Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, A. R. Egypt

Polysubstituted pyrazoles, part 4[1]: Synthesis, antimicrobial and antiinflammatory activity of some pyrazoles

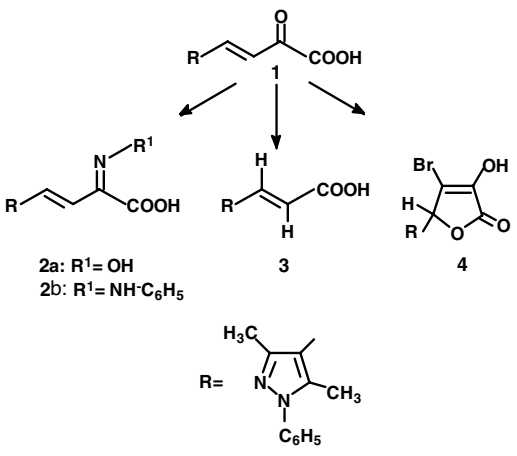
A. M. Farghaly, F. S. G. Soliman, M. M. A. El Semary and Sh. A. F. Rostom

As a continuation of an earlier interest in polysubstituted pyrazoles, the synthesis of some derivatives of 1*H*-pyrazol-4-yl-2-oxo-but-3-enoic acid and ethyl 4-hydroxy-1*H*-pyrazole-3-carboxylates of potential antimicrobial and antiinflammatory activity is described. One compound showed *in vitro* antibacterial activity and two compounds displayed *in vivo* antiinflammatory potency in rats.

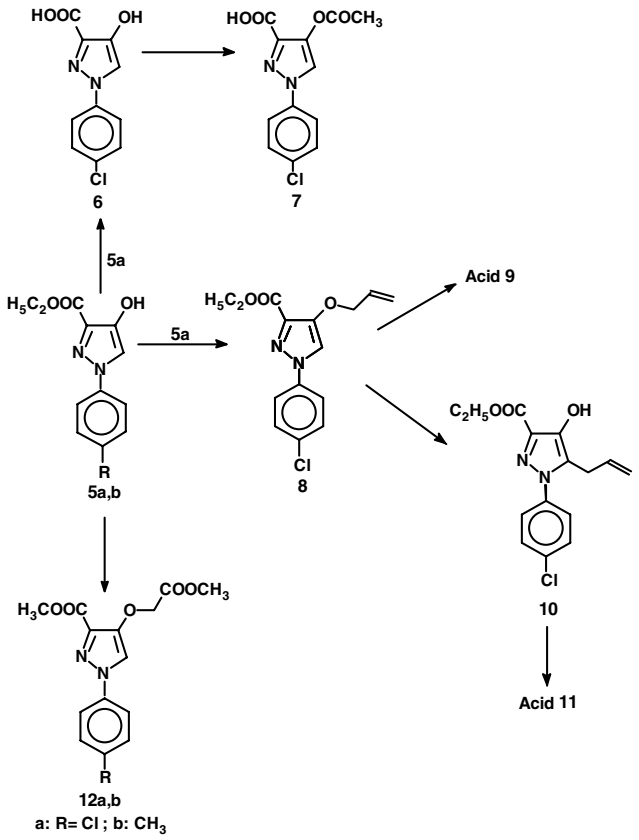
1. Introduction

A tremendous number of pyrazoles has been synthesized and investigated for their biological activities. However, the most impressive properties of these compounds are their antipyretic, analgesic and antiinflammatory potencies. Pyrazoles possessing a hydroxyl group at position 4, their esters and ether derivatives and those which contain a carboxyl group or carboxamides have attracted most attention [2–10]. Some of these derivatives displayed a wide range of biological effects including antimicrobial and antiinflammatory activities. Based on the aforementioned background and as a continuation of our search for potent antimicrobial and non-steroidal antiinflammatory pyrazoles with a reduced incidence of side effects [11–14], certain 1*H*-pyrazole derivatives were selected for preparation. Thus, we were interested in investigating the antimicrobial potency of the key intermediate; 4-(3,5-dimethyl-1-phenyl-1*H*-pyrazole-4-yl)-2-oxo-but-3-enoic acid (**1**) [1], which has previously been reported [15]. It belongs to the arylidenepyruvic acid class of compounds of potential antimicrobial activity. However, the expected strong acidity of this keto-acid ruled out the idea of screening it for antiinflammatory activity. Therefore, conversion of **1** to the corresponding oxime **2a** and phenylhydrazone **2b** as well as 3-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)propenoic acid **3** were considered to be interesting structural modifications of the parent keto-acid for both activities. It was also planned to screen 3-bromo-2-hydroxy-4-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-4-crotonolactone (**4**) which has also been described earlier [15] for both activities (Scheme 1). The chemical and biological properties of the

Scheme 1

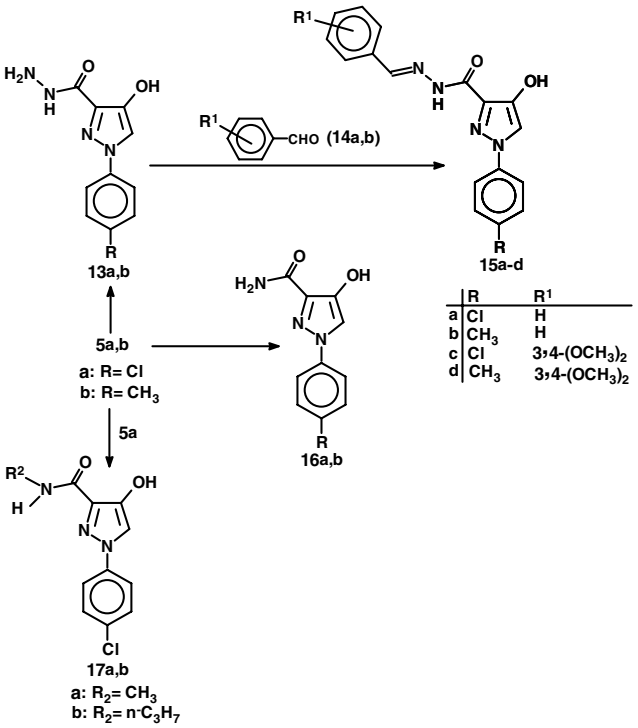


Scheme 2



α,β-unsaturated-γ-lactones may add some significance with respect to the predicted bioactivities of the compound. The N-1 phenyl and C-3 methyl groups would confer lipophilicity to the molecule. Furthermore, the synthesis of new derivatives of ethyl 4-hydroxy-1*H*-pyrazol-3-carboxylate was considered (Schemes 2, 3). The substitution pattern was carefully selected by analogy with aspirin, diflunisal and flufenisal whose pharmacotoxicological profiles are well documented, and antiinflammatory pyrazoles carrying identical functionality [5–8]. The phenyl substitution at N-1 was designed to encounter Cl or CH_3 to enhance the activity, if any. On the other hand, pyrazole-amides (Scheme 3) were designed by analogy with salicylamide, the active pyrazole carboxamides [8–9] and the naturally occuring antiviral antitumor *C*-nucleoside, pyrazofurin; 4-hydroxy-3-β-D-ribofuranosyl-1*H*-pyrazole-5-carboxamide [16].

Scheme 3



2. Investigations and results

2.1. Synthesis of the compounds

The desired compounds were synthesized by the reactions outlined in Schemes 1–3. Reacting sodium 4-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-2-oxo-but-3-enoate (**1**) with hydroxylamine hydrochloride or phenylhydrazine hydrochloride in water at room temperature yielded the corresponding oxime **2a** or phenylhydrazone **2b**, respectively. The conversion of **1** to 3-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)propenoic acid **3** was carried out, as described by Friedman and Mai [17], using perhydrol in an aqueous alkaline medium. Compound **4** (3-bromo-2-hydroxy-4-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-crotonolactone) was prepared from **1** [15], while the intermediate ethyl 4-hydroxy-1-(4-substituted phenyl)-1*H*-pyrazole-3-carboxylates **5a**, **b** were prepared following the procedure described for analogous compounds [15, 18]. Both compounds have been described before by Garg and Singh [19] but with much lower m.p's. Alkaline hydrolysis of **5a** and acidification yielded the acid **6** in a good yield. Acetylation of the latter with acetic anhydride under mild conditions gave 4-acetoxy-1-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylic acid (**7**). Alkylation of **5a** with allyl bromide in the presence of sodium methoxide in anhydrous methanol provided ethyl 4-allyloxy-1-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylate (**8**) in 52% yield. The ester **8** was hydrolyzed to the acid **9** on treatment with aqueous alcoholic sodium hydroxyde solution followed by acidification. Claisen rearrangement of compound **8** in refluxing bromobenzene led to ethyl 5-allyl-1-(4-chlorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (**10**) which was hydrolyzed directly without purification to the acid **11** using aqueous alcoholic sodium hydroxide solution. Methyl 1-[(4-chloro or 4-methylphenyl)-3-methoxycarbonyl-1*H*-pyrazol-4-yloxy] acetates **12a**, **b** were obtained when the sodium salts of the appropriate **5a** or **b** were reacted with ethyl chloroacetate in refluxing methanol (Scheme 2). Reacting the pyrazole esters **5a**, **b** with hydrazine hydrate in methanol yielded the respective acid hydrazides **13a**, **b**. Condensation of the latter pyrazoles with benzaldehyde (**14a**) or 3,4-dimethoxybenzaldehyde (**14b**) gave the corresponding 3-(arylidene-hydrazinocarbonyl)-4-hydroxy-1-(4-chlorophenyl or 4-methyl-phenyl)-1*H*-pyrazoles **15a**–**d** (Table 1). Ammonolysis of **5a, b** with concentrated ammonia solution at 100 °C in a sealed tube gave good yields of the corresponding amides **16a**, **b**. Analogously, heating **5a** with methylamine or *n*-propylamine resulted in the respective *N*-substituted carboxamides **17a**, **b** (Scheme 3).

2.2. Antimicrobial screening

Compounds **1**, **2a**, **b**, **4**, **5a**, **b**, **6**, **8**, **12a**, **b**, **13a**, **6**, **15a**–**d**, **16a**, **b**, **17a**, **b**, were subjected to preliminary screening for *in vitro* activities against clinically isolates of *S. aureus* (Oxford strain) as Gram-positive aerobic bacteria; *E. coli* and *K. aerogens* as Gram-negative anaerobic bacteria; *P. aeruginosa* as Gram-negative aerobic bacteria; and one *C. albicans* strain as a representative for fungi. The agar diffusion method in tryptic soy broth was adopted to determine the growth inhibition zones [20]. Compounds which showed acceptable inhibition zone diameters ($\geq$ 17 mm) at the concentration level used (20 µl of 10 mg/ml dimethylformamide) were evaluated for their minimum inhibitory concentrations (MIC) in µl/ml against the most sensitive organism, using the two-fold serial dilu-

Table 1: 3-(Arylidenehydrazinocarbonyl)-4-hydroxy-1-(4-substituted phenyl)-1H-pyrazoles 15a–d

Compd.	R	R^1	Yield (%)	M.P. (°C) Cryst. Solvent	Molecular formula Molecular weight	IR (cm^{-1})
15a	Cl	H	80	233–34 $CHCl_3$	$C_{17}H_{13}ClN_4O_2$ 340.8	3400–2500 (OH and NH); a band split at 1668 (C=O amide I), 1607 and at 1566; 1496 (C=N, C=C, amide II and aromatics).
15b	CH_3	H	87	225–26 $CHCl_3$	$C_{19}H_{17}ClN_4O_4$ 400.9	3500–2500 (OH and NH); a band split at 1640 (C=O amide I), 1598 and at 1573; 1496 (C=N, C=C, amide II and aromatics); 1267 (C–O–C).
15c	Cl	3,4-$(OCH_3)_2$	65	145–47 C_2H_5OH/H_2O	$C_{18}H_{16}N_4O_2$ 320.4	3500–2550 (OH and NH); a band split at 1666 (C=O amide I),1598 and at 1545; 1439 (C=N, C=C, amide II and aromatics).
15d	CH_3	3,4-$(OCH_3)_2$	66	160–62 C_2H_5OH/H_2O	$C_{20}H_{20}N_4O_4$ 380.4	3500–2600 (OH and NH); a band split at 1667 (C=O amide I), 1598 and at 1546; 1439 (C=N, C=C, amide II and aromatics); 1246 (C–O–C).

Table 2: Growth inhibition zone diameters of the active compounds against *S. aureus* (Oxford strain) and their minimum inhibitory concentrations (MIC)

Compd.	Growth inhibition zone diameters (mm)	MIC (μg/ml)
2b	18	>500
12a	19	>500
13a	24	50
16a	17	250
17a	18	>500
Streptomycin		10

tion technique [20]. Streptomycin was used as a reference drug and a control was used for the solvent. Of the compounds tested, compounds **2b**, **12a**, **13a**, **16a** and **17a** showed inhibitory effects on the growth of *S. aureus* (Table 2). Their MIC values showed that the hydrazide **13a** was the most potent. However, this activity was reduced in the amide **16a** and even more in the *N*-methylated analog **17a**.

2.3. Preliminary antiinflammatory screening

Compounds **3**, **7**, **9**, **11**, and **16a** were chosen to be screened for their *in vivo* antiinflammatory activity in male Sprague-Dawly rats weighing 150–200 mg by applying the cotton-pellet granuloma method [21]. The effect of the test compounds on the growth of granuloma induced by the cotton pellets was taken as the activity parameter. Each group of animals comprised 6 rats. Ketoprofen, 2-(3-benzoylphenyl)propionic acid, was selected as the reference drug. The results recorded in Table 3, revealed that compound **3** is more potent than ketoprofen; whereas compound **9** is nearly equiactive with the reference drug at the same dose level. By contrast, compounds **7** and **16a** aggravated the inflammation conditions as indicated by the increase in the weight of granuloma tissues over that of the control.

3. Experimental

Melting points were determined in open-glass capillaries on a Griffin apparatus and are uncorrected. The IR spectra were recorded for KBr discs, on a Perkin-Elmer 421 spectrophotometer, or on a Shimatzu 408 spectrophotometer. The ^{1}H NMR spectra were determined on a Joel Fx 90q Fourrier transform 200 MHz or on a Varian EM-90 MHz NMR spectrometer using TMS as the internal standard. Microanalysis, for samples dried over $CaCl_2$ at room temperature under reduced pressure, were carried out at the Microanalytical Unit, Faculty of Science, University of Cairo, A.R.Egypt. Light petroleum b.p. 60–80 °C.

Table 3: Effect of the tested compounds and ketoprofen (0.01 mmol/pellet) on the growth of granuloma tissues in subcutaneously implanted cotton pellets

Compd.	Dry weight of granuloma		p*
	Mean (mg ± S.E.)	Inhibition %**	
Control	73.17 ± 1.140	–	–
Ketoprofen	67.50 ± 1.024	−7.74	≤0.005
3	61.80 ± 1.300	−15.48	≤0.001
7	87.00 ± 1.527	+18.90	NS***
9	67.67 ± 1.280	−7.50	≤0.01
11	75.80 ± 1.620	+3.50	NS
16a	84.33 ± 1.540	+15.25	NS

* P = Significance in relation to control
** Change of the mean dry weight of granuloma from control granuloma
*** NS = Non significant

3.1. 4-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-but-3-enoic acid oxime (**2a**)

A solution of Na_2CO_3 (0.21 g; 2 mmol) in H_2O (5 ml) was added to a stirred suspension of **1** [15] (1.1 g, 4 mmol) in H_2O (10 ml) and the mixture was stirred until the evolution of CO_2 ceased and a clear deep yellow solution was obtained. To this solution, a solution of hydroxylamine hydrochloride (0.42 g, 6 mmol) in H_2O (5 ml) was added while stirring. After stirring for 3 h at RT, the solution was acidified with HOAc and the precipitated oxime was filtered, washed with H_2O and dried. It was crystallised from CH_3OH as creamy white needles, m.p. 158–160 °C; yield: 0.95 g (83.2%). IR: 3650–2250 with multiple splits (OH-acid and oxime), 1722 (C=O); a band splitt at 1624 and at 1572, 1532, 1499 (C=N-oxime, C=N, C=C and aromatics), 965 cm^{-1} (N–O-oxime).
$C_{15}H_{15}N_3O_3$ (285.3)

3.2. 4-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4yl)-2-oxo-but-3-enoic acid phenylhydrazone (**2b**)

A solution of phenylhydrazine hydrochloride (0.58 g, 4 mmol) in H_2O (5 ml) was added, while stirring, to a solution of the sodium salt of **1** prepared as described under **2a**. Stirring was maintained for 3 h at RT during which the orange product was separated out. It was filtered, washed with H_2O, dried and crystallised from MeOH as orange microcrystals, m.p. 151–152 °C; yield: 1.0 g (83.3%). IR: 3600–2000 with multiple splits (OH-acid and NH); 1648 (C=O); 1593 a band splitt at 1505 and 1427 cm^{-1} (C=N, C=C and aromatics).
$C_{21}H_{20}N_4O_2$ (360.4)

3.3. 3-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)propenonic acid (**3**)

Perhydrol (0.6 ml) was added, dropwise while stirring, to an ice cooled sodium salt solution of **1**, prepared by treating the acid (1.3 g, 5 mmol) in H_2O (20 ml) with Na_2CO_3 (0.25 g, 2.5 mmol) in H_2O (10 ml). Stirring and cooling were maintained for 2 h until the evolution of gases ceased. The resulting solution was acidified with 2 N H_2SO_4 and the precipitate was filtered, washed with H_2O and dried. It was crystallized from aqueous EtOH as white needles, m.p. 150–152 °C; yield 0.7 g (57.8%). IR: 3250–2250 with multiple splits (OH-acid); 1682 (C=O); a band split at 1613 and at 1545, 1539 cm^{-1} (C=N, C=C and aromatics). 90 MHz-^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3 H, CH_3); 2.32 (s, 3 H, CH_3); 5.95 (d, J = 15 Hz, 1 H, =CH–CO); 7.0–7.35 (m, 5 Ar-H); 7.6 (d, J = 15 Hz, 1 H, CH=C).
$C_{14}H_{14}N_2O_2$ (242.3)

3.4. 3-Bromo-2-hydroxy-4-(3,5-dimethyl-1-phenyl-1H-pyrzol-4-yl)-4-crotonolactone (**4**)

This was prepared as previously described [15]. IR: 3600–2000 with multiple splits (OH); 1767 (enol-lactone form); 1685 (keto-lactone form); a band split at 1596 and at 1536, 1501 cm^{-1} (C=N, C=C and aromatics).

3.5. Ethyl 1-(substituted phenyl)4-hydroxy-1H-pyrazole-3-carboxylates **5a, b**

These were prepared following the conditions reported earlier [18].

3.5.1. Ethyl 4-hydroxy-1-(4-chlorophenyl)-1H-pyrazole-3-carboxylate (**5a**)

M.p. 131–132 °C (reported 80 °C [19]); yield 69.9%. IR: 3550–2500 with multiple splits (OH); 1697 (C=O ester); 1579, 1500, 1497 (C=N, C=C and aromatics); 1247, 1067 (C–O–C); 827 cm^{-1} (C–Cl).

3.5.2. Ethyl 4-hydroxy-1-(4-methylphenyl)-1H-pyrazole-3-carboxylate (**5b**)

M.p. 113–115 °C (reported 99 °C [19]; yield 63.6%. IR: 3550–2550 with multiple splits (OH) ; 1696 (C=O ester); 1619, 1510 (C=N, C=C and aromatics); 1279, 1089 cm^{-1} (C–O–C).

3.6. 1-(4-Chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid (**6**)

The ester **5a** (1.3 g, 5 mmol) was heated at 60 °C with a solution of NaOH (0.4 g, 10 mmol) in a mixture of H_2O (30 ml) and EtOH (10 ml) for 1.5 h. Subsequently, the deep orange reaction mixture was acidified with dilute H_2SO_4 and the yellow product was filtered, washed with H_2O and air dried. It was crystallized from benzene containing a few drops of EtOH, as fine yellow crystals, m.p. 240–241 °C; yield 1.0 g (83.8%). IR: 3750–2400 (OH); 1670 (C=O acid); 1545, 1500, 1460 (C=N, C=C, and aromatics); 830 cm^{-1} (C–Cl). 200 MHz- ^{1}H NMR (DMSO-D_6), δ: 7.60 (d, J = 10 Hz, 2 H, two Ar–H); 7.88 (d, J = 10 Hz, 2 H, two-Ar-H); 8.11 (s, 1 H, H at C_5 pyrazole).
$C_{10}H_7ClN_2O_3$ (238.7)

3.7. 4-Acetoxy-1-(4-chlorophenyl)-1H-pyrazole-3-carboxylic acid (7)

The acid **6** (1.2 g; 5 mmol) was warmed with $(CH_3CO)_2O$ (4 ml) for 15 min, then the mixture was allowed to attain RT. The yellow solid precipitated was washed by decantation with light-petroleum, filtered and air dried. It was crystallized from C_6H_6 as yellow microcrystals, m.p. 170–172 °C; yield 0.9 g (64.12%). IR (cm^{-1}): 3600–2100 with multiple splits (OH acid); a band split at 1752 (C=O acetyl) and at 1684 (C=O acid); 1548, 1532, 1498 (C=N, C=C and aromatics), 822 cm^{-1} (C–Cl).
$C_{12}H_9ClN_2O_4$ (280.7)

3.8. Ethyl 4-allyloxy-1-(4-chlorophenyl)-1H-pyrazole-3-carboxylate (8)

A solution of Na (0.15 g, 6 mmol) in anh. CH_3OH (10 ml) was added to a solution of **5a** (1.6 g; 6 mmol) in anh. CH_3OH (20 ml). The resulting sodio derivative was treated with allyl bromide (0.5 g, 6.6 mmol) and the mixture was refluxed at 80 °C for 12 h. The reaction mixture was then filtered and the filtrate was concentrated under vacuum. The residue was treated with dilute NaOH and the solid was filtered, washed with H_2O and dried. It was crystallized from benzene-light petroleum as yellow needles, m.p. 92–93 °C; yield 0.95 (51.9%). Some unreacted ester (about 0.4 g) could be recovered upon acidification of the alkaline filtrate. IR: 1720 (C=O ester); 1570, 1500 (C=N, C=C and aromatics); 1270, 1070 (=C–O–C), 830 cm^{-1} (C–Cl).
$C_{15}H_{15}ClN_2O_3$ (306.8)

3.9. 4-Allyloxy-1-(4-chlorophenyl)-1H-pyrazole-3-carboxylic acid (9)

The ester **8** (1.5 g, 0.5 mmol) was heated with a solution of NaOH (0.4 g, 10 mmol) in a mixture of H_2O (20 ml) and C_2H_5OH (10 ml) for 1 h. The brown reaction mixture was filtered and acidified with dilute H_2SO_4; the precipitated solid was separated, washed with H_2O and air dried. It was crystallized from benzene-light petroleum as fine brown needles, m.p. 128–130 °C; yield 0.9 g (64.6%). IR: 3500–2250 (OH-acid); 1700 (C=O acid); a band split at 1590 and at 1567, 1493 (C=N, C=C and aromatics); 1276, 1062 (C–O–C); 823 cm^{-1} (C–Cl).
$C_{13}H_{11}ClN_2O_3$ (278.8)

3.10. Ethyl 5-allyl-1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylate (10)

A solution of **8** (0.9 g, 3 mmole) in bromobenzene (10 ml) was refluxed for 3 h and then concentrated under vacuum. The resulting dark brown solution was diluted with light petroleum and the precipitated brown solid was filtered, dried and crystallized from light petroleum as brown microcrystals, m.p. 84–86 °C; yield 0.65 g (72.2%). The compound was utilized without further purification in the next reaction.

3.11. 5-Allyl-1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid (11)

The ester **10** (0.6 g, 2 mmo) was heated at 60 °C with a solution of NaOH (0.16 g, 4 mmol) in a mixture of H_2O (10 ml) and EtOH (5 ml) for 1 h. After being cooled at RT, the brownish solution was acidified with dilute H_2SO_4 and the precipitated product was filtered, washed with H_2O and dried. It was crystallized from benzene-light petroleum as brownish crystals, m.p. 150–152 °C; yield 0.4 g (71.7%). IR: 3438–2600 with multiple splits (OH); 1685 (C=O-acid); a band split at 1527, 1494 (C=N, C=C and aromatics); 839 cm^{-1} (C–Cl). 90 MHz-^{1}H NMR ($CDCl_3$): δ 3.3 (d, J = 6 Hz, 2 H, CH_2); 4.8–5.2 (m, 3 H, CH=CH_2-); 7.12–7.45 (m, 4 Ar–H).
$C_{13}H_{11}ClN_2O_3$ (278.8)

3.12. Methyl [1-(4-substituted phenyl)-3-methyoxycarbonyl-1H-pyrazol-4-yloxy) acetates (12)

General procedure: A solution of Na (0.14 g, 6 mmol) in anh. CH_3OH (10 ml) was added to a solution of **5a**, **b** (6 mmol) in anh. CH_3OH (20 ml). The resulting sodium salt solution was treated with ethyl chloroacetate (0.86 g, 7 mmol) and the mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was treated with dilute NaOH, filtered, washed thoroughly with H_2O and dried. It was crystallized from EtOH as buff needles.

3.12.1. Methyl [1-(4-chlorophenyl)-3-methoxycarbonyl-1H-pyrazol-4-yloxy] acetate (12a)

M.p. 137–138 °C; yield 0.8 g (41%). IR: A band at 1663 shouldered at 1706 and at 1642 (C=O-ester); a band split at 1529, 1513 and 1474 (C=N, C=C and aromatics); 815 cm^{-1} (C–Cl). 200 MHz-^{1}H NMR (DMSO-D_6): δ 3.75 (s,3 H, CH_3); 3.9 (s, 3 H, CH_3); 4.8 (s, 2 H,CH_2); 7.6 (d, J = 10 Hz, 2 H, two Ar–H); 7.8 (d, J = 10 Hz, 2 H, two Ar–H); 8.55 (s, 1 H, H at C-5 in pyrazole).
$C_{14}H_{13}ClN_2O_5$ (324.8)

3.12.2. Methyl [1-(4-methylphenyl)-3-methoxycarbonyl–1H-pyrazol-4-yloxy] acetate (12b)

M.p. 180–182 °C; yield 0.7 g (38.3%). IR: 1680 shouldered at 1760 (C=O ester); a band split at 1590, 1524 and 1461 cm^{-1} (C=N, C=C and aromatics).
$C_{15}H_{16}N_2O_5$ (304.3)

3.13. 4-Hydroxy-1-(4-substituted phenyl)-1H-pyrazole-3-carboxylic acid hydrazides (13)

General procedure: A solution of the appropriate **5a**, **b** (6 mmol) and hydrazine hydrate (0.79 g, 1.2 mmol) in MeOH (20 ml) was refluxed for 2 h. After being cooled to RT, the deposited yellow product was filtered, washed with cold MeOH and dried. It was crystallized from MeOH as deep yellow clusters.

3.13.1. 4-Hydroxy-1-(4-chlorophenyl)-1H-pyrazole-3-carboxylic acid hydrazide (13a)

M.p. 213–215 °C; yield 1.0 g (65%). IR: 3400–3550 (OH and NH); 1670 (C=O, amide I band); a band split at 1595, 1570 and 1550, 1490 cm^{-1} (C=N, amide II band, C=C and aromatics).
$C_{10}H_9ClN_4O_2$ (252.7)

3.13.2. 4-Hydroxy-1-(4-methylphenyl)-1H-pyrazole-3-carboxylic acid hydrazide (13b)

M.p. 184–185 °C; yield 0.85 g (60.9%).
$C_{11}H_{12}ClN_4O_2$ (232.3)

3.14. 3-(Arylidenehydrazinocarbonyl)-4-hydroxy-1-(4-substituted phenyl)-1H-pyrazoles (15a–d)

General procedure: A mixture of the appropriate acid hydrazide **13a**, **b** (4 mmole) and the aromatic aldehyde **14a**, **b** (4 mmol) was refluxed in C_2H_5OH (20 ml) containing 2 drops of concentrated H_2SO_4 for 1 h. The solvent was then removed under vacuum and the residue was washed with ether, filtered, and crystallized from the solvent. The IR data are included in Table 1. 90 MHz-^{1}HNMR ($CDCl_3$) of **15b**: δ 3.68 (s, 3 H, OCH_3); 3.80 (s, 3 H, OCH_3); 6.6 (s, 1 H, CH=); 6.98–7.30 (m, 7 H, Ar–H); 7.94 (s, H at C-5 pyrazole); 9.43 (s, 1 H, NH–).

3.15. 4-Hydroxy-1-(4-substituted phenyl)-1H-pyrazole-3-carboxamides (16a, b)

General procedure: The appropriate **5a**, **b** (0.2 g) was heated with concentrated NH_4OH (3 ml) at 100 °C in a sealed ampoule for 1.5–2 h. The dark solution was then acidified with concentrated HCl and the product was filtered, washed with H_2O and dried. It was crystallized from C_2H_5OH.

3.15.1. 4-Hydroxy-1-(4-chlorophenyl)-1H-pyrazole-3-carboxamide (16a)

M.p. 220–222 °C; yield 0.16 g (75%). IR: 3400–2500 (OH and NH); a band split at 1682 (C=O amide I) and at 1609; 1500; 1461 (C=N amide II and aromatics); 824 cm^{-1} (C–Cl).
$C_{15}H_8ClN_3O_2$ (237.7)

3.15.2. 4-Hydroxy-1-(4-methylphenyl)-1H-pyrazole-3-carboxamide (16b)

M.p. 185–186 °C; yield 0.1 g (56%). IR: 3400–2600 (OH, NH); a band split at 1655 (C=O amide I) and at 1566; 1513 cm^{-1} (C=N , amide II and aromatics).
$C_{11}H_{11}N_3O_2$ (217.2)

3.16. N-Substituted 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxamides (17a, b)

General procedure: The appropriate **5a**, **b** (0.2 g) was heated with methyl or n-propylamine **16a**, **b** (3 ml) at 100 °C in a sealed ampoule for 1–2 h. The solution was acidified with HCl and the precipitate was filtered, washed with H_2O, dried and crystallized from C_2H_5OH.

3.16.1. N-Methyl 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxamide (17a)

M.p. 190–191 °C; yield 0.12 g (71.4%). IR: 3600–2500 (OH–NH); a band split at 1660 (C=O, amide I) and at 1576; 1555; 1492 (C=N, amide II and aromatics), 824 cm^{-1} (C–Cl).
$C_{11}H_{10}ClN_3O_2$ (251.7)

3.16.2. N-propyl 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxamide (17b)

M.p. 187–188 °C; yield 0.14 g (75%).
$C_{13}H_{14}ClN_3O_2$ (279.8)

Acknowledgements: The authors are grateful to Dr. Ahmed H. Yousry, Lecturer in Microbiology, High Institute of Public Health, University of Alexandria, A.R. Egypt, for the antimicrobial screening. They also thank Dr. Adnan A. Bekhit, Lecturer in Organic Chemistry, Faculty of Pharmacy, University of Alexandria, for helping in conducting the antiinflammatory screening.

[1]Part 3: [1]

References

1 Soliman, F. S. G.; Labouta, J. M.: Pharmazie **37**, 170 (1982)
2 Bruno, O.; Bondavalli, F.; Ranise, A.; Schenone, P.; Losasso, C.; Cilenti, L.; Matera, C.; Marmo, E.: Farmaco **45**, 147 (1990)
3 Bruno, O.; Bondavalli, F.; Ranise, A.; Schenone, P.; Cenicolar, M. L.; Donnoli, D.; Fillippelli, W.; Losasso, C.; Costantino, M.; Marmo, E.: Farmaco **46**, 477 (1991)
4 Biere, H.; Böttcher, I., Kapp, J. F.: Arch. Pharm. **316**, 588 (1983)
5 Vinge, E.; Bjorkman, S.: Acta Pharmacol. Toxicol (Copenh.) **59**, 165 (1986)
6 Menozzi, G.; Mosi, L.; Schenone, P.; Donnoli, D.; Schiariti, F.; Marmo, E.: Farmaco **45**, 167 (1990)
7 Bernard, M.; Hulley, E.; Molenda, H.; Stochla; Wrzeciono, U.: Pharmazie **41**, 560 (1986)
8 Vertuani, G.; Giori, P.; Guareneri, M.; Sarto, G. P.: J. Pharm. Sci. **74**, 1013 (1985)
9 Daidon, G.; Plescia, S; Raffa, D.; Bajordi, M.L.; Milici, M.: Farmaco **40**, 683 (1985)
10 Fadel, T. A.; Youssef, A. F.; Ahmed, A. N.; El Bitar, H. I.: Bull. Pharm. Sci. Assiut Univ. (Egypt) **13**, 145 (1990)
11 Farghaly, A. M; Chaaban, I.; Khalil, M.A.; Bekhit, A. A.: Alex. J. Pharm. Sci. **4**, 52 (1990)
12 Farghaly, A. M; Chaaban, I.; Khalil, M. A.; Bekhit, A. A.: Arch. Pharm. **323**, 311 (1990)
13 Farghaly, A. M; Chaaban, I.; Khalil, M. A.; Bekhit, A. A.: Arch. Pharm. **323**, 833 (1990)
14 Khalil, M. A.; Soliman, R.; Farghaly, A. M; Bekhit, A. A: Arch. Pharm. **327**, 27 (1994)
15 Roushdi, I. M.; El-Sebai, A. I.; Shafik, R. M.; Soliman, F. S. G.: Pharmazie **27**, 731 (1972)
16 Goodchild, J.; Buchman, J. G.; Wightman, R. H.; in Sammes, P. G.; Topics in Antibiotic Chemistry, vol 6, pp. 189, 312, Ellis Horwood Limited, Chichester l982
17 Friedman, E.; Mai, H.: Helv. Chim. Acta **14**, 1213 (1931)
18 Soliman, F. S. G.; Shafik, R. M.: Pharmazie **30**, 436 (1975)
19 Garg, H. G.; Singh, P. P.: J. Pharm. Sci. **59**, 656 (1970)
20 Conte, J. E.; Barriere, S. L.: Manual of Antibiotics and infectious Diseases, 1st ed., p. 135, Lea and Febiger, USA 1988
21 Winter, C. A.; Risley, E. A.; Nuss, G. W.: J. Pharmacol. Exp. Ther. **141,** 369 (1964)

Received April 20, 2000
Accepted June 15, 2000

Prof. Dr. Farid S. G. Soliman
Department of Pharm. Chemistry
Faculty of Pharmacy
University of Alexandria,
Alexandria
A.R. Egypt
farid.sg@globalnet.com.eg