Synthesis of Novel Pyrazolopyrrolopyrazines, Potential Analogs of Sildenafil

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Synthesis of novel pyrazolopyrrolopyrazines is herein described with the aim to reach new specific PDE-5 inhibitors of potential clinical interest in male erectile dysfunction.

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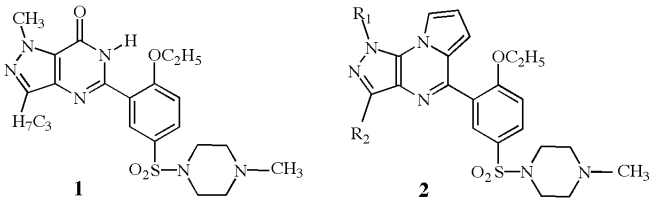
Sildenafil [1] (**1**, VIAGRA®, Scheme 1) is a potent inhibitor of phosphodiesterase type 5 (PDE 5) [2] whose effectiveness in treating male erectile dysfunction was recently discovered. PDE5 is the primary cGMP hydrolyzing enzyme present in the *corpus cavernosal* smooth muscle of the penis. Upon sexual stimulation, nitric oxyde (NO) is released and activates guanylyl cyclase which produces cGMP [3]. The latter initiates a protein phosphorylation cascade that causes a decrease in intracellular calcium, resulting in vasorelaxation. Inhibition of PDE5 by sildenafil elevates levels of cGMP and hence leads to an improved erection. Despite the efficacy of **1**, clinically notable adverse effects such as headache, nausea, cutaneous flushing and visual disturbance [4,5] have been noted with its use and attributed to its limited selectivity against other PDE enzymes. Thus, with the aim to reach more selective PDE5 inhibitors, devoid of such side effects, this paper describes the access to new Sildenafil analogs **2**, belonging to the pyrrolopyrazine series, which were prepared in order to study the replacement of the pyrimidone moiety with a pyridopyrazine system.

Scheme 1

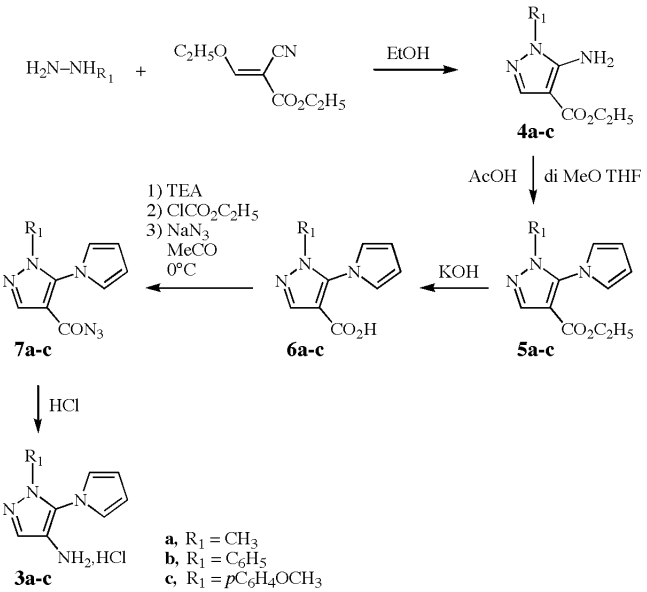


1 **2**

Compounds **2** were prepared according to a Pictet-Spengler-type reaction [6] starting from various 4-amino-5-pyrrolylpyrazoles **3** substituted or not in the 3-position.

The unsubstituted ones were synthesized according to the following sequence (Scheme 2). Treatment of ethyl (ethoxymethylene)cyanoacetate with an appropriate *N*-substituted hydrazine yielded the expected ethyl 5-aminopyrazole-4-carboxylates [7,8] **4a-c**. Compounds **4a-c**, involved in a Clauson-Kaas reaction [9,10,11], followed by an alkaline hydrolysis, led to the 5-pyrrolylpyrazole-4-carboxylic acids **6a-c** [11]. The latter were converted into the acyl azides **7a-c** before being submitted to a

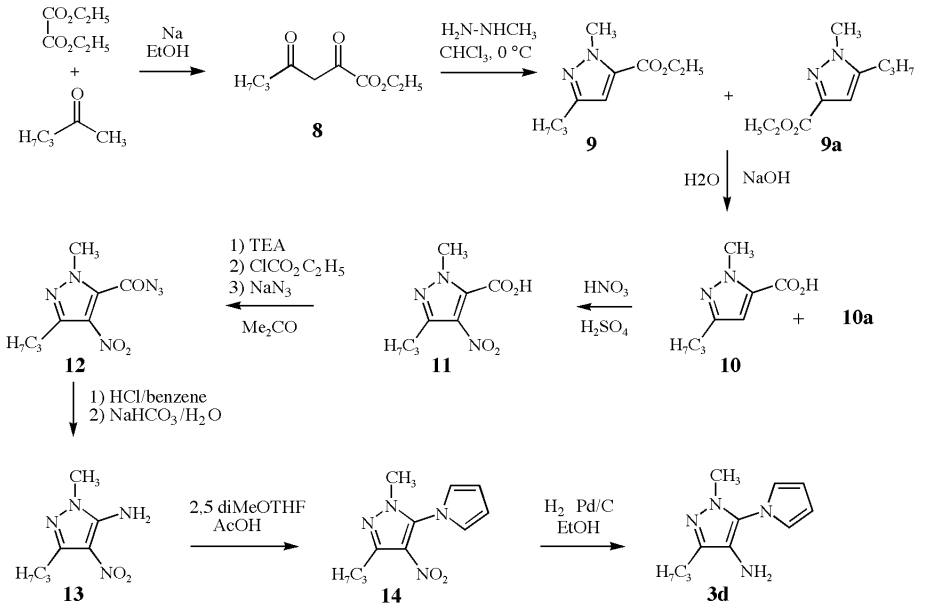
Scheme 2



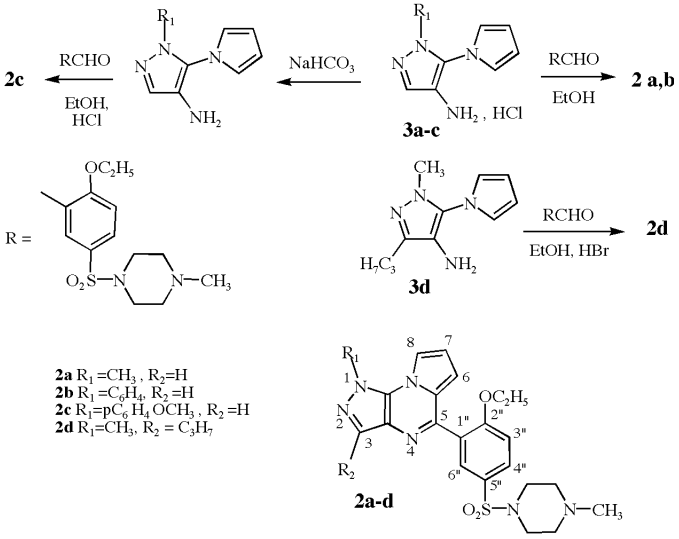
Weinstock-Curtius rearrangement [12] in a refluxing aqueous hydrochloric acid solution. The sequence afforded finally the hydrochloric acid salts of the attempted 1-methyl-, 1-ethyl- and 1-(4-methoxyphenyl)-4-amino-5-pyrrolylpyrazoles **3a-c**, with overall yields of 17%, 67% and 31% respectively from **4a-c**.

Access to the more closely related analog of Sildenafil **2d** required the preparation of 1-methyl-3-propyl-4-amino-5-(pyrrol-1-yl)pyrazole **3d** (Scheme 3). The latter was synthesized according to another pathway [13] starting from diethyloxalate and pentan-2-one that were reacted together in the presence of sodium to give the diketoester **8**, under its enolic form. Treatment of **8** with methylhydrazine produced a mixture of the suitably substituted pyrazole derivative **9** and of its isomer **9a** (60/40). The saponification in an alkaline medium led to a mixture of the carboxylic acids **10** and **10a**, from which **10** was isolated by fractional crystallization. The subsequent nitration of the pyrazole ring of **10** yielded the nitro derivative **11** that was, as above, involved in a Curtius rearrangement to give the intermediate **13**. A Clauson-Kaas reaction, followed by a catalytic hydrogenation using hydrogen and

Scheme 3



Scheme 4



palladium on charcoal, finally converted **13** into **3d**, obtained in a global yield of 23% starting from **8**.

The Pictet-Spengler preparation of **2a-d** was achieved starting from **3a-d** by reaction with 2-ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]benzaldehyde [14,15] (Scheme 4). The reaction was carried on in refluxing ethanol starting either from the ammonium salts **3a,b**, from the free base **3d** or previously displaced from **3c** with sodium hydrogen carbonate, in the presence of hydrochloric (for **3c**) or hydrobromic (for **3d**) acid. Titled compounds **2a-d** were obtained with yields ranging from 15% to 71%).

Biological evaluation of **2a-d** demonstrated that they are 10 fold less potent than Sildenafil to inhibit PDE5.

EXPERIMENTAL

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a Genesis Series FTIR spectrometer. ^{1}H NMR (400 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Elemental analyses for new compounds were performed at the "Institut de Recherche en Chimie Organique Fine" (Rouen).

General Procedure for the Preparation of Ethyl 5-Amino-1*H*-pyrazole-4-carboxylates (**4a-c**).

To a solution of ethyl (ethoxymethylene)cyanoacetate (20 g, 142 mmoles) in ethanol (100 ml), was added the *N*-substituted hydrazine (142 mmoles). The resulting mixture was refluxed for 12 hours then the solvent was evaporated under reduced pressure to give **4a**, **4b** and **4c** in 86%, 99% and 86% yield respectively.

Ethyl 5-Amino-1-methyl-1*H*-pyrazole-4-carboxylate (**4a**) [8].

This compound was obtained as a yellow powder (20.66 g, 122 mmoles, diethyl ether/hexane 60/40) starting from methylhydrazine (6.34 g), mp 98 °C, ir: 1682 (C=O), 1307 (C-O), 3400 (NH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.24 (t, J = 7.12 Hz, 3H, CH_3), 3.52 (s, 3H, CH_3), 4.17 (q, J = 7.12 Hz, 2H, CH_2), 5.16 (s, 2H, NH_2), 7.50 (s, 1H, H3) ppm.

Ethyl 5-Amino-1-phenyl-1*H*-pyrazole-4-carboxylate (**4b**) [8].

This compound was obtained as a yellow powder (32.81 g, 142 mmoles, diethyl ether) starting from phenylhydrazine (15.35 g), mp 100 °C, ir: 1690 (C=O), 1285 (C-O), 3400 (NH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.26 (t, J = 7.16 Hz, 3H, CH_3), 4.21 (q, J =

7.16 Hz, 2H, CH_2), 6.33 (s, 2H, NH_2), 7.54 (s, 5H, phenyl), 7.71 (s, 1H, H3) ppm.

Ethyl 5-Amino-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxylate (**4c**) [8].

This compound was obtained as a yellow powder (31.9 g, 122 mmoles, diethyl ether) starting from 4-(methoxyphenyl)hydrazine (19.62 g), mp 110 °C, ir: 1685 (C=O), 1255 (C-O), 3425 (NH) cm^{-1} ; ^1H nmr (DMSO-d_6): δ 1.25 (t, J = 7.16 Hz, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.21 (q, J = 7.16 Hz, 2H, CH_2), 6.18 (s, 2H, NH_2), 7.05 (d, J = 7.9 Hz, 2H, H3' and H5'), 7.41 (d, J = 7.9 Hz, 2H, H2' and H6'), 7.71 (s, 1H, H3) ppm.

General Procedure for the Preparation of Ethyl 5-Pyrrol-1-yl-1*H*-pyrazole-4-carboxylates (**5a-c**).

To a solution of ethyl 5-amino-1*H*-pyrazole-4-carboxylate (**4a-c**) (58 mmoles) in acetic acid (70 ml), was added dropwise 2,5-dimethoxytetrahydrofurane (58 mmoles). The resulting mixture was refluxed for 3 hours and acetic acid was evaporated under reduced pressure. The oily residue was neutralised with sodium hydrogen carbonate then was extracted with diethyl ether (2 x 500 ml). The organic layers were collected, dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give **5a**, **5b** and **5c** in 85%, 90% and 94% yield respectively.

Ethyl 1-Methyl-5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylate (**5a**) [11].

This compound was obtained as a beige powder (11.01 g, 50 mmoles, cyclohexane) starting from **4a** (9.81 g), mp 87 °C, ir: 1693 (C=O), 1514 (C=C), 1235 (C-O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.20 (t, J = 7.08 Hz, 3H, CH_3), 3.67 (s, 3H, CH_3), 4.17 (q, J = 7.08 Hz, 2H, CH_2), 6.38 (s, 2H, Hβ pyrrole), 6.79 (s, 2H, Hα pyrrole), 7.95 (s, 1H, H3) ppm.

Ethyl 1-Phenyl-5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylate (**5b**) [11].

This compound was obtained as a beige powder (14.60 g, 52 mmoles, diethyl ether) starting from **4b** (13.40g), mp 113 °C, ir: 1720 (C=O), 1605 (C=C), 1235 (C-O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.14 (t, J = 7.08 Hz, 3H, CH_3), 4.13 (q, J = 7.08 Hz, 2H, CH_2), 6.18 (s, 2H, Hβ pyrrole), 6.85 (s, 2H, Hα pyrrole), 7.13 (m, 2H, phenyl), 7.37 (m, 3H, phenyl), 8.21 (s, 1H, H3) ppm.

Ethyl 1-(4-Methoxyphenyl)-5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylate (**5c**) [11].

This compound was obtained as a beige powder (16.90 g, 54 mmoles, acetonitrile), starting from **4c** (15.15 g), mp 140 °C, ir: 1720 (C=O), 1605 (C=C), 1235 (C-O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.17 (t, J = 6.96Hz, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.16 (q, J = 6.96Hz, 2H, CH_2), 6.20 (s, 2H, Hβ pyrrole), 6.87 (s, 2H, Hα pyrrole), 6.91 (d, J = 7.9 Hz, 2H, H3' and H5'), 7.08 (d, J = 7.9 Hz, 2H, H2' and H6'), 8.20 (s, 1H, H3) ppm.

General Procedure for the Preparation of 5-Pyrrol-1-yl-1*H*-pyrazole-4-carboxylic acids (**6a-c**).

To a solution of ethyl 5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylate **5a-c** (90 mmoles) in ethanol (100 ml), was added an 10% aqueous potassium hydroxide solution (160 ml). The reaction mixture was refluxed for 1.5 hours then was cooled at room temperature over night. Ice and water (300 ml) were added. The beige solid which precipitated progressively with addition of an 37% aqueous hydrochloric acid solution was collected by filtration to give **6a, 6b** and **6c** in 97%, 94% and 82% yield respectively.

1-Methyl-5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylic Acid (**6a**) [11].

This compound was obtained as a beige powder (16.92 g, 88 mmoles, acetonitrile) starting from **5a** (19.70 g), mp 198 °C, ir: 2955 (OH), 1720 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.5 (b s, 1H, OH), 3.56 (s, 3H, CH_3), 6.27 (s, 2H, Hβ pyrrole), 7.00 (s, 2H, Hα pyrrole), 7.89 (s, 1H, H3) ppm.

1-Phenyl-5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylic Acid (**6b**) [11].

This compound was obtained as a beige powder (21.50 g, 85 mmoles, acetonitrile) starting from **5b** (25.30 g), mp 185 °C, ir: 3480 (OH), 1695 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.5 (b s, 1H, OH), 6.16 (s, 2H, Hβ pyrrole), 6.96 (s, 2H, Hα pyrrole), 7.11 (m, 2H, phenyl), 7.36 (m, 3H, phenyl), 8.16 (s, 1H, H3) ppm.

1-(4-Methoxyphenyl)-5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylic Acid (**6c**) [11].

This compound was obtained as a beige powder (20.90 g, 74 mmoles, acetonitrile) starting from **5c** (28.00 g), mp 174 °C, ir: 3402 (OH), 1686 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.5 (b s, 1H, OH), 3.77 (s, 3H, OCH_3), 6.20 (s, 2H, Hβ pyrrole), 6.87 (s, 2H, Hα pyrrole), 6.90 (d, J = 7.8 Hz, 2H, H3' and H5'), 7.05 (d, J = 7.8 Hz, 2H, H2' and H6'), 8.17 (s, 1H, H3) ppm.

General Procedure for the Preparation of 5-Pyrrol-1-yl-1*H*-pyrazole-4-carboxylic Azides (**7a-c**).

To a solution of carboxylic acid **6** (52 mmoles) in acetone (300 mL), cooled at 0 °C (ice-salt bath) was added triethylamine (7.3 ml, 52 mmoles). While maintaining the temperature at 0 °C, ethyl chloroformate (4.97 ml, 52 mmoles) was then added slowly. The mixture was stirred for 30 minutes at 0 °C and then a solution of sodium azide (3.38 g, 52 mmoles) in water (10 ml) was added dropwise. The mixture was stirred at 0°C for 1 hour, the precipitate was filtered and the solvent was removed under reduced pressure at room temperature. The solid residue was dissolved in diethyl ether, filtered and evaporation of the solvent at room temperature afforded the azides **7a, 7b** and **7c** in 72%, 91% and 78% yield respectively. The latter were used without further purification.

1-Methyl-5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylic azide (**7a**).

This compound was obtained as a white powder (8.15 g, 38 mmoles) starting from **6a** (9.90 g), mp 62 °C, ir: 2140 (N_3), 1688 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.34 (s, 3H, CH_3), 6.32 (s, 2H, Hβ pyrrole), 7.07 (s, 2H, Hα pyrrole), 8.00 (s, 1H, H3) ppm.

1-Phenyl-5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylic azide (**7b**).

This compound was obtained as a white powder (14.70 g, 47 mmoles) starting from **6b** (13.17 g), mp 112 °C, ir: 2139 (N_3), 1694 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.20 (s, 2H, Hβ pyrrole), 6.86 (s, 2H, Hα pyrrole), 7.14 (m, 2H, phenyl), 7.38 (m, 3H, phenyl), 8.25 (s, 1H, H3) ppm.

1-(4-Methoxyphenyl)-5- pyrrol-1-yl 1*H*-pyrazole-4-carboxylic azide (**7c**).

This compound was obtained as a white powder (13.80 g, 40 mmoles) starting from **6c** (14.75 g), mp 99 °C, ir: 2140 (N_3), 1669 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.79 (s, 3H, OCH_3),

6.30 (s, 2H, Hβ pyrrole), 6.68 (s, 2H, Hα pyrrole), 6.85 (d, J = 9 Hz, 2H, H3' and H5'), 7.03 (d, J = 9 Hz, 2H, H2' and H6'), 8.11 (s, 1H, H3) ppm.

General Procedure for the Preparation of 4-Amino-5-pyrrol-1-yl-1*H*-pyrazole, Hydrochloride (**3a-c**).

To a 10 *N* boiling aqueous hydrochloric acid solution (10 ml), was added 5-pyrrol-1-yl-1*H*-pyrazole-4-carboxylic azide **7a-c**. The mixture was refluxed for 10 minutes. After cooling at room temperature, the hydrochloride salts **3a**, **3b**, **3c** precipitated from the reaction mixture in 32%, 88% and 60% yield respectively.

4-Amino-1-methyl-5-pyrrol-1-yl-1*H*-pyrazole, Hydrochloride (**3a**).

This compound was obtained as a white powder (0.6 g, 3 mmoles, ethanol) starting from **7a** (2 g, 9.4 mmoles), mp 138 °C, ir: 3392-3327 (NH), 1521 (C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.40 (s, 3H, NH_3^+), 3.60 (s, 3H, CH_3), 6.36 (s, 2H, Hβ pyrrole), 7.17 (s, 2H, Hα pyrrole), 7.66 (s, 1H, H3) ppm.

Anal. Calcd for $C_8H_{11}N_4Cl$: C, 48.36; H, 5.58; N, 28.20. Found: C, 48.32; H, 5.44; N, 28.02.

4-Amino-1-phenyl-5-pyrrol-1-yl-1*H*-pyrazole, Hydrochloride (**3b**).

This compound was obtained as a white powder (1.66 g, 6 mmoles, isopropanol) starting from **7b** (2 g, 7.2 mmoles), mp 203 °C, ir: 3413-3335 (NH), 1492 (C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.44 (s, 3H, NH_3^+), 6.28 (s, 2H, Hβ pyrrole), 6.93 (s, 2H, Hα pyrrole), 7.05 (m, 2H, phenyl), 7.35 (m, 3H, phenyl), 7.92 (s, 1H, H3) ppm.

Anal. Calcd for $C_{13}H_{13}N_4Cl$: C, 59.88; H, 5.02; N, 21.49. Found: C, 59.67; H, 6.88; N, 21.53.

4-Amino-1-(4-methoxyphenyl)-5-pyrrol-1-yl-1*H*-pyrazole, Hydrochloride (**3c**).

This compound was obtained as a white powder (1.13 g, 4 mmoles, acetonitrile) starting from **7c** (2 g, 6.4 mmoles), mp 120°C, ir: 3407-3332 (NH), 1505 (C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.40 (s, 3H, NH_3^+), 3.82 (s, 3H, OCH_3), 6.32 (s, 2H, Hβ pyrrole), 6.93 (s, 2H, Hα pyrrole), 6.94 (d, J = 8.8 Hz, 2H, H3' and H5'), 7.03 (d, J 8.8 = Hz, 2H, H2' and H6'), 8.13 (s, 1H, H3) ppm.

Anal. Calcd for $C_{14}H_{15}N_4OCl$: C, 57.83; H, 5.20; N,19.27. Found: C, 57.56; H, 5.39; N, 19.03.

Ethyl 2,4-Dioxoheptanoate (**8**) [13].

To a sodium ethoxide solution prepared from sodium (3.11 g, 135 mmoles) dissolved in ethanol (500 ml), was added at 0 °C a mixture of diethyl oxalate (37 ml, 270 mmoles) and propan-2-one (29 ml, 270 mmoles). The reaction mixture was stirred at 0 °C for 3-4 hours then was left at room temperature overnight. The solution was cooled again in an ice-bath and sulfuric acid (20%) was added until pH=2. The sodium sulfate precipitate was filtered and washed with ethanol. The filtrate was poured into water and was extracted with benzene (2 x 200 ml). The organic layers were collected, washed with an aqueous sodium bicarbonate solution till neutrality and then with water, dried over magnesium sulfate and evaporated to yield 35.19 g (70%, 189 mmoles) of a red oil (**8**) that was not purified; ir: 2966 (CH), 1732 (C=O), 1633 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.97 (t, J = 7.44 Hz, 3H, CH_3), 1.37 (t, J = 6.96 Hz, 3H, CH_3), 1.69 (st, J = 7.44 Hz, 2H, CH_2), 2.33 (s, 1H, OH), 2.48 (t, J = 7.44 Hz, 2H, CH_2), 4.33 (t, J = 6.96 Hz, 2H, CH_2), 6.37 (s, 1H, CH) ppm.

1-Methyl-3-propyl-1*H*-pyrazole-5-carboxylic Acid (**10**) and 1-Methyl-5-propyl-1*H*-pyrazole-3-carboxylic Acid (**10a**).

To a solution of **8** (90.93 g, 490 mmoles) in dichloromethane (750 ml), was added methylhydrazine (24.5 ml, 490 mmoles) at 0 °C for one hour. The reaction mixture was left at room temperature overnight and then refluxed for the same time. The solvent was evaporated, water was added and the organic layer was extracted with ethyl acetate (2 x 500 ml) to yield, after evaporation, a mixture of **9** and **9a** as a white powder that was refluxed for 4 hours with an aqueous sodium hydroxide solution (5%, 500 ml). After cooling, the solution was acidified with an 10 *N* aqueous hydrochloric acid solution. The yellow precipitate was filtered, then stirred at room temperature in diethyl ether (100 ml) and finally filtered once again to give **10** as a white powder in 54% yield (44.36 g, 264 mmoles), mp 112 °C, ir: 3470-2430 (OH), 1681 (C=O), 1496 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.02 (t, J = 7.44 Hz, 3H, CH_3), 1.72 (st, J = 7.44 Hz, 2H, CH_2), 2.59 (t, J = 7.44 Hz, 2H, CH_2), 3.65 (s, 3H, CH_3), 5.2 (b s, 1H, OH), 6.64 (s, 1H, H4) ppm.

Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.66. Found: C, 57.33; H, 7.39; N, 16.55.

The ethereal filtrate was evaporated to dryness and the solid residue was recrystallized from diethyl ether /petroleum ether to give **10a** as a white powder in 40% yield (32.9 g, 196 mmoles), mp 138 °C, ir : 2970-2320 (OH), 1707 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.00 (t, J = 7.44 Hz, 3H, CH_3), 1.67 (st, J = 7.44 Hz, 2H, CH_2), 2.62 (t, J = 7.44 Hz, 2H, CH_2), 4.16 (s, 3H, CH_3), 6.5 (b s, 1H, OH), 6.75 (s, 1H, H4) ppm.

Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N,16.66. Found: C, 57.23; H, 7.52; N, 16.35.

1-Methyl-4-nitro-3-propyl-1*H*-pyrazole-5-carboxylic acid (**11**).

To a solution of **10** (25 g, 148 mmoles) in sulfuric acid (150 ml), was added at –5 °C nitric acid (13 ml, 309 mmoles). The reaction mixture was stirred for 15 minutes at 0 °C and for 30 minutes at room temperature. The solution was then stirred at 80 °C for 4 hours. After temperature decreased to room temperature, iced water was poured into the reaction mixture until a precipitate appeared. The later was collected by filtration, dried and recrystallized from cyclohexane to give **11** as a white powder in a quantitative yield (31.52 g, 148 mmoles), mp < 50 °C, ir: 2955 (OH), 1720 (C=O), 1358 (NO_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.04 (t, J= 7.34 Hz, 3 H, CH_3), 1.71 (st, J = 7.34 Hz, 2H, CH_2), 2.59 (t, J = 7.34 Hz, 2H, CH_2), 3.94 (s, 3H, CH_3), 5.6 (b s, 1H, OH) ppm.

Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.06; H, 5.20; N, 19.71. Found: C, 45.23; H, 5.35; N, 19.43.

1-Methyl-4-nitro-3-propyl-1*H*-pyrazole-5-carboxylic Azide (**12**).

Compound **12** was prepared in a similar way as described for **7a-c** starting from **11** (21.6 g, 101 mmoles) to give **12** in 75% yield (18 g, 75 mmoles) as a yellow powder that was used without further purification, mp 130 °C, ir: 2146 (N_3), 1698 (C=O), 1359 (NO_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.03 (t, J = 7.44 Hz, 3H, CH_3), 1.70 (st, J = 7.44 Hz, 2H, CH_2), 2.94 (t, J = 7.44 Hz, 2H, CH_2), 3.91 (s, 3H, CH_3) ppm.

5-Amino-1-methyl-4-nitro-3-propyl-1*H*-pyrazole (**13**).

To a solution of **12** (9 g, 37.8 mmoles) in benzene (250 ml),

was added a 10 *N* aqueous hydrochloric acid solution (10 ml). The reaction mixture was refluxed for 3 hours. After this time, benzene was evaporated and the solid that precipitated from water was treated with sodium hydrogen carbonate until alkalinity. The solid was collected by filtration, dried and then recrystallized from acetonitrile to give **13** in 86% yield (6 g, 32.6 mmoles) as a yellow powder, mp 165 °C, ir: 1626 (C=C), 1341 (NO_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.03 (t, J = 7.44 Hz, 3H, CH_3), 1.70 (st, J = 7.44 Hz, 2H, CH_2), 1.96 (t, J = 7.44 Hz, 2H, CH_2), 3.65 (s, 3H, CH_3), 5.19 (s, 2H, NH_2) ppm.

Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57; N, 30.42. Found: C, 45.47; H, 6.39; N, 30.24.

1-Methyl-4-nitro-3-propyl-5-pyrrol-1-yl-1*H*-pyrazole (**14**).

Compound **14** was prepared in a similar way as described for **5a-c** starting from **13** (5 g, 27 mmoles) and 2,5-dimethoxytetrahydofurane (3.8 ml, 27 mmoles) to give an yellow oil in 85% yield (5.4 g, 23 mmoles), ir: 1555 (C=C), 1344 (NO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.97 (t, J = 7.56 Hz, 3H, CH_3), 1.64 (st, J = 7.56 Hz, 2H, CH_2), 1.99 (t, J = 7.56 Hz, 2H, CH_2), 3.84 (s, 3H, CH_3), 6.22 (s, 2H, Hα pyrrole), 6.68 (s, 2H, Hβ pyrrole) ppm.

Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.29; H, 6.18; N, 23.56.

4-Amino-1-methyl-3-propyl-5pyrrol-1-yl-1*H*-pyrazole (**3d**).

A solution of **14** (5.4 g, 23 mmoles) in ethanol (100 ml) was autoclaved for 2 hours in presence of palladium on charcoal at 60 °C, under a 30 Kg hydrogen pressure. Ethanol was evaporated, water was added and the product was extracted with ethyl acetate to give **3d** as an yellow oil in 90% yield (4.2 g, 21 mmoles), ir: 3390-3326, 1525 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.94 (t, J = 7.48 Hz, 3H, CH_3), 1.52 (st, J = 7.48 Hz, 2H, CH_2), 2.5 (b s, 2H, NH_2), 2.58 (t, J = 7.48 Hz, 2H, CH_2), 3.63 (s, 3H, CH_3), 6.16 (s, 2H, Hα pyrrole), 7.21 (s, 2H, Hβ pyrrole) ppm.

Anal. Calcd for $C_{11}H_{16}N_4$: C, 64.67; H, 7.90; N,27.43. Found: C, 64.58; H, 7.76; N, 27.75.

5-[2-Ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methylpyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazine (**2a**).

To a solution of **3a** (0.35 g, 1.18 mmoles) in ethanol (50 ml), was added 2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)benzaldehyde (0.55 g, 1.16 mmoles) and the reaction mixture was refluxed for 48 hours. The solvent was then evaporated to dryness and the solid residue was washed with an aqueous sodium hydrogen carbonate solution. After collection by filtration, the solid was washed with ether, filtered and recrystallized from acetonitrile to give **2a** as yellow crystals in 19% yield (0.1 g, 0.33 mmoles), mp 192 °C, ir: 3156 (CH), 1595 (C=C), 1349 (C-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.20 (t, J = 7.8 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.48 (s, 4H, CH_2), 3.08 (s, 4H, CH_2), 4.12 (q, J = 7.8 Hz, 2H, CH_2), 4.42 (s, 3H, CH_3), 6.57 (m, 1H, H7), 6.88 (m, 1H, H6), 7.11 (m, 1H, H8), 7.87 (m, 3H, H3, H3", H4"), 8.01 (m, 1H, H6") ppm.

Anal. Calcd for $C_{22}H_{26}N_6O_3S$: C, 60.81; H, 5.76; N, 18.50. Found: C, 61.00; H, 5.80; N, 18.70.

5-[2-Ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-phenylpyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazine (**2b**).

Compound **2b** was prepared in a similar way as described for **2a** starting from **3b** (2g, 7.67 mmoles) and 2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)benzaldehyde (6.4 g, 7.57 mmoles) to give grey crystals in 71% yield (2.8 g, 5.3 mmoles), mp 258 °C (acetonitrile), ir: 3124 (CH), 1596 (C=C), 1347 (C-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.13 (t, J = 7.8 Hz, 3H, CH_3), 2.71 (s, 3H, CH_3), 2.80 (s, 2H, CH_2), 3.13 (s, 2H, CH_2), 3.42 (s, 2H, CH_2), 3.76 (s, 2H, CH_2), 4.22 (q, J = 7.8 Hz, 2H, CH_2), 6.83 (m, 1H, H7), 6.87 (m, 1H, H6), 7.00 (m, 1H, H8), 7.50 (m, 1H, H3"), 7.70 (s, 5H, phenyl), 7.78 (s, 1H, H3), 7.92 (m, 1H, H4"), 8.42 (m, 1H, H6") ppm.

Anal. Calcd for $C_{27}H_{28}N_6O_3S$: C, 62.77; H, 5.46; N, 16.27. Found: C, 62.56; H, 5.34; N, 16.14.

5-[2-Ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-(4-methoxyphenyl)pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazine (**2c**).

Compound **3c** (1.5 g, 5.15 mmoles) was washed with an aqueous sodium hydrogen carbonate solution to liberate the corresponding free base. The latter was reacted with 2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)benzaldehyde (0.85 g, 1.79 mmoles) in refluxing ethanol for 48 hours. A 10 *N* aqueous hydrochloric acid solution (0.5 ml) was added every 2 hours for the first ten hours. The reaction mixture was then treated as for **2a** and **2b** to give **2c** as yellow crystals in 52% yield (1.6 g, 2.7 moles), mp 250 °C (acetonitrile), ir: 3115 (CH), 1600 (C=C), 1332 (C-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.14 (t, J = 7.8 Hz, 3H, CH_3), 2.71 (s, 3H, CH_3), 2.95 (s, 2H, CH_2), 3.14 (s, 2H, CH_2), 3.42 (s, 2H, CH_2), 3.77 (s, 2H, CH_2), 3.88 (s, 3H, CH_3), 4.21 (q, J = 7.8 Hz, 2H, CH_2), 6.79 (m, 1H, H7), 6.85 (m, 1H, H6), 7.00 (m, 1H, H8), 7.66 (d, J = 6.8 Hz, 2H, H2' and H6'), 7.21 (d, J = 6.8 Hz, 2H, H3' and H5'), 7.51 (m, 1H, H3"), 7.77 (s, 1H, H3), 7.93 (m, 1H, H4"), 8.37 (m, 1H, H6") ppm.

Anal. Calcd for $C_{28}H_{30}N_6O_4S$: C, 61.52; H, 5.53; N,15.38. Found: C, 61.56; H, 5.58; N, 15.42.

5-[2-Ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methyl-3-propylpyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazine (**2d**).

To a solution of **3d** (0.26 g, 1.274 mmoles) in ethanol (40 ml), was added 2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)benzaldehyde (0.4 g, 1.274 mmoles). The reaction mixture was refluxed for 24 hours in the presence of hydrobromic acid (25 ml), then the solution was treated as for **2a-c** to give **2d** as green crystals in 15% yield (0.18 g, 0.19 mmoles), mp 188 °C, ir: 2960 (CH), 1598 (C=C), 1352 (C-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.91 (t, J = 8.44 Hz, 3H, CH_3), 1.09 (t, J = 5.08 Hz, 3H, CH_3), 1.69 (st, J = 8.44 Hz, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.97 (t, J = 8.44 Hz, 2H, CH_2), 3.13 (m, 4H, piperazine), 3.44 (m, 4H, piperazine), 3.95 (s, 3H, CH_3), 4.14 (q, J = 5.08 Hz, 2H, CH_2), 6.58 (m, 1H, H7), 6.79 (m, 1H, H6), 7.46 (m, 1H, H8), 7.88 (m, 2H, H3", H4"), 7.92 (m, 1H, H6") ppm.

Anal. Calcd for $C_{25}H_{32}N_6O_3S$: C, 64.63; H, 6.94; N, 18.09. Found: C, 64.56; H, 6.88; N, 18.02.

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