New Water-Soluble Sulfonylphosphoramidic Acid Derivatives of the COX-2 Selective Inhibitor Cimicoxib. A Novel Approach to Sulfonamide Prodrugs

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The synthesis and pharmacological evaluation of new water-soluble phosphoramidate derivatives of the COX-2 selective inhibitor cimicoxib (**4**) are described. The sulfonylphosphoramidic acid derivative **10** was converted to **4** in human plasma and showed excellent in vivo activity in the rat carrageenan-edema test. Pharmacokinetic evaluation in dogs indicated that **10** behaved as a prodrug, immediately converting to **4** and giving an identical profile to that of the parent compound. These results represent the first description of phosphoramidic acids as prodrugs for the sulfonamido group. Compound **10** also exhibited an important and sustained analgesic effect in the hyperalgesia test in rats and a high aqueous solubility at pH higher than 7. This profile led to the selection of **10** (UR-14048) for further development in the parenteral treatment of acute pain.

In the management of severe or moderately severe pain, parenteral treatments are preferred because of the rapid onset of action. Such situations often arise in hospitals, after surgery or after injury.[1] Recent surveys have shown that postoperative pain is considered poorly managed, due to side-effect limitations of available injectable medications, such as opioids and nonsteroidal antiinflammatory drugs (NSAID). In this regard, the most used nonnarcotic analgesic for these indications, ketorolac (**1**), has been associated with the appearance of significant side effects.[2]

Inhibition of cyclooxygenase (COX), one of the key enzymes involved in the degradation of arachidonic acid to prostaglandins, is the main target for NSAID. A decade ago, two isoforms of COX were identified:[3] one (COX-2) is inducible and expressed mainly in inflammatory cells and the other (COX-1) is cytoprotective and constitutively expressed in many tissues such as stomach, kidney, and platelets. This discovery led to the development of COX-2 selective inhibitors,[4] which showed a similar efficacy to nonselective NSAID but reduced gastrointestinal toxicity. Rofecoxib[5] and celecoxib[6] were the first COX-2 selective inhibitors to reach the market, followed by valdecoxib (**2**)[7] and etoricoxib.[8] However, none of these agents was suitable for parenteral formulation due to low water solubility. The strategy of developing water-soluble prodrugs was foreseen, and parecoxib[9] (**3**), the sodium salt of the propanoyl prodrug of valdecoxib, was recently marketed for the hospital treatment of postoperative pain. The elegant work of Talley and co-workers showed that among different acyl derivatives only the propionyl group provided the desired in vivo conversion in several species to the parent compound.

As a result of our efforts toward the development of safer antiinflammatory agents, we identified cimicoxib (**4**),[10] a new COX-2 inhibitor, which is currently undergoing phase II clinical trials for the oral treatment of acute pain and osteoarthritis. Taking into account the medical need for postsurgical pain treatments, the development of a parenteral formulation was undertaken. However, it was soon realized that the low water solubility of **4** precluded this approach.

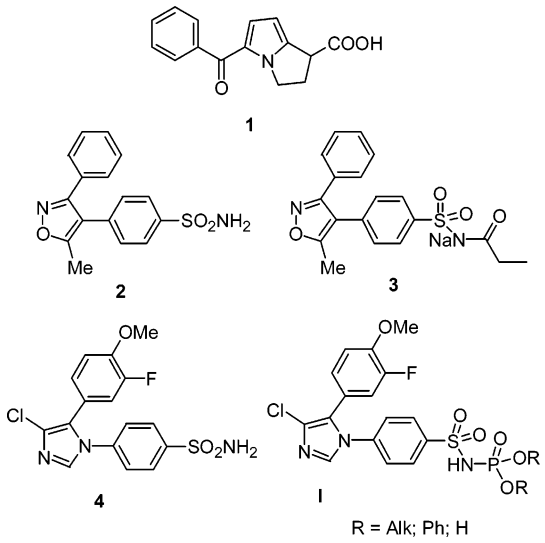

Figure 1.

A search for possible sulfonamide prodrugs indicated that the only reports described in the literature were those of valdecoxib derivatives[9] and a previous report[11] based also on acyl sulfonamides. Other approaches including sulfonylamidines, sulfonylureas,[11] and sulfonyl imidates[12] were unsuitable for our purposes, since these functions did not carry ionizable groups. The preparation of phosphoramidate derivatives of general formula **I** (Figure 1) was envisaged as an interesting approximation, since high water solubility seemed to be achievable through the formation of alkaline salts, due to the predicted pK_a value of 5 for the NH group. We

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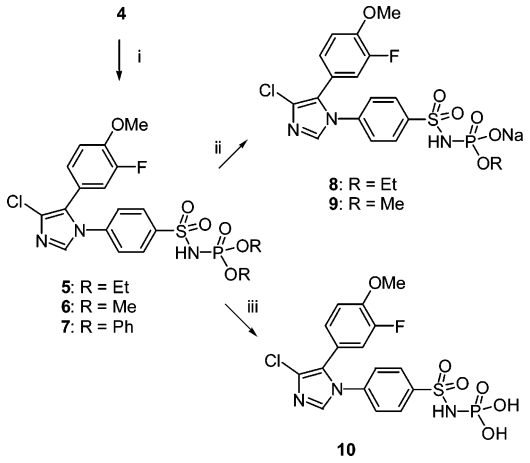
Scheme 1[a]



[a] (i) 2 N NaOH, $ClPO(OR)_2$, THF, 20 °C, 6 h; (ii) NaI, acetone, 50 °C, 18 h; (iii) (1) $ISiMe_3$, CH_2Cl_2, 0 °C, 1 h, (2) H_2O/acetone, 20 °C, 18 h.

report here our results on the investigation of the use of phosphoramidate salts as a new approach to water-soluble sulfonamide prodrugs.

Chemistry

The synthesis of **I** from **4** proved to be more difficult than expected. Initially, we envisioned the reaction with the corresponding dialkyl chlorophosphate to give dialkyl phosphoramidates, followed by stepwise hydrolysis of the ester groups. However, attempts to adapt alternative procedures reported in the literature[13−15] gave unsatisfactory results. Only when using an adaptation of a method[16] that involves reaction of the previously formed sulfonamide sodium salt with diethyl chlorophosphate was the diethyl derivative **5** isolated in 30% yield. To increase yields and avoid the formation of the intermediate salt, the in situ addition of NaOH to **4** was investigated. It was found that maintaining the reaction mixture in solution, by adding 2 N NaOH simultaneously to the dropwise addition of 7 equiv of diethyl chlorophosphate, resulted in high yields (74−86%) of **5**. The same procedure was applied for the preparation of the dimethyl (**6**) and diphenyl (**7**) esters.

The monoethyl and monomethyl esters **8** and **9** were isolated as sodium salts by treatment of the corresponding diesters **5** and **6** with sodium iodide.[17]

There are only four described procedures for the preparation of phosphoramidic acid derivatives of sulfonamides,[18] which in the best case[18a] involves a four-step synthesis. After trying without success the direct conversion of **4** into **10** by treatment with $POCl_3$ in pyridine, we turned our attention to the hydrolysis of dialkyl esters with trimethylsilyl iodide, which had been reported for obtaining phosphonic acid derivatives of guanidines.[19] When **5** was treated with 5 equiv of iodotrimethylsilane, followed by aqueous hydrolysis, the phosphoramidic acid **10** was obtained in 80% yield. This two-step procedure has been used to prepare 200 g of compound **10**. (Scheme 1).

The sodium and potassium salts of **10** were prepared by treatment with NaOH or KOH, respectively, in ethanol, followed by recrystallization.

Table 1. PK Parameters of **4** after Iv Administration of 2 Mg/kg **4** or 1 Mg/kg **10** to Dogs

parameter	2 mg/kg of **4**	1 mg/kg of **10**
$t_{1/2}$ (h)	5.0 ± 0.3	4.9 ± 0.7
AUC/dose (ng h/ mL)	3253.4 ± 781.8	3641.1 ± 1384.8
Cl (mL/h/kg)	292.2 ± 46.1	273.2 ± 125.8
Vd (mL/kg)	2116.8 ± 387.0	1856.9 ± 529.1

Results and Discussion

The possible prodrug behavior of derivatives **5**−**10** was initially evaluated by studying their conversion in human plasma to the parent compound **4**. While the esters **5**−**9** remained unchanged for the 24 h evaluation period, compound **10** was converted to **4**, with a conversion of 40% after 24 h incubation.

Compound **10** was then evaluated in the rat carrageenan-induced paw edema assay. It was intravenously administered at 3 mg/kg to rats, 10 min before edema induction by injection of λ-carrageenan. Paw volume was then measured at different times after injection and the percentage of inhibition calculated by comparison of the areas under the curve of treated and control groups. Compound **10** showed good potency, with 34.8 ± 2.9% inhibition, identical to that of the parent compound **4** and similar to that of parecoxib **3** (32.6 ± 2.8%), administered at the same dose.

A preliminary pharmacokinetic study of compound **10** in dogs was then undertaken in order to evaluate its in vivo conversion to **4** in a different species. The plasma half-life of **10** was not determined in this experiment, but high levels of **4** were detected within minutes of the intravenous administration of **10**. The pharmacokinetic parameters obtained for **4** given as an intravenous suspension of **4** or as an intravenous solution of **10** were roughly the same (see Table 1), indicating an immediate and complete in vivo conversion. Moreover, in vitro metabolic studies in human microsomes indicated a 74% conversion of **10** to **4** after incubation for 2 h. This result suggests that **10** could have a short half-life in humans, rapidly converting to the active drug **4**.

To determine the in vivo activity in an experimental model of acute inflammatory pain, **10** was evaluated in comparison to ketorolac (**1**) and parecoxib (**3**) in the carrageenan-induced thermal hyperalgesia test[20] in rat after intravenous administration at 3, 10, and 30 mg/kg. Morphine (4 mg/kg) was used as a positive control. As indicated in Figure 2, compound **10** at 3 mg/kg showed a significant increase in the withdrawal latency to thermal stimulation of the inflamed paw, as compared to vehicle controls. The activity profile of **10** was similar to that of ketorolac (**1**) and parecoxib (**3**), but **10** exhibited a faster onset of action. Morphine exerted a more potent effect initially, but it rapidly disappeared and was negligible at 4 h.

As indicated above, an adequate aqueous solubility was of critical importance in order to develop an intravenous dosage form. The highly acidic character of **10** (experimental[21] pK_{a1}, 1.70; pK_{a2}, 5.46; pK_{a3}, 9.83) provided a pH of 2.6 and a solubility of only 1.3 mg/mL, when dissolving a sample of 5 mg in 1 mL of water. However, an equilibrium solubility[22] greater than 100 mg/mL was observed in phosphate-buffered aqueous media at pH = 7 or higher. The trisodium, dipotassium, and tripotassium salts of **10** were prepared, giving also

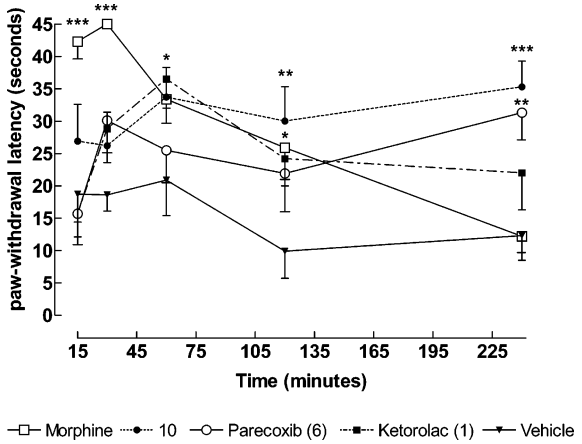


Figure 2. Time course evaluation in the rat thermal hyperalgesia model after intravenous administration of ketorolac (**1**, 3 mg/kg), parecoxib (**3**, 3 mg/kg), **10** (3 mg/kg), and morphine (4 mg/kg). ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$ versus vehicle.

high solubilities in water. Finally, the in situ preparation of the trisodium salt of **10** (by adding 3 equiv of NaOH) gave a solubility greater than 50 mg/mL in 0.9% NaCl. These results indicated the feasibility of **10** for the development of an intravenous formulation.

In summary, we have described the synthesis and pharmacological evaluation of new phosphoramidate derivatives of the COX-2 selective inhibitor cimicoxib, **4**. The sulfonylphosphoramidic acid derivative **10** was converted to **4** in human plasma and showed excellent in vivo activity in the rat carrageenan test. Pharmacokinetic evaluation in dogs indicated that **10** behaved as a prodrug, immediately converting to **4** and giving an identical profile to the parent compound. These results represent the first description of phosphoramidic acids as prodrugs for the sulfonamido group. Compound **10** exhibited also an important and sustained analgesic effect in the hyperalgesia test in rats and a high aqueous solubility at pH higher than 7. For this reason, compound **10** (UR-14048) has been selected for further development in the parenteral treatment of acute pain.

Experimental Section

Melting points were determined with a Mettler FP 80 central processor melting point apparatus and are uncorrected. ^{1}H NMR(300 MHz) spectra were recorded on a Bruker Avance DPX-300 spectrometer. They are reported in ppm on the δ scale, from the reference indicated. Combustion analyses were performed with a Carlo Erba 1108 analyzer. Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on SDS silica gel Chromagel 60 ACC (230−400 mesh). Analytical thin-layer chromatography (TLC) was performed with Macherey-Nagel 0.25 mm silica gel SIL G-25 plates.

Diethyl *N*-[4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)-imidazole-1-yl]phenylsulfonyl]phosphoramidate (5). To a mixture of 4-[4-chloro-5-(3-fluoro-4-methoxyphenyl)imidazol-1-yl]benzenesulfonamide (**4**, 2.0 g, 5.2 mmol) in 1 N NaOH (7.2 mL) (pH 13.4) under a nitrogen atomosphere was added a solution of diethyl chlorophosphate (5.2 mL, 36.4 mmol) in THF (28 mL) during 5 h. To keep the reaction mixture in solution a 2 N NaOH aqueous solution was added simultaneously. Once the addition was finished, the mixture was stirred for 1 h at room temperature. Ethyl acetate was added and the phases were separated. The organic phase was washed with 0.01 N NaOH and the combined aqueous phases were brought to pH 4 and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and the solvent was eliminated to afford **5** as a white solid (2.0 g, 74%): mp 188 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 1.29 (t, J = 7.1 Hz, 6 H), 2.0 (b b, H_2O + NH), 3.90 (s, 3 H), 4.12 (m, 4 H), 6.93 (m, 3 H), 7.23 (d, J = 8.7 Hz, 2 H), 7.63 (s, 1 H), 8.02 (d, J = 8.7 Hz, 2 H). Anal. ($C_{20}H_{22}ClN_3O_6PS$) C, H, N.

Following a similar procedure compound **6** [Anal. ($C_{18}H_{18}ClFN_3O_6PS\cdot0.5H_2O$) C, H, N] and **7** [Anal. ($C_{28}H_{22}ClFN_3O_6PS\cdot H_2O$) C, H; N: calcd, 6.65; found, 5.92] were obtained.

Ethyl *N*-[4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)imidazol-1-yl]phenylsulfonyl]phosphoramidate Sodium Salt (8). To a suspension of **5** (1 g, 1.9 mmol) in acetone (14 mL) was added NaI (284 mg, 1.9 mmol), and the resulting mixture was stirred at reflux overnight under an argon atmosphere. It was concentrated to dryness and the crude product obtained was purified by chromatography on silica gel using EtOAc/MeOH/AcOH mixtures of increasing polarity as eluent. The product obtained was next recrystallized from ^{i}PrOH to afford 554 mg of **8** as a white solid (57%): ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD δ TMS) 1.20 (m, 3 H), 3.74 (m, 2 H), 3.90 (s, 3 H), 4.30 (s, H_2O + NH), 6.95 (m, 3 H), 7.29 (d, J = 7.7 Hz, 2 H), 7.74 (s, 1 H), 8.06 (d, J = 7.7 Hz, 2 H). Anal. ($C_{18}H_{17}ClFN_3NaO_6PS\cdot0.5H_2O$) C, H, N.

Following a similar procedure, compound **9** was obtained. Anal. ($C_{17}H_{15}ClFN_3NaO_6PS\cdot0.4^iPrOH$) C, H, N.

***N*-[4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)imidazole-1-yl]phenylsulfonyl]phosphoramidic Acid (10).** To a suspension of **5** (1.0 g, 1.9 mmol) in CH_2Cl_2 (22 mL) was added iodotrimethylsilane (1.3 mL, 9.6 mmol) dropwise, under a nitrogen atmosphere and at 0 °C. The mixture was stirred for 1 h at 0 °C and the solvent was eliminated. The residue was cooled to 0 °C and treated with a mixture of acetone (22 mL) and H_2O (0.76 mL). After stirring at 0 °C for 1 h the mixture was stirred at room temperature overnight. The suspension thus obtained was filtered and the solid was washed with acetone and dried. Compound **10** was obtained as a yellowish solid (0.7 g, 80%): mp 190−193 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.91 (s, 3 H), 4.46 (s, H_2O + 3 H), 6.95 (m, 3 H), 7.31 (d, J = 8.7 Hz, 2 H), 7.78 (s, 1 H), 8.04 (d, J = 8.7 Hz, 2 H). Anal. ($C_{16}H_{14}ClFN_3O_6PS$) C, H, N.

Trisodium *N*-[4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)imidazol-1-yl]phenylsulfonyl]phosphoramidate (10.3Na). To a solution of **10** (0.15 g, 0.3 mmol) in EtOH (2 mL),was added NaOH powder (39 mg, 0.96 mmol) in EtOH (4 mL), and the resulting mixture was stirred under argon atmosphere at room temperature for 1 h. The mixture was concentrated to dryness and the resulting solid was recrystallized from ^{i}PrOH (20 mL), to afford the trisodium salt of **10** as a white solid (0.16 g; 95%). Anal. ($C_{16}H_{11}ClFN_3Na_3O_6PS\cdot2H_2O$) C, H, N.

Carrageenan-Induced Rat Paw Edema Assay. Male, Sprague−Dawley rats (150−175 g) were used. Edema was produced by injecting 0.1 mL of a solution of 1% λ-carrageenan in the hindpaw. Paw volume was measured by water displacement with a plethysmometer (UGO BASILE) before and 1, 2, 3 and 4 h after treatment. The compounds were administered by intravenous route as a solution in PBS (1 mL/kg) 10 min before carrageenan injection and after being hydrated with H_2O (5 mL). The percentages of inhibition were calculated by comparing the areas under the curve of treated and control animals.

Incubation in Human Plasma. Human plasma was obtained by centrifugation (15 min, 2800*g*, 4 °C) of human blood. DMSO solutions of test compounds (equivalent to 1 μM of **7**) were added to individual tubes (1%) and these were maintained at 37 °C for 24 h. The concentration of **7** was determined using LC−MS.

Thermal Hyperalgesia Test. Male, Wistar rats were treated with an intraplantar injection of carrageenan (0.75 mg/paw). Two hours later, rats were submitted consecutively to thermal stimulation of both the noninflamed and the inflamed hindpaws by means of a mobile infrared radiant source. Test compounds were administered iv at the doses of 3, 10, and 30 mg/kg, 105 min after carrageenan, and compared with a

vehicle control group (10 rats per group). Behavioral measurements (basically, differences in the paw withdrawal latency) were performed at 15, 30, 60, 120, and 240 min after administration. Morphine (4 mg/kg iv), administered under the same experimental conditions, was used as reference substance.

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(21) Ionization constants were measured by potentiometric titration in 0.15 M KCl at 25 °C using a PCA200 instrument (Sirius Analytical Instruments).

(22) Equilibrium solubilities were obtained by adding solid compounds directly to an aqueous medium, followed by stirring at room temperature for 16 h. Suspensions were then filtered and the remaining concentration in the solution was measured by HPLC.

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