2.80 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2CH_2CH_3$), 3.13 (br s, 4H, 2"-H/6"-H), 4.18 (s, 3H, N1-$C\underline{H}_3$), 4.31 (q, *J* = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 7.20 (s, 1H, 4'-H), 10.21 (br s, 1H, N6-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 ($CH_2CH_2\underline{C}H_3$), 14.8 ($OCH_2\underline{C}H_3$), 22.1 ($CH_2\underline{C}H_2CH_3$), 27.6 ($\underline{C}H_2CH_2CH_3$), 38.2 (N–$\underline{C}H_3$), 45.6 (N4"-$\underline{C}H_3$), 46.0 (C-2"/C-6"), 53.8 (C-3"/C-5"), 68.9 ($O\underline{C}H_2CH_3$), 120.1 (C-4'), 120.9 (C-2'), 124.3 (C-7a), 137.0 (C-5'), 137.9 (C-3a), 143.8 (C-5), 146.3 (C-3), 153.1 (C-3'), 153.8 (C-7).

5-[3-Hydroxy-5-(4-methylpiperazin-1-ylsulfonyl)-2-thienyl]-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (9)

This fluorescent compound was obtained as a crude by-product upon concentrating the ethanolic mother liquor of **3**, and was purified on preparative TLC silica gel plates using CH_2Cl_2 / EtOH (95 : 5 v/v) as the developing solvent mixture. Yield of pure **9** 0.16 g (18%). mp 270 – 272 °C; R_f = 0.25. Anal. Calcd for $C_{18}H_{24}N_6O_4S_2$: C, 47.77; H, 5.35; N, 18.57; S, 14.17. Found: C, 47.51; H, 5.18; N, 18.26; S, 13.95. IR (KBr): ν/cm^{-1} = 3422 (m), 3092 (w), 2950 (w), 1681 (s), 1577 (s), 1351 (m), 1620 (s), 938 (s). MS m/z (%): 452.1293 ($M^{+\cdot}$, 10, requires: 452.1300), 382(14), 369(8), 290(27), 262(16), 235(3), 147(10), 136(9), 99(100), 83(78), 70(57), 56(43). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (t, J = 7.4 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.70 (m, 2H, $CH_2CH_2C\underline{H}_3$), 2.43 (s, 3H, N4"–C$\underline{H}_3$), 2.70 (t, J = 7.6 Hz, 2H, C$\underline{H}_2CH_2CH_3$), 2.79 (br s, 4H, 3"-H/5"-H), 3.30 (br s, 4H, 2"-H/6"-H), 4.06 (s, 3H, N1-C$\underline{H}_3$), 7.92 (s, 1H, 5'-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 ($CH_2CH_2\underline{C}H_3$), 21.5 ($CH_2\underline{C}H_2CH_3$), 27.2 ($\underline{C}H_2CH_2CH_3$), 37.6 (N–$\underline{C}H_3$), 43.9 (N4"-$\underline{C}H_3$), 44.5 (C-2"/C-6"), 53.1 (C-3"/C-5"), 100.7 (C-2'), 123.3 (C-7a), 130.2 (C-4'), 133.8 (C-5'), 138.9 (C-3a), 142.7 (C-3), 150.7 (C-5), 153.5 (C-7), 168.7 (C-3').

Collection of X-Ray diffraction data and the structure analysis

Crystals (light yellow needles) were obtained by slow evaporation of the solvent ethanol from the solution of **3**. Cystal size = 0.5 x 0.1 x 0.1 mm. Crystal data for $C_{20}H_{28}N_6O_4S_2$: MW = 480.61, monoclinic, space group $P2_1/n$ with a = 18.959 (9), b = 15.898 (4), c = 9.484 (3) Å, α = 90, β = 55.07, y = 90°, V = 2343.7 (14) Å^3, Z = 4, $d_{calc.}$ = 1.362 g/cm^{-3}, F (000) = 1016. Data collection was made at 213 (2) K, using an ENRAF-NONIUS CAD4 diffractometer operating in the omega scan mode. 4327 independent data were collected within the range θ = 5.45-65.25° using CuK_α radiation (λ = 1.54184 Å). The cell parameters and orientation matrix for the data collection were obtained using the setting angles of 25 reflections in the range (θ = 17.3 - 24.7°). The structure was solved by direct methods using the program SHELXS 86.[9] All non-hydrogen atoms were refined anisotropically by full-matrix least-squares based on F^2 with SHELXL 93.[10] The hydrogen atoms have been found in the difference Fourier map and were refined isotropically. This results in an R values R_1 = 0.0582 and wR_2 = 0.1555 for the observed data and 392 parameters. GOF = 1.022, largest peak and hole in final Fourier difference map were 0.395 and -0.429 e/ Å^3, respectively.

Supplimentary Material

Further information of the cyrstal structure determination (crystal data, atomic coordinates, anisotropic displacement parameters, hydrogen corrdinates and isotropic displacement parameters) can be ordered from Cambridge Crystallographic Data Center under the depository number CCDC, 137165.

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