Synthesis of Pyrazole Derivatives as Potential Bioisosteres of Thromboxane-Synthetase Inhibitors [1]

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A series of ω-carboalkenyl pyrazole derivatives have been synthesized as potential thromboxane-synthetase inhibitors considering the close bioisosteric relationship between the pyrazole ring and other heteroaromatic carboalkenyl compounds exhibiting inhibitory activity. (*E*)-7-(1-Phenylpyrazol-4-yl)hept-2-enoic acid (**4b**) were prepared in 28% overall yield from its minor bis-homologue, (*E*)-5-(1-phenylpyrazol-4-yl)pent-2-enoic acid (**4a**), obtained from 4-formyl-1-phenylpyrazole (**6**) in 17% overall yield. Compounds **4a**, **4b**, **7**, **8** and **13** were screened for their ability to inhibit the *in vitro* rabbit blood platelet aggregation induced by collagen using the Born test. Among the active compounds **4a** exhibited an important inhibition at 1 μM concentration.

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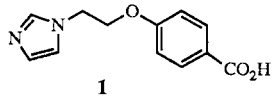
Introduction.

Thromboxane A_2 (TX A_2) is a potent pro-aggregatory and vasoconstrictor substance, produced by action of a cytochrome P-450 dependent enzyme - thromboxane synthetase (TXS) - on prostaglandin endoperoxide (PGH_2), formed in the arachidonic acid (AA) metabolism of blood platelets and other tissues [2].

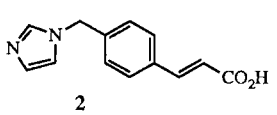
Thromboxane synthetase inhibitors may have therapeutic utility in several conditions where platelets are believed to play a role in the pathogenesis of the disease process, *e.g.* ischemia, arrhythimias, pulmonary hypertension and thromboembolic disorders [3].

An increasing variety of heterocyclic compounds has been described as TXSI, including 1-substituted imidazoles derivatives as shown in Chart 1. Representative of these compounds, dazoxibem (**1**) [2,4] inhibit Fe-CO complexation of TXS, suggesting that they act through heterocyclic nitrogen atom and carboxylic functions [5,6]. Ozagrel (**2**) [7,8], another substituted imidazole carboxylic acid derivative has been reported as the first therapeutically useful anti-thrombotic agent licensed in 1988 in Japan [9]. Recently, Banfi and co-workers have related the synthesis of derivative **3** [10], as a potential TXSI, this report has induced us to disclose here our own results in this field [11].

Chart 1



1



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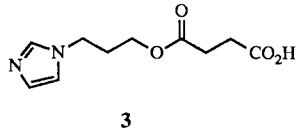

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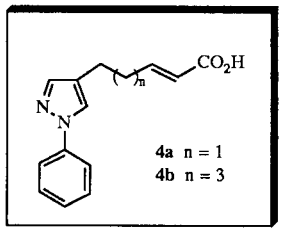
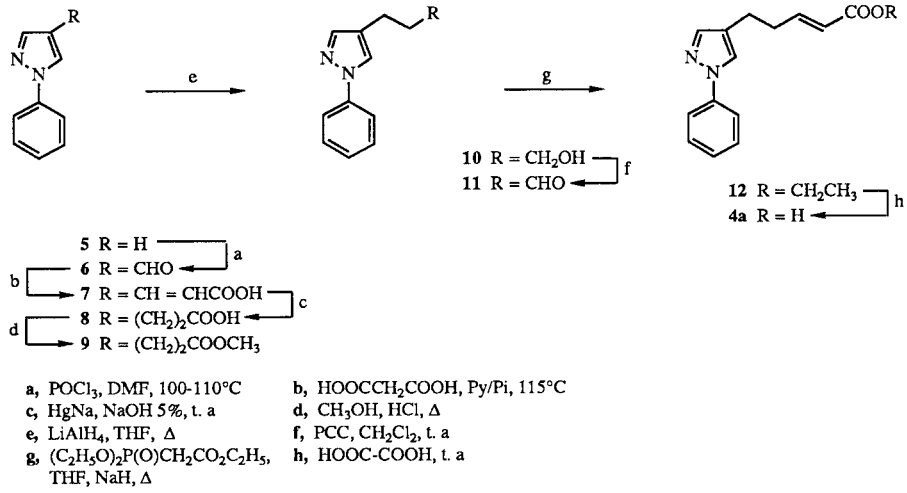


Investigation of the structure-activity relationships in the TXSI series has shown some of the essential structural features related to an effective TXSI activity: the presence of a sterically hindered nitrogen containing heterocyclic ring, a carboxylic acid terminus located 8-10 Å from the heterocyclic nitrogen atom [2,4-6,12,13]. Considering the close bioisosteric relationship [14] between the imidazole and pyrazole ring we became interested in undertaking the synthesis of the 1-phenylpyrazole 4-alkenyl carboxylic acid derivatives **4**, structurally related to compounds shown in Chart 1. Previous Dreiding models examination of **4a**, where n = 1, and **4b**, where n = 3, indicate that these derivatives possess all of the minimal structural requirements to present an anti-aggregating profile, including the *N*-phenyl ring at N-1, considered as an hydrophobic moiety, desirable to an action on TXS [6]. In the derivative **4a**, the molecular model distance between the N-2 pyrazole ring and the terminal carboxyl oxygen atom could be estimated as 8.7-8.9 Å. In addition, in the derivative **4b** this distance was anticipated as being in the 10.30-10.80 Å range, considering that both derivatives can adopted the "hairpin" conformation [15] in the acid side chain.

Chemistry.

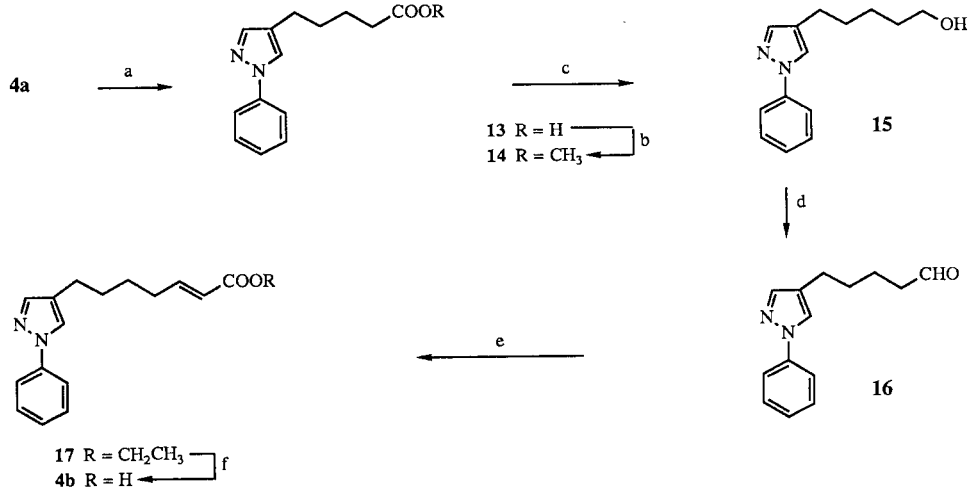
The ω-carboalkenyl pyrazole derivatives **4** were synthesized from accessible N-phenylpyrazole (**5**) [16], following the route shown in Schemes 1 and 2, exploring the intermediacy of the known acid **7** [17].

Scheme 1



a, $POCl_3$, DMF, 100-110°C
b, $HOOCCH_2COOH$, Py/Pi, 115°C
c, HgNa, NaOH 5%, t. a
d, CH_3OH, HCl, Δ
e, $LiAlH_4$, THF, Δ
f, PCC, CH_2Cl_2, t. a
g, $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, THF, NaH, Δ
h, HOOC-COOH, t. a

Scheme 2



a, HgNa, NaOH 5%, t. a
b, CH_3OH, HCl, Δ
c, $LiAlH_4$, THF, Δ
d, PCC, CH_2Cl_2, t. a
e, $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, THF, NaH, Δ
f, HOOC-COOH, t. a

The synthesis of the (*E*)-5-(1-phenylpyrazole-4-yl)pent-2-enoic acid was effected by bis-homologation of the 3-(*N*-phenylpyrazol-4-yl)propanaldehyde (**11**), obtained from the corresponding acid **8**. In turn, this acid was prepared by amalgam hydrogenation [18] of the corresponding unsaturated derivative **7**, obtained in 80% yield by the known sequence: a) 1-phenylpyrazole (**5**) formylation at C-4 by using Vilsmeier-Haack conditions [19]; b) malonic acid condensation of this aldehyde **6** in pyridine:piperidine. The desired propanaldehyde derivative **11** was obtained from **8** by initial esterification to **9**, using standard acidic conditions, followed by reduction of the corresponding methyl ester with lithium aluminium hydride in tetrahydrofurane and subsequent pyridinium chlorochromate oxidation [20] of the hydroxyl compound **10**. The bis-homologation step was performed in high yields by using ethyl (triphenylphosphoranylidene) acetate under Wadsworth-Emmons reaction conditions [21] to product in good yield, the unsaturated ester **12**, which after saponification using a saturated solution of oxalic acid gave the acid **4a** in 23% overall yield, from **7** (Scheme 1).

The *E* configuration of the side-chain double bond of **4a** was determined by measuring the coupling constants of the olefinic protons in the pmr spectrum. This derivative showed a signal centered at δ 7.07 ppm with J = 15.6 Hz, perturbed by allylic coupling, as the A-part of an ABX-system, corresponding to the β-hydrogen. The upfield signal, corresponding to the B-part of this system occurred

at δ 5.82 ppm as a doublet with J = 15.6 Hz, the X-part of this system appeared masked by the signals at δ 2.76-2.53 ppm.

The 1-phenylpyrazoleheptenoic acid (**4b**) was synthesized from **4a** by using a similar synthetic sequence (Scheme 2). For instance, amalgan hydrogenation of **4a** gave the corresponding saturated acid **13**, which could be next esterified to **14**. Lithium aluminium hydride reduction of **14** furnished the alcohol **15** in 85% overall yield. Subsequent oxidation of this hydroxyl compound using pyridinium chlorochromate [20] gave the corresponding aldehyde **16**, which afforded the ester **17** by using the Wadsworth-Emmons reaction conditions. Subsequent ester hydrolysis gave the desired acid **4b** in 28% overall yield from **4a** [22].

The configuration of the side-chain double bond in this derivative was determined by the same method used in **4a**. The olefinics proton signals occurs at δ 7.05 and 5.84 ppm showing a coupling constant value typical to the *E*-configuration.

The three-dimensional crystal structure analysis of **4a** could be undertaken, indicating a measured distance between the nitrogen atom at 2-position of the heterocyclic ring and the terminal side chain carboxylate in the 8.84-8.55 Å range [23]. Unfortunately the derivative **4b** could not be submitted to cristalographic analysis due to problems in obtaining an adequate crystaline unit.

Compounds **4a, 4b, 7, 8** and **13** were examined for inhibition of collagen-induced platelet aggregation of rabbit platelet-rich plasma *in vitro*. This agregation test was performed by using the Born test [24] with collagen as the inducer at 5 μg/ml concentration. Among these pyrazole acids, compounds possessing an unsaturation in the acidic carbon chain with C-5 length, *i.e.* **4a**, were clearly superior in platelet antiaggregating activity than the corresponding saturated carbon chain derivative **13**. In particular, compound **4b** showed potent platelet antiaggregating activity at a concentration of 1 *μM*. In contrast, the derivatives presenting a C-3 carbon chain length, *i.e.* **7** and **8** showed substantially more moderate platelet antiaggregating activity against collagen at the same concentration [25].

EXPERIMENTAL

Nuclear magnetic resonance (pmr) spectra, unless otherwise stated, were determined in deuteriochloroform containing *ca.* 1% tetramethylsilane as an internal standard with a Bruker AC 200 spectrometer at 200 MHz or with a Bruker HP 80 SY at 80 MHz. The cmr spectra were recorded on a Bruker AC 200 spectrometer at 50 MHz also using deuteriochloroform with TMS as internal standard. Infrared spectra were obtained with a Perkin-Elmer 735 spectrophotometer. The mass spectra were obtained with a Varian MAT-SS-100 MS computer system.

Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous magnesium or sodium sulfate powder. The progress of all reactions was monitored by thin-layer chromatography which was performed on 2.0 cm x 6.0 cm aluminium sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under an ultraviolet light, sprayed with concentrated sulfuric acid was used to visualisation. For column chromatography Merck silica gel (70-230 mesh or 230-400 mesh) was used. Solvents used in the reactions were generally redistilled prior to use and stored over 3-4 Å molecular sieves. Reactions were generally stirred under a dry nitrogen atmosphere.

N-Phenylpyrazole (**5**) was prepared in 85% yield by the previously desribed procedure [16].

4-Formyl-1-phenylpyrazole (**6**) was obtained in 80% yield from **5**, as crystals, mp 83-84° by using the modified Vilsmaier-Haack conditions described by Finar [19]. Spectroscopic data were identical to those previously reported [19].

(*E*)-3-(1-phenylpyrazol-4-yl)prop-2-enoic Acid (**7**) [17].

A mixture of malonic acid (12.4 g, 119.2 mmoles) and pyridine (30 ml, 58.1 mmoles) was treated with 4-formyl-1-phenylpyrazole (10 g, 58.1 mmoles) and 1 ml of piperidine. The reaction mixture was heated at 115° for 4 hours, then cooled by addition of a few chips of ice followed by addition of water (*ca.* 55 ml). After acidification, the white solid product was collected by filtration, washed with water to provide 11.4 g (90%) of **7**. A sample was crystallized from ethanol to give the analytical sample, mp 185-186° (lit 186-187°) [17].

3-(1-Phenylpyrazol-4-yl)propanoic Acid Ethyl Ester (**9**).

To a solution of 3 g (14.4 mmoles) of **7** in 5% aqueous sodium hydroxide (54 ml) was added portionwise an excess of sodium amalgam (108 mmoles) [18]. After 24 hours the mercury was eliminated and to the solution was added hydrochloric acid (*ca.* 42 ml) until the reaction was acidic. The mixture was treated with chloroform (45 ml) and the organic layer containing **8** was worked up as usual to furnish 2.9 g of a solid. Crystallization from ethanol yielded 2.55 g (84%) of (**8**), mp 76-77° (lit 77°) [26].

Esterification of **8** (3 g, 13.6 mmoles) with methanol using standard acidic conditions yielded the corresponding ester **9** (2.7 g, 89%) as an oil after chromatographic purification (silica gel-ethyl acetate); pmr: δ 7.92-7.23 (m, 7H, Ar-H + pyrazole-H), 3.62 (s, 3H, OCH_3), 2.76-2.23 ppm (m, 4H, CH_2-CH_2); ms: (m/e) 230 ($M^{\cdot+}$), 157 (100%).

4-(3-(Hydroxypropyl)-1-phenylpyrazole (**10**).

To ester **9** (1.01 g, 4.28 mmoles) dissolved in dry tetrahydrofuran (30 ml) was added portionwise lithium aluminum hydride (0.32 g, 8.42 mmoles) under a nitrogen atmosphere. The resulting reaction mixture was refluxed for 2 hours and then cooled to room temperature. Water (0.35 ml) and aqueous 1 *N* sodium hydroxide solution (1.5 ml) were added carefully in sequence in order to precipitate the aluminum salts. These salts were removed by filtration and washed with chloroform, usual workup of the organic layer followed by evaporation furnished an oil as the crude product. Chromatographic purification (silica gel-ethyl acetate) gave the alcohol **10** (89%) as a pale yellow oil: pmr: δ 7.70-7.04 (m, 7H, Ar-H + pyrazole-H), 3.66 (t, 2H, J = 6.5 Hz, CH_2-O), 2.61 (t, 2H, J = 6.5 Hz, pyrazolyl-CH_2), 2.46 (s, 1H, exchangeable with deuterium oxide), 2.22-1.65 ppm (m, 2H, CH_2); ms: m/z 202 ($M^{\cdot+}$), 184, 171, 157 (100%).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26; N, 12.28. Found: C, 68.54; H, 5.26; N, 12.32.

3-(1-Phenylpyrazol-4-yl)propanaldehyde (**11**).

To a well stirred suspension of 7.6 g (35.2 mmoles) of freshly prepared pyrydinium chlorochromate [20] in 80 ml of anhydrous methylene chloride was added 5.01 g (24.7 mmoles) of pyrazole alcohol **10**. The reaction mixture was stirred at room temperature for 1 hour and then added to a mixture of 1:1 ether:*n*-pentane (80 ml). The slurry was well stirred, decanted and then eluted with ether through a Florisil column, to furnish 3.6 (73%) of **11**, as a colorless oil; pmr: δ 9.45 (s, 1H, CHO), 7.48-6.95 (m, 7H, Ar-H + pyrazole-H), 2.82 ppm (br., 4H, CH_2-CH_2) ms: (m/z): 200 ($M^{\cdot+}$), 171, 157 (100%). This aldehyde was used in the next step without further purification.

(*E*)-5-(1-Phenylpyrazol-4-yl)pent-2-enoic Acid (**4a**) [21].

A suspension of (carboethoxymethyl)triphenylphosphonium bromide (0.28 g, 1.27 mmoles), sodium hydride dispersion (50-55%, 0.1 g, *ca.* 4.34 mmoles) and aldehyde **11** (0.25 g, 1.22 mmoles) in tetrahydrofuran (20 ml) was heated at reflux for 1 hour. The solvent was removed under reduced pressure and the residue partitioned between chloroform and water. The organic extract was worked-up as usual and the resulting syrup was purified on a silica gel column with methylene chloride under a low pressure of nitrogen to provide, after evaporation, 0.24 g (65%) of ethyl ester **12** as a viscous oil; ir: ν CO 1682 cm^{-1}; pmr: δ 7.71-7.11 (m, 7H, Ar-H + pyrazole-H), 7.05 (part A of ABX system, d, 1H, J = 16 Hz, CH=C-COO), 5.84 (part B of ABX system, d, 1H, J = 16 Hz, C=CH-COO) 4.22 (q, 2H, J = 7.2 Hz, OCH_2), 2.67-2.45 (m, 4H, CH_2-CH_2), 1.27 ppm (t, 3H, J = 7.2 Hz, CH_3); ms: m/z 270 ($M^{\cdot+}$), 245, 171, 157 (100%).

A solution of 0.25 g (0.92 mmole) of ester **12** in 20 ml of chloroform was treated with 20 ml of aqueous saturated solution of oxalic acid and well stirred at room temperature under nitrogen atmosphere. After 10 hours the organic layer was dried and evaporated to afford **4a**, crystallized from ethanol, mp 114°; ir: OH 2922, CO 1675 cm^{-1}; pmr: δ 7.72-7.15 (m, 7H, Ar-H + pyrazole-H), 7.07 (part A of ABX system, d, 1H, J = 15.6 Hz, CH=C-COO), 5.88 (art B of ABX system, d, 1H, J = 15.6 Hz, C=CHCOO), 2.76-2.53 ppm (br, 4H, CH_2-CH_2); cmr: δ 171.2 (CO), 150.3 (C=), 121.5 (C=), 140.6 (pyrazole C-3), 140.0 (phenyl C-1'), 129.3 (phenyl C-2'), 126.2 (pyrazole C-5 or phenyl C-4'), 124.9 (pyrazole C-5 or phenyl C-4'), 121.9 (pyrazole C-4) and 118.9 ppm (phenyl C-2'); ms: m/z 242 ($M^{\cdot+}$), 224, 214, 183, 157 (100%).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.78; N, 11.57. Found: C, 69.62; H, 5.82; N, 11.52.

4-(7-Hydroxyheptyl)-1-phenylpyrazole (**15**).

As described for **7** 3.0 g (12.3 mmoles) of acid **4a** was treated with a mixture of malonic acid:pyridine, containing piperidine, to furnish 2.95 g (96%) of the saturated acid **13** as a white solid, crystallized from ethanol:water, mp 93-94°; pmr: δ 7.70-7.23 (m, 7H, Ar-H + pyrazole-H), 2.55 (br t, 2H, CH_2-COO), 2.37 (br t, 2H, pyrazolyl-CH_2), 1.67 ppm (br t, 4H, CH_2-CH_2); ms: m/z 244 ($M^{\cdot+}$), 242, 212, 157 (100%).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.85; H, 6.55; N, 11.47. Found: C, 68.79; H, 6.51; N, 11.78.

As described for compound **8** 0.5 g (2.04 mmoles) of the acid **13** was esterified to afford 0.45 g (86%) of methyl ester **14**, crystallized from ethanol, mp 43-44°; pmr: δ 7.76-7.22 (m, 7H, Ar-H + pyrazole-H), 3.65 (s, 3H, $COOCH_3$), 2.58 (t, 2H, J = 7 Hz, CH_2-COO) 2.35 (t, 2H, J = 7 Hz, pyrazolyl-CH_2), 1.72 ppm (br, 4H, CH_2-CH_2); ms: m/z 258 ($M^{\cdot+}$), 227, 198, 183, 157 (100%).

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.76; H, 6.97; N, 10.85. Found: C, 69.65; H, 7.05; N, 10.75.

The methyl ester **14** (0.51 g, 1.94 mmoles) was treated with 0.16 g (4.21 mmoles) of lithium aluminium hydride affording an oily residue. The residue was separated by column chromatography (silica gel-ethyl acetate) to give 0.42 g (92%) of **15**; pmr: δ 7.73-7.18 (m, 7H, Ar-H + pyrazole-H), 3.60 (t, 2H, J = 6.5 Hz, CH_2O), 2.52 (t, 2H, J = 7 Hz, pyrazolyl-CH_2), 1.93 (br s, 1H, exchangeable with deuterium oxide), 1.72-1.35 ppm (m, 6H, CH_3); ms: m/z 230 ($M^{\cdot+}$), 213, 198, 157 (100%).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.04; H, 7.82; N, 12.17. Found: C, 73.24; H, 7.65; N, 12.37.

7-(1-Phenylpyrazol-4-yl)pentanaldehyde (**16**).

As described to compound **10** 1.0 g, (4.34 mmoles) of pyrazole alcohol **15** was treated with an excess of pyridinium chlorochromate to furnish after the usual work up 0.6 g (60%) of the aldehyde **16** as a viscous oil; pmr: δ 9.46 (s, 1H, CHO), 7.72-6.86 (m, 7H, Ar-H + pyrazole-H), 2.46 (m, 4H, CH_2-CH_2), 1.82-1.54 ppm (m, 4H, CH_2-CH_2). This compound was directly used in the next step.

(*E*)-7-(1-Phenylpyrazol-4-yl)hept-2-enoic Acid (**4b**).

As described for compound **11** 0.5 g (2.19 mmoles) of the aldehyde **16** was treated with 0.49 g (2.25 mmoles) of a suspension of (carboethoxymethyl)triphenylphosphonium bromide to furnish a brown solid as product **17**. Oxalic acid hydrolysis of this product as described above for compound **12** afforded a white solid. Two recrystallizations from ethanol: water gave 0.29 g (64%) of **4b** as white crystals, mp 109-110°; ir: ν OH 2915, CO 1673 cm^{-1}; pmr: δ 7.69-7.22 (m, 7H, Ar-H + pyrazole-H), 7.05 (part A of a ABX system, dd, 1H, J = 16, 6.4 Hz, CH=CCOO), 5.84 (part B of a ABX system, d, 1H, J = 16 Hz, C=CHCOO), 2.53 (t, 2H, J = 6.5 Hz, pyrazolyl-CH_2), 2.24 (t, 2H, J = 6.5 Hz, CH_2-C=), 1.68-1.57 ppm (br, 4H, CH_2-CH_2); cmr: δ 171.5 (CO), 151.5 (C=), 120.9 (C=), 140.8 (pyrazole C-3), 140.2 (phenyl C-1'), 129.5 (phenyl C-3'), 126.0 (pyrazole C-5 or phenyl C-4'), 124.8 (pyrazole C-5 or phenyl C-4'), 123.3 (pyrazole C-4) and 118.9 ppm (phenyl C-2').

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.66; N, 10.37. Found: C, 71.35; H, 6.24; N, 10.45.

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