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Synthesis of the pyrazole isostere of valdecoxib

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Dedicated to Professor András Lipták on the occassion of his 70th birthday

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4-(5-Methyl-3-phenyl-1*H*-pyrazole-4-yl)-benzenesulfonamide, the pyrazole isostere of valdecoxib was synthesised. The title compound was prepared by a six-step procedure starting from commercially available deoxybenzoin **1**. The pyrazole isostere **13** showed slight anti-inflammatory and analgesic activities.

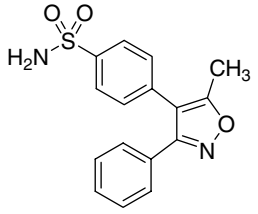
1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of pain and inflammation. These compounds non-selectively inhibit the two isoforms of the cyclooxygenase enzyme (COX-1 and COX-2) and thus block the formation of prostaglandines and have analgesic, antipyretic, and anti-inflammatory activities (Allison et al. 1992).

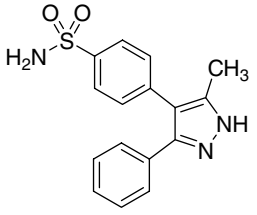
COX-1 produces physiologically important prostaglandins, while COX-2, the inducible form, is expressed during inflammation (Xie et al. 1991; Kujubu et al. 1991; Hla and Neilson 1992).

Based on this discovery, it was proposed that a selective inhibitor of COX-2 would be an attractive approach to the treatment of inflammation conditions, without the gastric and renal toxicity.

Valdecoxib as well as other coxibs such as celecoxib, etoricoxib, rofecoxib are considered as selective COX-2 inhibitors with fewer gastrointestinal side effects than traditional NSAIDs. As a part of our research we now describe the synthesis of 4-(5-methyl-3-phenyl-1*H*-pyrazole-4-yl)-benzenesulfonamide **13**, the pyrazole isostere of valdecoxib.



Valdecoxib



13

2. Investigations, results and discussion

2.1. Synthesis

Claisen condensation of the deoxybenzoin **1** with diethyl oxalate provided the expected 1,3-dicarbonyl adduct **3** in 50% yield (Borsche and Hahn 1939; Schummet et al. 1991), which underwent cyclization with hydrazine hydrate in ethanol at room temperature to give the 3,4-diphenyl-pyrazole. This contains two tautomeric forms, the stable 5-carbethoxy-1*H*-pyrazole **4a** along with the 3-carbethoxy-1H-pyrazole form **4b** as the minor component. Chlorosulfonation of **4a**, **b** afforded the 5-chlorosulfonyl derivative **5**, which could be converted by ammonia to give 3-phenyl-4-(4-aminosulfonyl-phenyl)-1*H*-pyrazole-5-carboxylic acid ethyl ester **6** in more than 70% yield. Reduction of **6** with $LiAlH_4$ in THF under argon yielded the hydroxy-methyl derivative **7**, which resisted catalytic hydrogenation attempting to synthesize the 5-methyl derivative (Scheme 1).

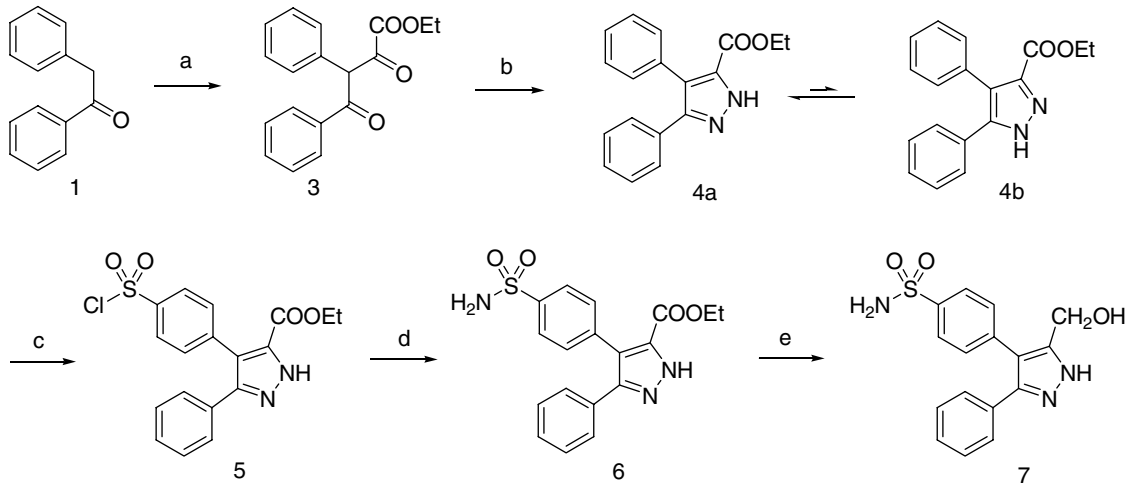
In a different approach, **13** could be synthetized by the reduction of **8** with $LiAlH_4$ in THF, followed by iodination with I_2/Ph_3P reagent at r.t. to give the iodo-derivative **10**, which could be easily reduced with $LiAlH_4$ at r.t. to yield 5-methyl-pyrazole **13** according to a known methodology (Krishnamurthy and Brown 1982). On the other hand treatment of **8** with iodine and an excess amount of triphenylphosphine at reflux temperature provided the phosphanylidene derivative **12**, which was hydrolyzed to **11** in 80% yield Finally, chlorosulfonation and ammonolysis were used to convert **11** to the title compound **13** (Scheme 2).

2.2. Pharmacological evaluation

The pyrazole isostere **13** prepared in the present study was tested for anti-inflammatory activity by the carrageenan-induced paw edema method (Winter et al. 1962). Groups of 6 male Wistar rats, weighing between 130–150 g orally received the test compounds (10 mg/kg) by gavage. Test compounds (valdecoxib and **13**) were suspended in 5% Tween 80 phys. saline. 60 min after the administration the rats were injected with 0.05 ml of 1% carrageenan. The paw volume was measured by means of a plethysmometer before and 4, 6, and 7 h after administration. The antiedematous effect was expressed as the inhibition percentage in comparison to vehicle-treated control:

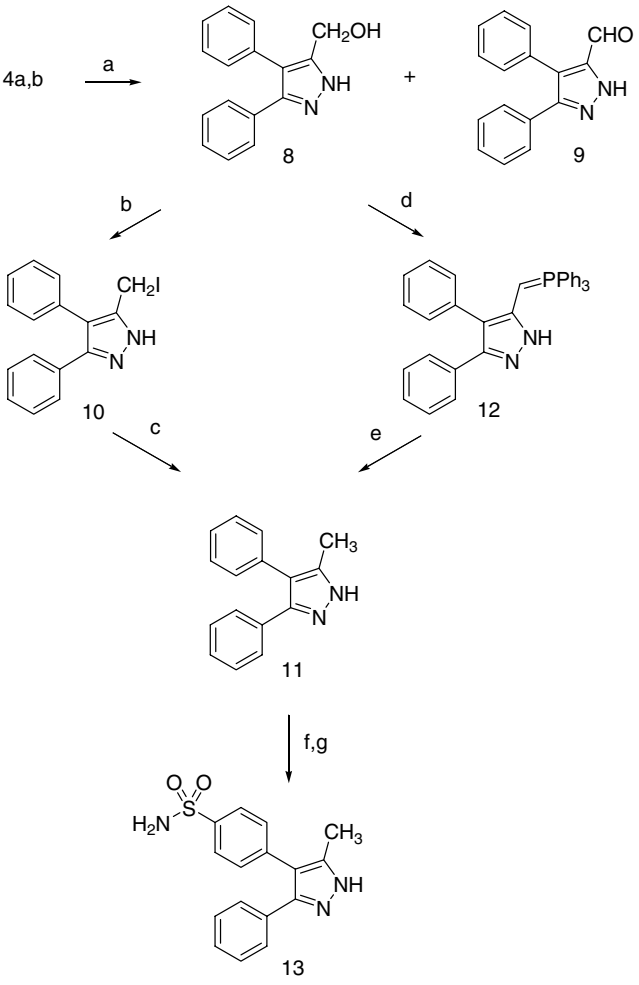
$$\% \text{ inhibition} = \frac{\text{volume control} - \text{volume treated}}{\text{volume control}} \times 100$$

Scheme 1



(a) $(COOEt)_2$, NaOEt/EtOH; (b) $N_2H_4 \cdot H_2O$, EtOH; (c) $ClSO_3H$; (d) NH_4OH/H_2O, CH_2Cl_2; (e) $LiAlH_4$, abs. THF

Scheme 2



(a) $LiAlH_4$, abs. THF; (b) I_2/Ph_3P, CH_3CN; (c) $LiAlH_4$, abs. THF; (d) 1. I_2/Ph_3P/ imidazol, CH_3CN, reflux, 2. $NaHCO_3$; (e) NaOH, MeOH, reflux; (f) $ClSO_3H$, CH_2Cl_2, reflux; (g) NH_4OH/H_2O, CH_2Cl_2

Table: Effects of valdecoxib and compound 13 on carrageenan-induced hind paw edema

Treatment	n	% Inhibition – post dose		
		4 h	6 h	7 h
Vehicle control (5% Tween-80-phys. saline)	6			
Valdecoxib 10 mg/kg p.o.	6	10.9	34.4	19.0
13 10 mg/kg p.o.	6	3.0	13.6	9.8

The results are summarized in the Table.
Subplantar injection of carrageenan provoked rapid swelling of the paw, which lasted for 7 h. The administration of valdecoxib at dose of 10 mg/kg produced a significant anti-inflammatory activity on carrageenan-induced edema 4–6 h post-administration. Compound **13** had weak anti-inflammatory activity in this experiment.

3. Experimental

3.1. General methods

Melting points were determined with a Büchi 535 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian INOVA-500 spectrometer, operating at 500 MHz. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane. Mass spectra were scanned on a Finnigan MAT 95SQ spectrometer. Column Chramatography was performed on Silica Gel 60 (0.043–0.060 mm), Merck.
Abbreviations: CC = Column Chromatography; EtOAc = ethyl acetate; THF = Tetrahydrofuran

3.2. Chemistry

3.2.1. 2,4-Dioxo-3,4-diphenyl-butyric acid ethyl ester (**3**)

In a 0–5 °C solution of 4.8 g (0.2 mol) of sodium in 50 ml of ethanol, 13.2 ml (0.1 mol) of diethyl oxalate was added and afterwards during 30 min 19 g (0.1 mol) of deoxybenzoin dissolved in 200 ml of ethanol was added. After 1 h the cooling bath was removed and the solution stirred at room temperature for 20 h. The sodium salt obtained was dissolved in 200 ml of water and acidified with 20 ml of cc. HCl and extracted 3 times with ethyl acetate. The combined organic layers were dried over anh. $MgSO_4$, and the solvent was removed by evaporation *in vacuo*. The title compound was crystallized from ethanol. Yield: 50%; m.p.: 98–100 °C (lit. 106–107 °C).

^{1}H NMR ($CDCl_3$): δ [ppm] 1.31 (t, 3 H); 4.10 (q, 2 H); 6.34 (s, 1 H); 7.26–7.68 (m, 8 H); 7.74–8.10 (m, 2 H); HRMS: Calc. 296.1043. Found: 296.1011.
$C_{18}H_{16}O_4$

3.2.2. 3,4-Diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**4a**, **b**)

To a stirred suspension of 0.59 g (2 mmol) of **3** in 50 ml of ethanol 0.10 g (2 mmol) of hydrazine hydrate was added and the mixture was stirred for 2 h at 0 °C. The precipitate was separated and recrystallized from ethanol. Yield: 80%; m.p.: 152–154 °C.
^{1}H NMR (DMSO-d_6): (tautomeric ratio: 60 : 40) δ [ppm] 1.10 (t, 3 H); 4.14 (br, q, 2 H, **4a**, **4b**); 7.2–7.33 (m, 10 H, **4a**, **4b**); 13.88 (br, NH, **4a**); 14.14 (br, NH, **4b**); HRMS: Calc. 292.1206. Found: 292.1215.
$C_{18}H_{16}N_2O_2$

3.2.3. 3-Phenyl-4-(4-chlorosulfonyl-phenyl)-1H-pyrazole-5-carboxylic acid ethyl ester (**5**)

25.60 g (0.22 mol) of chlorosulfonic acid was cooled to 0 °C, then 6.43 g (22 mmol) of **4a** was added over a period of 30 min. The mixture was stirred for 1.5 h at room temperature then 100 ml of water was carefully added and the precipitated product was collected by filtration and washed 3 times with 50 ml of water. Yield: 80%; m.p.: 185–195 °C.
^{1}H NMR ($CDCl_3$): δ [ppm] 1.14 (t, 3 H); 4.16 (q, 2 H); 7.06–7.62 (m, 9 H); 11.82 (br, NH); HRMS: Calc. 390.0436. Found: 390.0433.
$C_{18}H_{15}ClN_2O_4S$

3.2.4. 3-Phenyl-4-(4-aminosulfonyl-phenyl)-1H-pyrazole-5-carboxylic acid ethyl ester (**6**)

6.64 g (17 mmol) of **5** was dissolved in 60 ml of CH_2Cl_2 and 30 ml of aqueous ammonia solution (25%) was added. The reaction mixture was stirred overnight at room temperature and concentrated in vacuum. Water (100 ml) was added, acidified with 1 N HCl and extracted 3 times with 50 ml of ethyl acetate. The organic layer was washed with 50 ml of water, dried over $MgSO_4$ and evaporated *in vacuo* to give an oil which could be crystallized from ligroin. Yield: 75%; m.p.: 196–200 °C.
^{1}H NMR (DMSO-d_6): δ [ppm] 1.14 (t, 3 H); 4.17 (q, 2 H); 7.26–7.4 (m, 9 H); 7,77 (br, NH); 7,78 (s, 2 H, NH_2); HRMS: Calc. 371.0934. Found: 371.0931.
$C_{18}H_{17}N_3O_4S$

3.2.5. 4-(5-Hydroxymethyl-3-phenyl-1H-pyrazole-4-yl)-benzenesulfonamide (**7**)

To a solution of 4.45 g (12 mmol) of **6** in 40 ml of THF under argon atmosphere at 0 °C was added 20 mmol of 1 N $LiAlH_4$ in THF. The mixture was allowed to warm to ambient temperature and stirred for 4 h. 50 ml of 1 N HCl was added and extracted 3 times with 50 ml of ethyl acetate, dried over $MgSO_4$ and concentrated. The residue was purified by CC (EtOAc/MeOH 6 : 1, $R_f = 0.45$). Yield: 37%; m.p.: 93–95 °C.
^{1}H NMR (DMSO-d_6): (tautomeric ratio: 77 : 33) δ [ppm] 4.44 (br, 2 H, **7a**, **7b**); 5.34 (br, OH, **7a**); 5.09 (br, OH, **7b**); 7.22–7.48 (m, 9 H, **7a**, **7b**); 7,77; 7.78 (s, 2 H, NH_2, **7a**) 7.73; 7.75 (s, 2 H, NH_2, **7b**) 13.17 (br, NH, **7a**, **7b**); HRMS: Calc. 329.0829. Found: 329.0872.
$C_{16}H_{15}N_3O_3S$

3.2.6. 3,4-Diphenyl-5-hydroxymethyl-1H-pyrazole (**8**)

The conditions employed for the preparation of this compound were those described in 3.2.5., starting from **4a**, **b**. Yield: 70%; m.p.: 158–160 °C.
^{1}H NMR (DMSO-d_6): (tautomeric ratio: 64 : 36) δ [ppm] 4.38 (s, 2 H, **8b**); 4.44 (br, s, 2 H, **8a**); 4.87 (br, OH, **8b**); 5.30 (br, OH, **8a**) 7.22–7.38 (m, 10 H); 13.04 (br, NH, **8a**); 13.08 (br, NH, **8b**).
$C_{16}H_{14}N_2O$ (250.3)

3.2.7. 3,4-Diphenyl-1H-pyrazole-5-carbaldehyde (**9**)

The title compound was isolated beside **8** using CC (EtOAc/Hexane 1 : 1). Yield: 7%; m.p.: 122–124 °C.
^{1}H NMR (DMSO-d_6): δ [ppm] 7.25–7.45 (m, 10 H); 9.88 (br, CHO); 14.22 (br, NH).
$C_{16}H_{12}N_2O$ (248.2)

3.2.8. 5-Iodomethyl-3,4-diphenyl-1H-pyrazole (**10**)

In a 0 °C solution of 0.53 g (2 mmol) of triphenyl phosphine in 20 ml of acetonitrile was added 0.50 g (2 mmol) of I_2 and stirred for 2 h at this temperature then 0.45 g (1.8 mmol) of **8** was added. The suspension was allowed to warm to ambient temperature and stirred overnight. The precipitated product was collected by filtration and washed with acetonitrile. Yield: 27%.
^{1}H NMR (DMSO-d_6): δ [ppm] 4.42 (s, 2 H); 6.77 (br, NH); 7.23–7.45 (m, 10 H).
$C_{16}H_{13}IN_2$ (360.2)

3.2.9. 3,4-Diphenyl-5-methyl-1H-pyrazole (**11**)

Method A:
To a solution of 0.18 g (0.5 mmol) of **10** in 10 ml of THF under argon atmosphere at room temperature 0.5 mmol of 1 N $LiAlH_4$ in THF was added and stirred for 0.5 h. To the resulting suspension 10 ml of 1 N HCl was added and extracted twice with ethyl acetate. The organic layer was washed with 10 ml of $NaHSO_3$ (10% solution), dried over $MgSO_4$ and concentrated *in vacuo*. The residue could be crystallized from ethanol/water. Yield: 98%
Method B:
Compound **12** (5.94 g, 12 mmol) suspended in 30 ml of methanol and 12 ml of 2 N NaOH solution was added. After stirring under reflux for 1.5 h the reaction mixture was cooled to 0 °C and stirred for 2 h at this temperature. The precipitated product was collected by filtration and purified by CC (EtOAc/Hexane 6 : 1). Yield: 80%; m.p.: 164–168 °C.
^{1}H NMR (DMSO-d_6): δ [ppm] 2.20 (s, 3 H); 7.18–7.42 (m, 10 H); 12.82 (br, NH); HRMS: Calc. 234.1152. Found: 234.1136.
$C_{16}H_{14}N_2$

3.2.10. 3,4-Diphenyl-5-[(triphenyl-λ^5-phosphanylidene)-methyl]-1H-pyrazole (**12**)

To a solution of 13.30 g (50 mmol) of triphenyl phosphine and 2.04 g (30 mmol) of imidazole in 60 ml of acetonitrile 7.30 g (30 mmol) of I_2 was added. The resulting mixture was heated to reflux and 2.50 g (10 mmol) of **8** was added. After stirring under reflux for 8 h the mixture was cooled to room temperature and evaporated to dryness. The residue was dissolved in 30 ml of water and alkalified with $NaHCO_3$ (10% solution in water). The precipitated product was collected by filtration and dried at room temperature. Yield: 61%; m.p.: 242–245 °C.
^{1}H NMR (DMSO-d_6): δ [ppm] 5.05 (d, 1 H, ^2J(H–P) = 14.9 Hz); 6.95–7.02 (m, 2 H); 7.18–7.22 (m, 2 H); 7.27–7.33 (m, 6 H); 7.68–7.76 (m, 12 H); 7.83–7.86 (m, 3 H); 13.40 (br, NH); HRMS: Calc. 495.1985. Found: 495.2095.
$C_{34}H_{27}N_2P$

3.2.11. 4-(5-Methyl-3-phenyl-1H-pyrazole-4-yl)-benzenesulfonamide (**13**)

A mixture of 1.74 g (15 mmol) of chlorosulfonic acid in 15 ml of CH_2Cl_2 at 0–5 °C was added dropwise a solution of 0.70 g (3 mmol) of **11** in 20 ml of CH_2Cl_2. After stirring under reflux for 3 h the mixture was concentrated *in vacuo*. To the residue water was added and extracted twice with ethyl acetate, dried over $MgSO_4$ and evaporated to dryness. The resulting oil was dissolved in 20 ml of CH_2Cl_2, 5 ml of aqueous ammonia solution (25%) was added and stirred for 8 h at room temperature, then acidified with 1 N HCl and extracted with ethyl acetate. After evaporation to dryness the residue was added ethanol to precipitate a white solid. Yield: 55%; m.p.: 120–122 °C.
^{1}H NMR (DMSO-d_6): (tautomeric ratio: 70 : 30) δ [ppm] 2.20 (s, CH_3, **13b**); 2.25 (s, CH_3, **13a**); 7.22–7.40 (m, 9 H, **13a**, **13b**); 7.77;7,83 (s, 2 H, NH_2, **13a**, **13b**); 12.92 (br, NH, **13a**); 13.00 (br, NH, **13b**).
$C_{16}H_{15}N_3O_2S$ (313.3)

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