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Synthesis and Hypoglycemic Evaluation of Substituted Pyrazole-4-carboxylic Acids

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Abstract—The synthesis and in vivo activities of a series of substituted pyrazole-4-carboxylic acids as hypoglycemic agents are described. Modelization of some potent compounds, comparatively to the metformine, presents certain analogies permitting to predict the design of some novel antidiabetic drugs.

In recent years, the increase of people suffering from diabetes in the world had focused the attention toward a search for novel structural classes of hypoglycemic agents as thiazolidinediones,[1] the alpha-glucosidase inhibitors,[2] the meglitinides,[3] the beta-3-adrenergics agonists,[4] the AR inhibitors[5] and more recently protein Acrp 30.[6] However, all these drugs present secondary effects that involve numerous diseases for the patients.

Actually, the more used hypoglycemic drugs stand sulfonylureas[7] and more particularly the metformine for the treatment of diabetes of type II (NIDDM).

Historically, different substituted pyrazoles[8] were known for their hypoglycemic activity in vivo, but in a search for novel structural classes of drugs inhibiting the activity of the ATP-K^+ channel of the beta cell pancreatic membrane, inducing the production of insulin we turned our attention to substituted pyrazole-4-carboxylic acids

Chemistry

All substituted pyrazole-4-carboxylic acids described in this paper were prepared as shown in Scheme 1 from **1**, which was prepared according to the classical procedure described in literature.[9] The regioselective *O*-alkylatation of pyrazoles was carried out in two steps. First, the ethyl 1-acetyl-3-hydroxy-1H-pyrazole-4-carboxylate was synthesized by condensation of one equivalent of acetic acid anhydride in acetic acid. Then reaction of alkyl halide with pyrazole **2** using potassium carbonate as base in *N*,*N*-dimethylformide at 90 °C lead to the *O*-alkylated pyrazoles **3** in high yields. This methodology does not need a N-deprotection step.[10]

In a second step, a N_1 regioselective alkylation is obtained by deprotonation of N_1-hydrogen using sodium hydride in THF as solvent and reaction with different alkyl halides or sulfates and acrylates.[11] Compounds **6** were isolated after a classical procedure with good yields as shown in Table 1. The ethyl 3-hydroxy-1-methyl-1H-pyrazole-4-carboxylate **7** was obtained by deprotection of 3-hydroxyl group by boron tribromide in methylene chloride or hydrogen bromide in glacial acetic acid before saponification.[12]

All 3-hydroxy or 3-alkoxy-1H-pyrazole-4-carboxylic acids **4**, **5**, **8**, **9** were obtained after saponification and acidification of correspondent esters.[13] Compounds **4c** and **8(c,g,h,i,k)** were obtained as diacids.

Evaluation of the Biological Activity

The antidiabetic activity of compounds **4**, **5**, **8** and **9** has been determined from a pharmacological test based on

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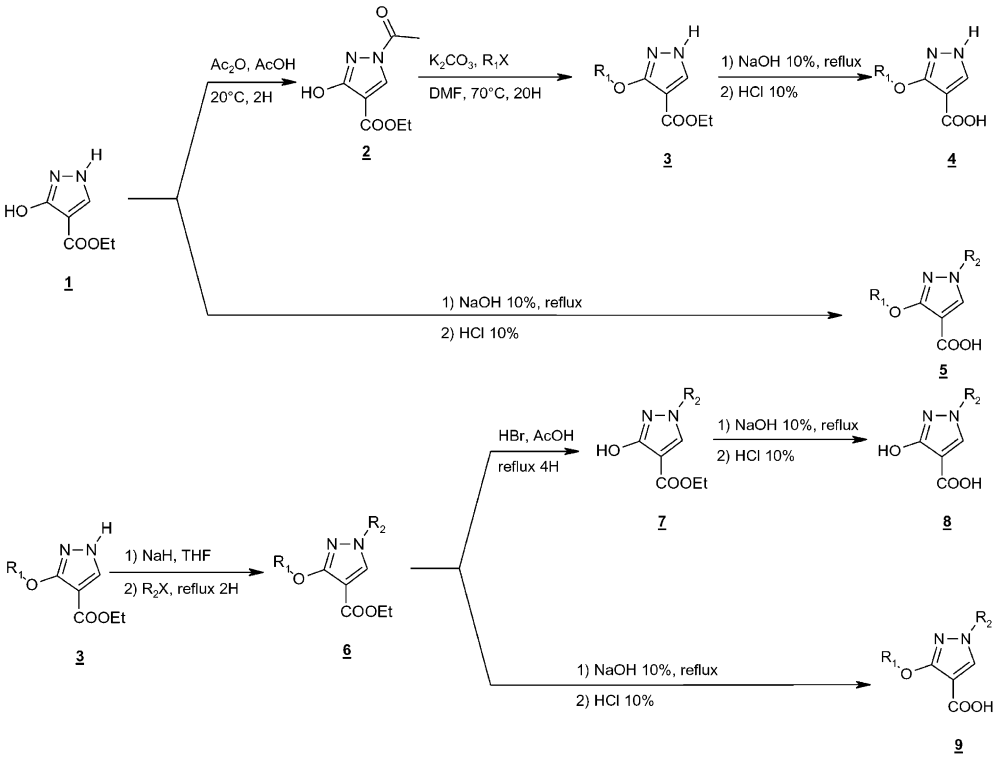
blood glyceamia measure. The results obtained are summarized in Table 2.

Tests were realized from Wistar rats suffering from diabetes of type II, which had been brought about by the administration of stepozocin in moderate dose. The glyceamia had been determined on plasma before treatment (J0), then 2 h after the first administration (J1) and 2 h after the last administration for 4 days chronic treatment (J4). During the test time, the glucose contribution from the intestine was negligible, as the rats had eaten nothing for 4 h. As the blood samples were taken at the extremity of the tail, the tests were realized on 10 rats at the same time, for each compounds at each concentration. The results of the present study Table 2 indicate that compounds **4a** emerges as the best hypoglycemic agent in the series.

Molecular Modeling

Molecular modeling studies of **4a** were performed using Sybyl software version 6.5[14] running on Silicon Graphics workstations. The low-energy conformation of **4a** superimposed to metformine Figure 1 permits us to think that it can act as this last compound.



Scheme 1.

Table 1. Esters and acids derivatives of pyrazoles

Compd	R_1	R_2	% Ester yield	Compd	% Acid yield
1	H	H	90	**5**	85
2	H	$COCH_3$	95	—	—
3a	CH_3	H	80	**4a**	68
3b	$C_6H_5CH_2$	H	90	**4b**	75
3c	2-CN-[1,1′-biphenyl]-4′-(CH_2)	H	90	**4c**[a]	94
6a	CH_3	CH_3	68	**9a**	100
6b	$C_6H_5CH_2$	$C_6H_5CH_2$	95	**9b**	78
6c	CH_3	2-CN–[1,1′-biphenyl]-4′–(CH_2)	82	**9c**[a]	80
6d	CH_3	CH_2=CH–CH_2	64	**9d**	90
6e	CH_3	$(CH_3)_2$C=CH–CH_2	77	**9e**	95
6f	$C_6H_5CH_2$	CH_3	84	**9f**	97
6g	$C_6H_5CH_2$	CH_3CH_2OOC–CH_2	62	**9g**[a]	80
6h	$C_6H_5CH_2$	CH_3OOC–$(CH_2)_2$	65	**9h**[a]	56
6i	$C_6H_5CH_2$	CH_3CH_2OOC–$(CH_2)_3$	67	**9i**[a]	88
6j	$C_6H_5CH_2$	Tetrazole—CH_2	90	**9j**	92
6k	$C_6H_5CH_2$	2-CN–[1,1′-biphenyl]-4′–(CH_2)	90	**9k**[a]	88
6l	$C_6H_5CH_2$	(4-Cl-phenyl)–NH-CO–$(CH_2)_2$	67	**9l**	63
7	H	CH_3	90	**8**	80

[a]Compounds obtained as diacids.

Table 2. Glyceamia evolution%

Compd	J1[a]		J4[b]	
	20 mg/kg[c]	200 mg/kg[c]	20 mg/kg[c]	200 mg/kg[c]
5	−12	7	−9	2
4a	−19	−4	−20	−8
4b	1	−1	−24	−15
4c	−7	0	−11	−5
9a	−7	−5	−10	−10
9b	−6	−14	−5	−9
9c	−5	1	−10	−3
9d	3	5	1	6
9e	3	−8	−3	−11
9f	−4	−5	2	−4
9g	−8	0	−6	−3
9h	−3	−13	−7	−3
9i	−1	−1	−3	−6
9j	0	−2	−7	−7
9k	−5	−4	−10	−3
9l	−16	−19	−10	−19
8	0	−12	−12	−16
Metformine	—	−24	—	−24

[a]2 h after the first administration.
[b]2 h after the last administration for 4 days chronic treatment.
[c]Dose of compound/kg of rat.

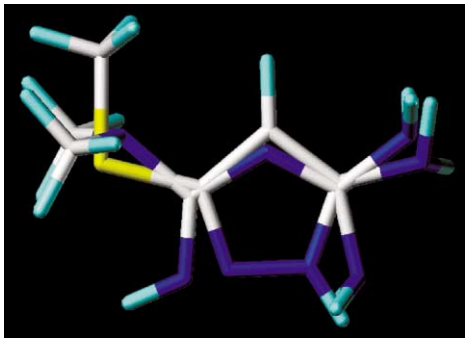


Figure 1. Superposition of **5a** and metformine.

The introduction of different pharmacophors moiety **9e** or **9l** shows no more activity comparatively to compound **4a.** These results and a study by modelization permit us to propose a new compound which was in progress and represent an important breakthrough in the design of structurally new compounds as potential therapeutics for the treatment of NIDDM and diabetes.

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10. Experimental procedure and datas for **3a**: Compound **1** (9 g, 60 mmol) was dissolved in acetic acid (150 mL). To the resulting solution was added acetic anhydride (5.4 mmol, 60 mL). The reaction mixture was stirred at room temperature for 3 h. Then the solvent was evaporated under reduced pressure. The precipitate was washed with water and then collected on a filter to give the pyrazole **2** 10.1 g (95%) as white needles; mp 138 °C ; ^{1}H NMR ($CDCl_3$) δ 1.4 (t, J = 7.15 Hz, 3H, CH_3), 2.7 (s, 3H, CO**CH$_3$**), 4.4 (q, J = 7.15 Hz, 2H, CH_2), 4.7 (s, 1H, OH), 8.5 (s, 1H, H_5) ; ^{13}C NMR ($CDCl_3$) δ 14.2 (**C**H_3), 21.7 (CO**C**H_3), 61.6 (**C**H_2), 103.6 (C_4), 134 (C_5), 163.2 (C_3), 164.5 (**C**OOCH$_2$), 169.2 (N**C**OCH$_3$) ; IR (KBr) ν 3117 (OH), 1740 (**C**OCH$_3$), 1695 (**C**OOCH$_2$) cm^{-1}. MS 199 (M + H, 70). Anal. calcd for $C_8H_{10}N_2O_4$: C, 59.69 ; H, 4.55 ; N, 12.00. Found : C, 59.74 ; H, 4.53 ; N, 11.97. A solution of ethyl 1-acetyl-3-hydroxy-1*H*-pyrazole-4-carboxylate **2** (2 g, 10 mmol) and potassium carbonate (1.4 g, 10 mmol) in anhydrous DMF (50 mL) was stirred at room temperature during 30 min. Methylsulfate (12 mmol) in DMF (20 mL) was added dropwise over 15 min and the reaction mixture was warmed for 20 h at 70 °C. The solvent was evaporated under vaccum, the residue was dissolved in water and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The resultant crude product was crystallized in diisopropyl ether to give (1,6 g) of the corresponding *O*-methylated product **3a**. (93% yield). White solid; mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.1 Hz, CH_2**CH$_3$**), 1.8 (s, 1H, NH), 4 (s, 3H, O**CH$_3$**), 4.3 (q, J = 7.1 Hz, **CH$_2$**CH$_3$), 7.9 (s, 1H, H_5) ; ^{13}C NMR ($CDCl_3$) δ 15 (**C**H_3), 56.9 (O**C**H_3), 60.4 (**C**H_2), 99.6 (C_4), 134.5 (C_5), 163.3 (C_3), 163.5 (**C**OOCH$_2$) ; IR (KBr) ν 3257 (NH), 1667 (C=O) cm^{-1}. MS 171 (M + H, 90).
11. Experimental procedure and datas for **6a**. To a stirred suspension of sodium hydride (1.5 g, 35.2 mmol) in anhydrous tetrahydrofurane (30 mL) was added dropwise a solution of

pyrazole **3a** (6 g, 35.2 mmol) in anhydrous tetrahydrofurane (20 mL). The solution was stirred for 30 min at room temperature then methyl iodide (5.3 mL, 84.5 mmol) was added and the solution was stirred for 2 h at room temperature. Water is added and the mixture was extracted with ethyl acetate, the organique layer was dried on magnesium sulfate and evaporated under reduced pressure to give the pyrazole **6a** in 68% yields. White solid; mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, $J = 7.1$ Hz, $CH_2C\mathbf{H_3}$), 3.7 (s, 3H, $NC\mathbf{H_3}$), 4 (s, 3H, $OC\mathbf{H_3}$), 4.2 (q, $J = 7.1$ Hz, $C\mathbf{H_2}CH_3$), 7.6 (s, 1H, H_5) ; ^{13}C NMR ($CDCl_3$) δ 15 ($\mathbf{C}H_3$), 39.9 ($N\mathbf{C}H_3$), 57.1 ($O\mathbf{C}H_3$), 60.4 ($\mathbf{C}H_2$), 96.7 (C_4), 135.7 (C_5), 163 (C_3), 163.2 ($\mathbf{C}OOCH_2$) ; IR (KBr) ν 1667 (C=O) cm^{-1}. MS 185 (M + H, 90).

12. Experimental procedure and datas for **7**. A solution of pyrazole **6a** (10 g, 55 mmol) in a 33% solution of hydrogen bromide in glacial acetic acid (50 mL) was reflux for 4 h. Then the solvent was evaporated under reduced pressure. The precipitate was washed with water and collected on a filter to give the pyrazole **7** 8.5 g (90%) as white needles; mp 156 °C; ^{1}H NMR (DMSO-d_6) δ 1.4 (t, $J = 7.15$ Hz, 3H, CH_3), 3.8 (s, 3H, $NC\mathbf{H_3}$), 4.3 (q, $J = 7.15$ Hz, 2H, CH_2), 7.5 (s, 1H, H_5), 9 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 14.5 ($\mathbf{C}H_3$), 39.6 ($N\mathbf{C}H_3$), 60.6 ($\mathbf{C}H_2$), 97.5 (C_4), 102.2 (C_5), 163.2 (C_3), 165.2 ($\mathbf{C}OOCH_2$); IR (KBr) ν 3117 (OH), 1708 ($\mathbf{C}OOCH_2$) cm^{-1}. MS 170 (M + H, 70).

13. Experimental procedure and datas for the acid **4a**. A solution of **3a** 5,5 g (32 mmol) in 10% NaOH (150 mL) and EtOH (80 mL) was refluxed for 20 h. After evaporation of EtOH, the solution was cooled to 10 °C and acidified to pH 1 with 10% HCl. The precipitated solid **6a** was collected by filtration, washed with water and dried to give (3.1 g) white needles. 68% yield; mp > 270 °C; ^{1}H NMR (DMSO-d_6) δ 3.8 (s, 3H, $OC\mathbf{H_3}$), 7.9 (s, 1H, H_5) ; ^{13}C NMR (DMSO-d_6) δ 55.6 ($O\mathbf{C}H_3$), 98.2 (C_4), 134.4 (C_5), 162 (C_3), 163.4 ($\mathbf{C}O$) ; IR (KBr) ν 3100–3300 (COOH + NH), 1670 (CO) cm$^{-1,}$ MS 143 (M + H, 82). Anal. calcd for $C_5H_6N_2O_3$: C, 42.26; H, 4.26; N, 19.71. Found: C, 43.30; H, 4.32; N, 19.64.

14. *SYBYL-6,5*; Tripos Associates, Inc: 1699, South Hanley Road, St Louis, MO 63144, USA.