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Bioorganic & Medicinal Chemistry Letters 15 (2005) 2259–2263
Bioorganic & Medicinal Chemistry Letters

Novel approach to pro-drugs of lactones: water soluble imidate and *ortho*-ester derivatives of a furanone-based COX-2 selective inhibitor

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Received 3 February 2005; revised 1 March 2005; accepted 3 March 2005

Abstract—Interest in water soluble COX-2 inhibitors that can be administered intravenously led to the development of novel pro-drugs of a furanone based COX-2 inhibitor **2**. Transforming the lactone moiety of the furanone to an imidate or an *ortho*-ester with a hydrophilic, endogenous appendage resulted in water soluble pro-drugs that converted to the parent drug in vivo.

There exists a clinical need for the acute treatment of inflammation where the oral administration of analgesics is inadequate. In areas such as post-operative pain[1] and stroke,[2] rapid administration of selective COX-2 inhibitors have been shown to have a beneficial effect. As such, there is continued interest in developing water soluble COX-2 inhibitors for intravenous administration. Currently there is only one injectable COX-2 inhibitor, paracoxib,[3] which is awaiting FDA approval. In addition, other water soluble COX-2 inhibitors have been reported in the literature.[4,5]

Previous attempts at developing water soluble forms of furanone based COX-2 inhibitors resulted in analogues, such as compound **1**, with lower potency in a COX-2 whole blood functional assay (Fig. 1).[6]

In contrast, furanone based COX-2 inhibitor, **2**, exhibits excellent potency, selectivity, pharmacokinetic characteristics, and safety profile. The drawback to **2** is that it is insoluble in aqueous solution.[7] We thus sought to identify water soluble pro-drugs of the inhibitor **2** and herein we report our progress.

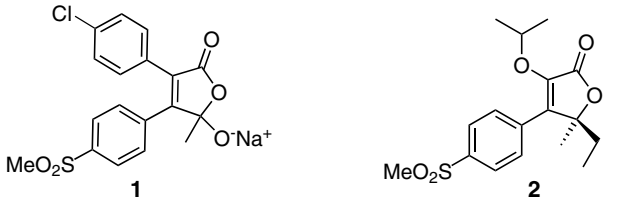

Figure 1.

Our efforts to develop a pro-drug of compound **2** followed a set of criteria: To be administered intravenously, the derivatives need to be highly water soluble and stable in aqueous solution. Additionally we wanted to incorporate endogenous or nontoxic solubilizing groups into the pro-drug, which in vivo, would rapidly convert to the parent drug and not compromise the safety profile of **2** (Fig. 2).

Our initial strategy focused on synthesizing a ring-opened form of the lactone moiety, where solubilizing endogenous substituents would be appended onto the resultant alcohol and acid functionalities (Route A, Fig. 2). Upon in vivo administration, it was envisioned that these groups would cleave to regenerate the lactone

Keywords: COX-2; Stroke; Pro-drug; *ortho*-Ester.
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doi:10.1016/j.bmcl.2005.03.009

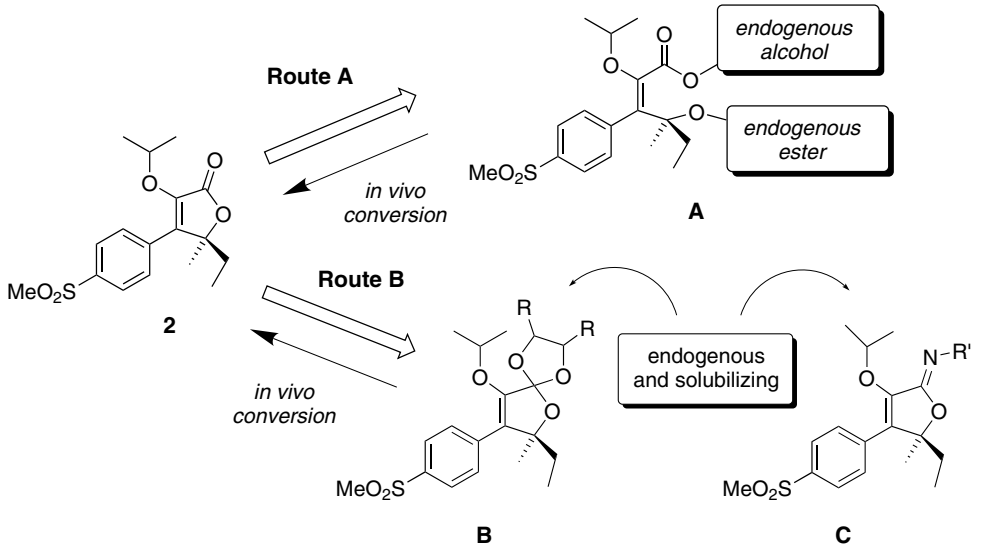
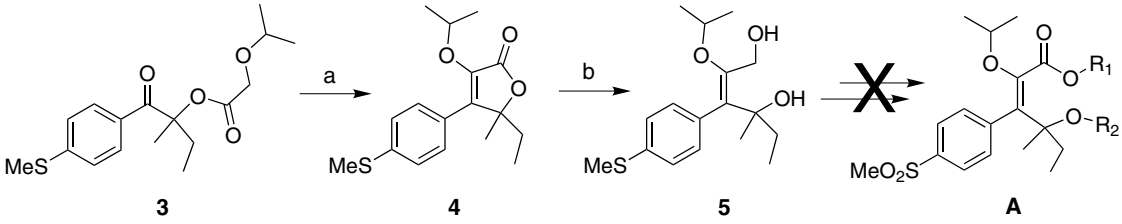


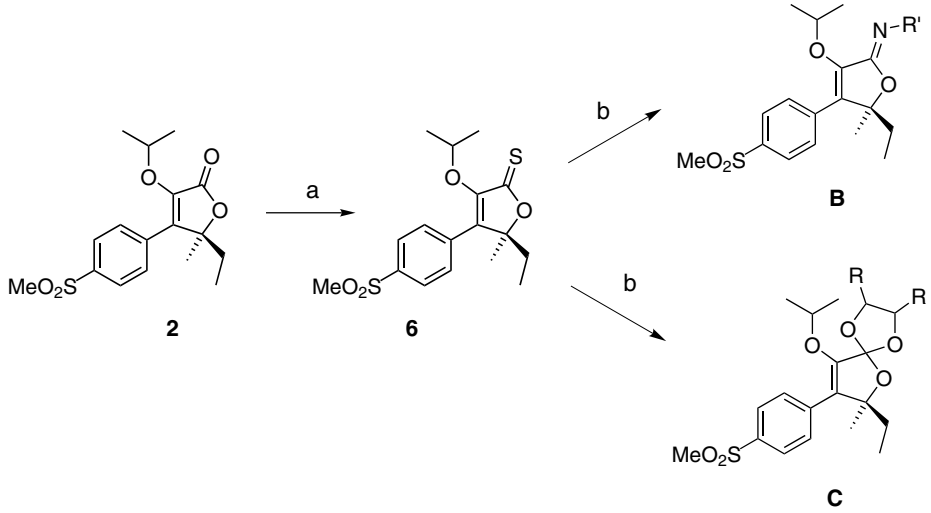
Figure 2. Pro-drug strategies.



Scheme 1. Reagents and conditions: (a) DBU, toluene, reflux, 24 h; (b) (i) $LiAlH_4$, THF, 0 °C; (ii) DIBAL, THF, −10 °C.

2.[8] Due to the thermodynamic stability of the lactone in **2**, we attempted to access the open form through a stepwise reduction–oxidation route (Scheme 1). Reducing the methyl sulfide derivative **4** (generated from the known compound **3**)[9] with $LiAlH_4$ and DIBAL gave the diol **5**. However, further attempted derivatization of **5** to the desired pro-drug, either through the oxidation of the primary alcohol or capping of the tertiary alcohol led to extensive decomposition.

We thus turned our attention to converting the lactone of **2** to an imidate or *ortho*-ester derivative that incorporated a water-solubilizing, endogenous moiety (Route B, Fig. 2). This strategy relies on the premise that imidates

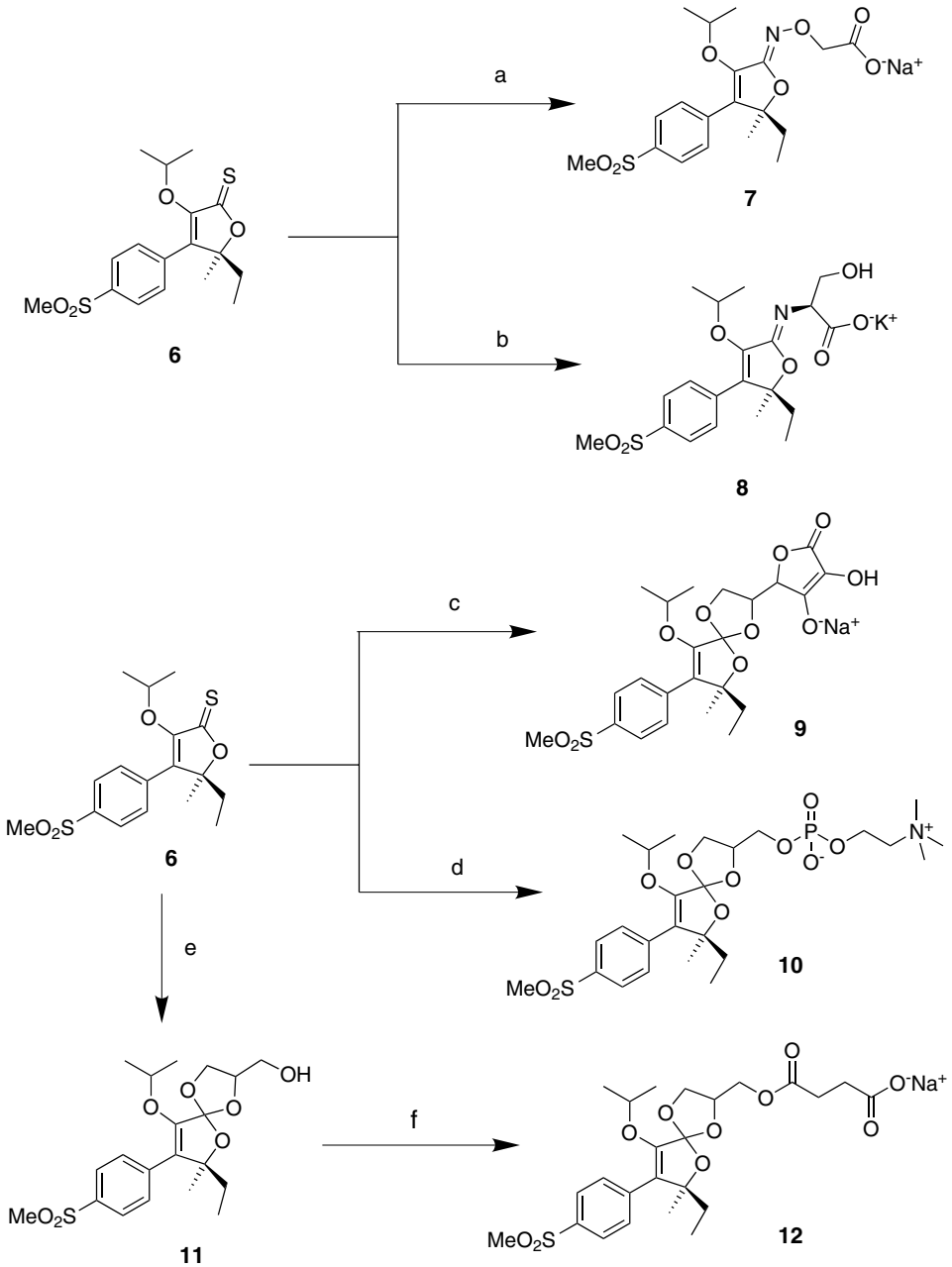


Scheme 2. Reagents and conditions: (a) Lawesson's reagent, toluene, reflux (95%); (b) diol or amine, AgOTf, Et_3N, MeCN (50–75%).

and *ortho*-esters would be stable in aqueous solution yet suitably labile in vivo, thus effecting rapid release of the desired inhibitor **2**.

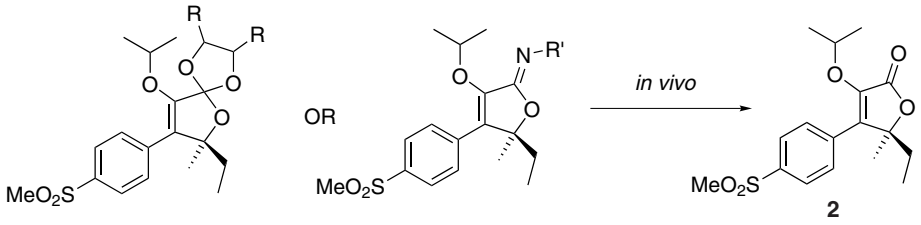
Attempted direct conversion of **2** to **B** or **C** proved unsuccessful due to its inherent thermodynamic stability. However, previous research demonstrated that acetals and imidates could be synthesized from activated thioketones.[10,11] Building upon this chemistry, we successfully synthesized water soluble imidate and *ortho*-ester derivatives of lactone **2** via the thiolactone intermediate **6**. Thus, refluxing compound **2** with Lawesson's reagent in toluene afforded the corresponding thiolactone **6** in excellent yield (95%) (Scheme 2). The imidate and *ortho*-ester derivatives were then synthesized through a metal ion mediated desulfurization–condensation reaction between the thioester and an amine or diol. Thus, reaction of **6** with AgOTf and Et_3N in the presence of the appropriate nucleophile gave the corresponding pro-drug **B** or **C** in 50–75% yield.[12]

A series of imidates and *ortho*-esters were synthesized using this protocol as shown in Scheme 3 where each of the pendant groups is a compound endogenous to the human body.



Scheme 3. Reagents and conditions: (a) (i) H_2NOH, AgOTf, Et_3N, MeCN; (ii) 2-bromoacetic acid, NaOH; 48%; (b) (i) L-serine-OMe, AgOTf, Et_3N, MeCN; (ii) KOTMS, THF; 64%; (c) (i) dibenzyl ascorbate, AgOTf, Et_3N, MeCN; (ii) H_2, Pd/C, MeOH; 37%; (d) GPC, AgOTf, Et_3N, MeCN; 75%; (e) glycerol, AgOTf, Et_3N, MeCN; 80%; (f) succinic anhydride, DMAP, Et_3N, CH_2Cl_2; 55%.

Table 1.

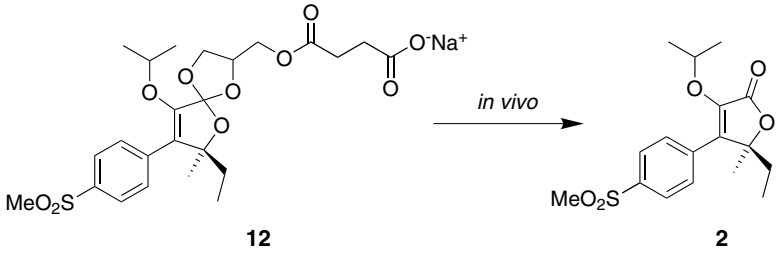


Compd	Solubility (mg/mL)[a]	Stability[b]	Levels of **2** @ 0.5 h[c] (μM)	Levels of pro-drug @ 0.5 h[c] (μM)
7	10	Y	<0.1	ND
8	>20	Y	<0.1	ND
9	>20	No	0.1	ND
10	>20	Y	0.2	0.2
11	<1	Y	2.8[d]	1.4[d]
12	2	Y	0.4	<0.1

[a] Solubility is measured in deionized water @ 25 °C.
[b] 4 mg/mL solution in water. Stability judged @ 24 h by LC–MS.
[c] Concentration of **2** following a 2 mg/kg i.v. dose of pro-drug in Sprague–Dawley rats ($n = 2$); measuring at 5, 15, 30, 60 min. Value quoted is @ 30 min.
[d] Dosed in PEG-400 solution.

Thus thiolactone **6** was reacted with hydroxylamine followed by 2-bromoacetic acid to give the imidate **7**. Condensation of **6** with L-serine methyl ester and subsequent saponification afforded the amino acid imidate derivative **8**. The ascorbic acid derivative **9** was synthesized by condensing thiolactone **6** with dibenzyl ascorbate,[13] followed by deprotection under catalytic hydrogenation conditions. Compounds **10** and **11** were synthesized by the condensation of **6** with glycerol and glycerylphosphorylcholine (GPC), respectively. Further derivatization of **11** by acylation with succinic anhydride furnished compound **12**.

Next we examined the physiochemical properties of compounds **7**–**12** and their ability to behave as pro-drugs and release **2** in vivo (Table 1). Compounds **7**–**10** exhibited good solubility in water of >10 mg/mL, while **11** and **12** showed reduced solubility of <1 and 2 mg/mL, respectively. Stability in solution was determined by HPLC analysis, and all of the pro-drugs were stable after 24 h in water, with the exception of **9**, which demonstrated rapid decomposition. To ascertain the rates of conversion of the pro-drugs in vivo, the compounds were dosed as a saline solution of the salt form (except for **11**, which was dosed in a PEG-400



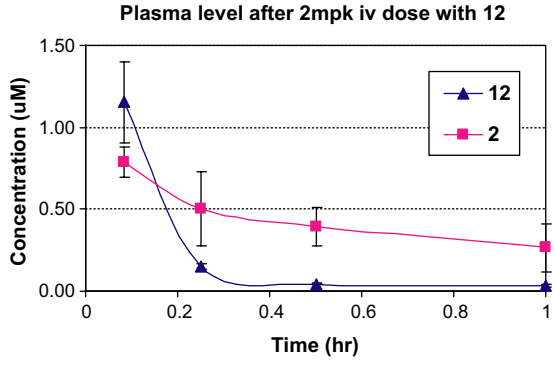


Figure 3. Graph of in vivo conversion of pro-drug **12**.

solution) in Sprague–Dawley rats at 2 mg/kg intravenously. Plasma levels were measured for levels of the respective pro-drug and the desired COX-2 inhibitor **2** at 5, 15, 30, and 60 min time points. The plasma levels measured at 30 min are given below (Table 1).

As can be ascertained from Table 1, imidates **7** and **8** failed to give appreciable amounts of the parent drug **2**, yet the levels of each pro-drug dropped rapidly in vivo. Apparently, in vivo conversion of **7** and **8** was poor, which suggests that the imidate derivatives are stable in vivo and are cleared rapidly as the pro-drug in the rat model.

Gratifyingly, *ortho*-esters **9**–**12** demonstrated superior pharmacokinetic characteristics. Of the compounds that were dosed at 2 mg/kg, only compounds **11** and **12** converted to yield appreciable levels of the parent drug **2** in the plasma at 30 min. Pro-drug **12** reached 0.4 μM in the plasma and the less soluble derivative **11** was measured at 2.8 μM. In comparison, the COX-2 IC_{50} concentration of inhibitor **2** is 0.4 μM in human whole blood.

Figure 3 graphically illustrates the in vivo profile of **12** and demonstrates the desired pro-drug profile; a rapid drop in concentration of pro-drug as it is converted to parent COX-2 inhibitor **2**. Compound **12**, however, was not completely soluble in water at the desired concentration of 4 mg/mL. Nevertheless, **12** clearly demonstrated proof of concept that *ortho*-ester based water soluble pro-drugs of **2** can give significant levels of the drug in the plasma when dosed intravenously.

In conclusion, we have demonstrated a novel strategy for preparing water soluble pro-drugs of the potent and selective COX-2 inhibitor **2** by formation of an *ortho*-ester from the lactone moiety. This led to water soluble and stable pro-drugs such as **12**, which upon intravenous administration delivered **2** in vivo.

Acknowledgments

The authors would like to thank Mike Gardner and Merryl Cramer for help with pharmacokinetic studies.

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