Cyclization-Activated Prodrugs: *N*-(Substituted 2-hydroxyphenyl and 2-hydroxypropyl)carbamates Based on Ring-Opened Derivatives of Active Benzoxazolones and Oxazolidinones as Mutual Prodrugs of Acetaminophen†

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N-(Substituted 2-hydroxyphenyl)- and *N*-(substituted 2-hydroxypropyl)carbamates based on masked active benzoxazolones (model A) and oxazolidinones (model B), respectively, were synthesized and evaluated as potential drug delivery systems. A series of alkyl and aryl *N*-(5-chloro-2-hydroxyphenyl)carbamates **1** related to model A was prepared. These are open drugs of the skeletal muscle relaxant chlorzoxazone. The corresponding 4-acetamidophenyl ester named chlorzacetamol is a mutual prodrug of chlorzoxazone and acetaminophen. Chlorzacetamol and two other mutual prodrugs of active benzoxazolones and acetaminophen were obtained in a two-step process via condensation of 4-acetamidophenyl 1,2,2,2-tetrachloroethyl carbonate with the appropriate anilines. Based on model B, two mutual prodrugs of acetaminophen and active oxazolidinones (metaxalone and mephenoxalone) were similarly obtained using the appropriate amines. All the carbamate prodrugs prepared were found to release the parent drugs in aqueous (pH 6–11) and plasma (pH 7.4) media. The detailed mechanistic study of prodrugs **1** carried out in aqueous medium at 37 °C shows a change in the Brönsted-type relationship log $t_{1/2}$ vs pK_a of the leaving groups ROH: log $t_{1/2}$ = 0.46pK_a − 3.55 for aryl and trihalogenoethyl esters and log $t_{1/2}$ = 1.46pK_a − 16.03 for alkyl esters. This change is consistent with a cyclization mechanism involving a change in the rate-limiting step from formation of a cyclic tetrahedral intermediate (step k_1) to departure of the leaving group ROH (step k_2) when the leaving group ability decreases. This mechanism occurs for all the prodrugs related to model A. Regeneration of the parent drugs from mutual prodrugs related to model B takes place by means of a rate-limiting elimination–addition reaction (E1cB mechanism). This affords acetaminophen and the corresponding 2-hydroxypropyl isocyanate intermediates which cyclize at any pH to the corresponding oxazolidinone drugs. As opposed to model A, the rates of hydrolysis of mutual prodrugs of model B clearly exhibit a catalytic role of the plasma. It is concluded from the plasma studies that the carbamate substrates can be enzymatically transformed into potent electrophiles, *i.e.*, isocyanates. In the case of the present study, the prodrugs are 2-hydroxycarbamates for which the propinquity of the hydroxyl residue and the isocyanate group enforces a cyclization reaction. This mechanistic particularity precludes their potential toxicity in terms of potent electrophiles capable of modifying critical macromolecules.

Chemical modifications of drugs into labile derivatives, commonly referred to as prodrugs, are carried out to improve their physicochemical (*e.g.*, solubility, lipophilicity) and biological (*e.g.*, bioavailability) properties.[1] This useful approach for improving drug delivery has been successfully applied to a wide variety of drugs (*e.g.*, drugs containing carboxyl or hydroxyl functions,[2] β-lactam antibiotics[3]), and their advantages in clinical practice have been reviewed.[4] In particular, esterification of therapeutically active agents to provide ester prodrugs has been largely exploited owing to the fact that the organism is rich in enzymes such as esterases able to hydrolyze them.[1,5]

In more recent years, a better knowledge of the reactivity of carbamate esters[6] has promoted carbamylation as a means of prodrug strategy for amino and hydroxylic groups. Thus, (acyloxy)carbamates obtained by derivatization of the amino group of β-blockers[7] increase significantly their permeation through biological membranes. Those of norfloxacin[8] result in the repression of its bitter taste, while various carbamate esters derivatives of drugs possessing a hydroxyl group, *e.g.*, dopamine agonist (−)-3-(3-hydroxyphenyl)-*N*-propylpiperidine,[9] 7-hydroxybenzazepines,[10] and tertbutaline,[11] allow the first-pass metabolism to be escaped.

On the other hand, various ring-opened derivatives of cyclic drugs, including barbituric acids, hydantoins, 2,4-oxazolidinediones, and γ-lactones, have been proposed as prodrugs designed to potentially increase lipid or water solubility.[1] In neutral and alkaline aqueous solution, these open-drug derivatives, generally esters, were found to undergo a specific base-catalyzed cyclization to corresponding drugs involving an intramolecular nucleophilic attack of a nitrogen or oxyanion on the ester carbonyl moiety.

Various models based on the lactonization of γ-hydroxy amides[12] and γ-hydroxy esters[13] have been investigated, and some of them, like pilocarpic acid esters, were successfully applied to pilocarpine delivery.[14]

† This paper is dedicated to the memory of Professor Hans Bundgaard who was a significant contributor to studies of prodrugs and a referee of A. Vigroux's thesis.

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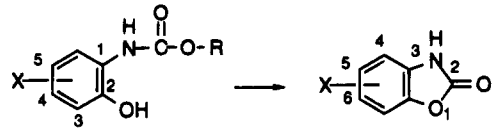
Chart 1

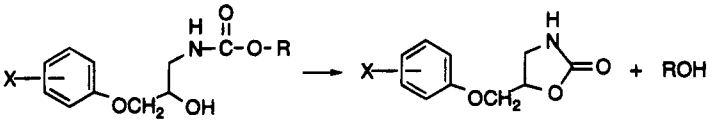
Model A



	Prodrugs (R = alkyl and aryl)	Drugs	
X = 5-Cl	1	Chlorzoxazone[a]	–
	Mutual Prodrugs (R = 4-AcNHC$_6$H$_4$)		
X = 5-Cl	1m	Chlorzoxazone[a]	Acetaminophen[c]
X = 4-Bz	2	6-Benzoylbenzoxazolone[b]	Acetaminophen[c]
X = 5-Bz	3	5-Benzoylbenzoxazolone[b]	Acetaminophen[c]

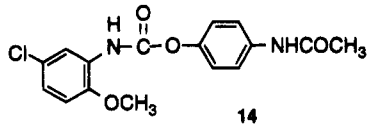
[a] Skeletal muscle relaxant. [b] Analgesic. [c] Analgesic, antipyretic.

Model B



	Mutual Prodrugs (R = 4-AcNHC$_6$H$_4$)	Drugs	
X = 3,5(Me)$_2$	4	Metaxalone[d]	Acetaminophen
X = 2-OMe	5	Mephenoxalone[e]	Acetaminophen

[d] Skeletal muscle relaxant. [e] Tranquilizer.



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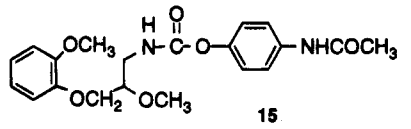

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Moreover, it has been shown that some carbamate esters evaluated as progenitors of a melanocytotoxic agent, 4-hydroxyanisole,[15] and a radiation sensitizer, 5-bromo-2′-deoxyuridine,[16] release parent drugs through a mechanism involving an intramolecular cyclization–elimination reaction.

According to these concepts, we report in this paper the synthesis of a series of *N*-(substituted 2-hydroxyphenyl and 2-hydroxypropyl)carbamates derived from models based on masked active benzoxazolones (model A) and oxazolidinones (model B), respectively, and their evaluation as potential drug delivery systems (Chart 1). Thus, based on model A, alkyl and aryl *N*-(5-chloro-2-hydroxyphenyl)carbamates **1** can be regarded as prodrugs of the skeletal muscle relaxant chlorzoxazone. By a particular approach, models A and B can be used to release ROH (=acetaminophen) in addition to (i) the basic benzoxazolones, chlorzoxazone and analgesic 6-benzoyl- and 5-benzoylbenzoxazolones,[17] from prodrugs related to model A, **1m**, **2**, and **3**, respectively, and (ii) the basic oxazolidinones, metaxalone and mephenoxalone, from prodrugs related to model B, **4** and **5**, respectively. It is noteworthy that the muscle relaxant–analgesic combinations, *e.g.*, chlorzoxazone and acetaminophen, have previously been described to be therapeutically superior to their individual components.[18]

Chemistry

Synthesis of alkyl and aryl *N*-(5-chloro-2-hydroxyphenyl)carbamates **1** by treatment of alcohol or phenol with 5-chloro-2-hydroxyphenyl isocyanate is excluded because this electrophilic intermediate is unstable. This lack of stability is due to an intramolecular cyclization reaction leading to the corresponding 5-chloro-2(3*H*)-benzoxazolone that can be considered as a masked form of the isocyanate. Prodrugs were then synthesized by reacting 1 equiv of alkyl or aryl chloroformate and 2 equiv of 5-chloro-2-hydroxyaniline in anhydrous ether. One of these equivalents was used to trap the released hydrogen chloride.[19] Chloroformates (ClCOOR) not commercially available[20] (R = $CH_2C{\equiv}CH$, $CH_2C{\equiv}CCH_3$, CH_2CHCl_2, CH_2CF_3, XC_6H_4 with X = 4-MeO, 3-AcNH, 3-Cl, 3-CF_3) were prepared in toluene by phosgenation[21] of the corresponding alcohols or phenols in the presence of *N*,*N*-dimethylaniline as the HCl-trapping agent. They were identified from their IR spectra by the characteristic peak in the 1780–1790 cm^{-1} region[22] due to the carbonyl group and converted to carbamates

Table 1. Physical Properties, Rate Constants (k_p), and Hydrolysis Half-Lives of Alkyl and Aryl *N*-(4- or 5-Substituted-2-hydroxyphenyl)carbamates (4- or 5-X-2-$OHC_6H_3NHCOOR$, model A)

compd	R	mp, °C	formula[a]	k_p,[b] s^{-1}	$t_{1/2}$,[c] s	pK_a(ROH)
			Prodrugs **1**, X = 5-Cl **1a**			
1a	C_2H_5	139	$C_9H_{10}ClNO_3$	8.63×10^{-7}	290 days[d]	16.00[e]
1b	CH_3	153	$C_8H_8ClNO_3$	1.05×10^{-6}	73 days[d]	15.54[e]
1c	CH_2CH_2Cl	136	$C_9H_9Cl_2NO_3$	2.75×10^{-5}	78 320	14.31[e]
1d	$CH_2C{\equiv}CCH_3$	151	$C_{11}H_{10}ClNO_3$	5.93×10^{-5}	33 990	14.16[f]
1e	$CH_2C{\equiv}CH$	128	$C_{10}H_8ClNO_3$	2.50×10^{-4}	6 509	13.55[e]
1f	CH_2CHCl_2	127	$C_9H_8Cl_3NO_3$	8.06×10^{-4}	2 546	13.15[f]
1g	CH_2CCl_3	118	$C_9H_7Cl_4NO_3$	1.14×10^{-2}	192	12.65[f]
1h	CH_2CF_3	143	$C_9H_7ClF_3NO_3$	1.40×10^{-2}	155	12.40[e]
1i	4-$NH_2C_6H_4$·HCl	223	$C_{13}H_{12}Cl_2N_2O_3$	8.06×10^{-2}	23.0	10.40[g]
1j	4-$MeOC_6H_4$	165	$C_{14}H_{12}ClNO_4$	9.76×10^{-2}	22.2	10.21[h]
1k	C_6H_5	193	$C_{13}H_{10}ClNO_3$	1.69×10^{-1}	12.0	10.00[h]
1l	4-$BocNHC_6H_4$	184	$C_{18}H_{19}ClN_2O_5$	1.84×10^{-1}	11.2	9.80[i]
1m	4-$AcNHC_6H_4$	194	$C_{15}H_{13}ClN_2O_4$	2.05×10^{-1}	7.1	9.49[j]
1n	3-$AcNHC_6H_4$	218	$C_{15}H_{13}ClN_2O_4$	2.79×10^{-1}	7.5	9.38[j]
1o	3-ClC_6H_4	151	$C_{13}H_9Cl_2NO_3$	5.03×10^{-1}	3.8	9.02[h]
1p	3-$CF_3C_6H_4$	154	$C_{14}H_9ClF_3NO_3$	7.00×10^{-1}	3.1	8.97[k]
			Mutual Prodrugs, R = 4-$AcNHC_6H_4$			
	X					
2	4-C_6H_5CO	177	$C_{22}H_{18}N_2O_5$	1.19×10^{-1}	5.8	9.49
3	5-C_6H_5CO	190	$C_{22}H_{18}N_2O_5$	2.21×10^{-2}	14	9.49

[a] Analytical results for C, H, and N are within ±0.4% of the theoretical values. Prodrugs **1** which may release toxic byproducts, such as methanol, concomitantly with chlorzoxazone were studied only for mechanistic considerations. [b] k_p values are the average values of k_{obsd} measured in the pH range 10−11 at 25 °C (μ = 0.5 M). The error in any measured rate constant is *ca.* ±3%. [c] $t_{1/2}$ values were obtained from the relation $k_{obsd} \times t_{1/2} = 0.69$. The rate constants ($k_{obsd}$) were measured in a pH 7.40 phosphate buffer at 37 °C (μ = 0.5 M) with error being *ca.* ±3%. [d] Extrapolated values from the Brönsted relationship $\log t_{1/2} = 1.46pK_a - 16.03$. [e] Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795. [f] Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205. [g] pK_a value of free aminophenol. Perrin, D. D. *Dissociation constants of organic bases in aqueous solution*; IUPAC Buttermorths: London, 1965; p 82. [h] Barlin, G. B.; Perrin, D. D. *Q. Rev.* **1966**, *20*, 75. [i] Value estimated from 9.64 and 9.74 pK_a's values measured at 25 °C for methyl and ethyl *N*-(4-hydroxyphenyl)carbamates, respectively. [j] Hupe, D. J.; Wu, D. *J. Am. Chem. Soc.* **1977**, *99*, 7653. [k] Calculated from equation pK_a = 9.92−2.23σ from reference listed in footnote h.

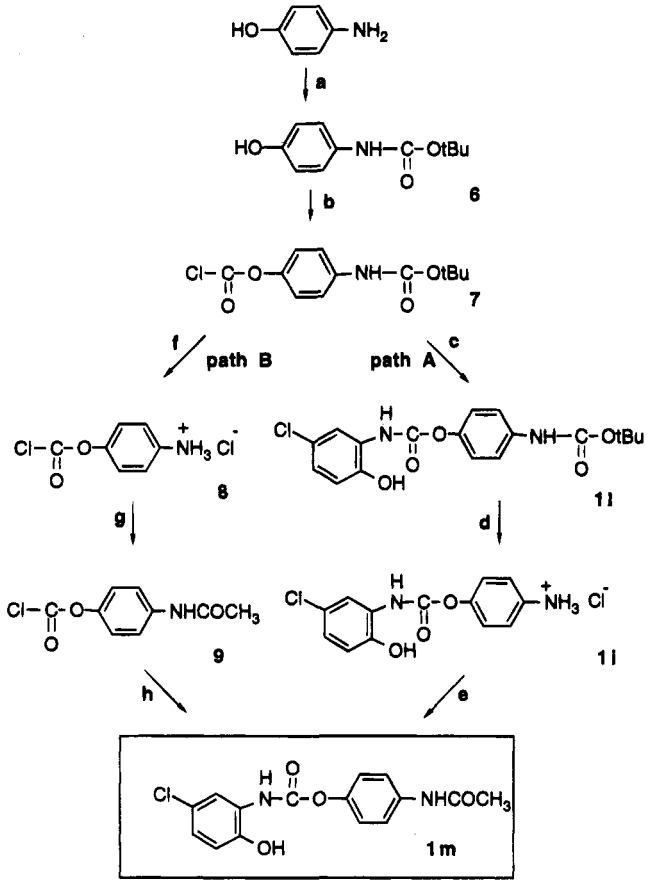
without further isolation, except for 3-acetamidophenyl chloroformate. The physical properties of synthesized compounds are listed in Table 1. Structures were confirmed by IR and NMR spectral data. According to the method used, synthesis of 4-acetamidophenyl *N*-(5-chloro-2-hydroxyphenyl)carbamate (**1m**), a mutual prodrug of chlorzoxazone and acetaminophen named chlorzacetamol,[23] requires use of 4-acetamidophenyl chloroformate which has not been previously described in the literature. In contrast, with 3-acetamidophenyl chloroformate, the para derivative could not be obtained directly by phosgenation of 4-hydroxyacetanilide. Indeed, phosgenation mainly occurred at the acetamide function, a yellow iminium salt precipitated and then disappeared in THF by addition of *N,N*-dimethylaniline. According to the von Braun reaction,[24] this intermediate product thermally decomposes to *p*-chlorophenol and acetonitrile which was identified from the $\nu_{C\equiv N}$ vibration at 2300 cm^{-1} by IR spectroscopy.

Therefore, synthesis of **1m** was achieved in a five-step process as shown in Scheme 1. First, protection of the amino group of 4-aminophenol by the *tert*-butoxycarbonyl group (Boc) using di-*tert*-butyl dicarbonate (1 equiv) in THF gives *tert*-butyl *N*-(4-hydroxyphenyl)-carbamate (**6**). Then, treatment of this carbamate by phosgene, or its derivatives diphosgene and triphosgene, affords 4-[(*tert*-butoxycarbonyl)amino]phenyl chloroformate (**7**). Deprotection of the amino group can be carried out in acidic media at different stages of the synthesis of **1m** according to pathways A and B.

Pathway A involving condensation between 5-chloro-2-hydroxyaniline and chloroformate **7** gives the biscarbamate **1l** followed by removal of the Boc group with formic and hydrochloric acids to produce 4-aminophenyl *N*-(5-chloro-2-hydroxyphenyl)carbamate (**1i**) as the HCl salt in high yields. Finally, mutual prodrug **1m** is obtained by using acetic anhydride with pyridine as catalyst. The reaction sequence is inversed in pathway B, *i.e.*, deprotection precedes condensation. So, 4-aminophenyl chloroformate (**8**) is first obtained as a stable HCl salt and then acetylated using acetyl chloride in THF to give 4-acetamidophenyl chloroformate (**9**). Further condensation of **9** in ether with the appropriate substituted aniline affords **1m** in good yield. It should be noted that all steps of Scheme 1 are achieved with good yields and that **1m** was obtained in an overall yield ranging from 47% to 57% for pathways A and B, respectively.

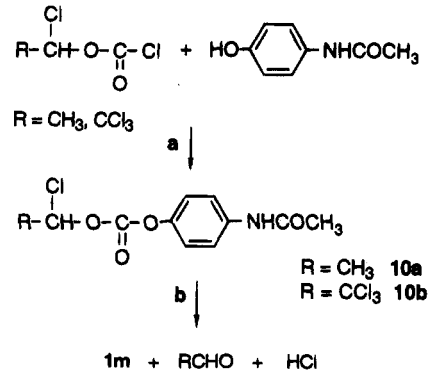
However, our goal was to reduce the number of steps in order to provide an efficient two-step synthesis of the mutual prodrug based upon the reactivity of 1-chloroalkyl chloroformates.[25] Therefore, carbonates **10** were prepared in THF in the presence of pyridine from the reaction of 4-hydroxyacetanilide with 1-chloroethyl and 1,2,2,2-tetrachloroethyl chloroformates.[26,27] Our attempts to synthesize **1m** from coupling 5-chloro-2-hydroxyaniline, a poor nucleophile, and 4-acetamidophenyl 1-chloroethyl carbonate (**10a**) failed. Indeed, TLC analyses indicated that the starting materials were largely unreacted even after refluxing for 5 days in THF. On the contrary, with the more electrophilic 4-acetamidophenyl 1,2,2,2-tetrachloroethyl carbonate (**10b**), the same aniline reacted much more easily at room temperature in THF to give **1m** (Scheme 2). It is noteworthy that the electrophilic aldehyde byproduct CCl_3CHO can react with the starting amine to give Schiff bases leading to a decrease in the yield of the carbamate. This side reaction was, however, minimized by running the reaction in the presence of water as cosolvent. In this case, formation of the aldehyde hydrate competed with

Scheme 1[a]



[a] (a) $(Boc)_2O$, THF, room temperature, 24 h, 93%; (b) $COCl_2$, DMA, AcOEt, 0–5 °C, 2 h, 93%; (c) 5-chloro-2-hydroxyaniline (2 eq), reflux (ether), 4 h, 85%; (d) HCOOH, HCl (1 M) in THF, room temperature, 24 h, 84%; (e) Ac_2O (2 eq), pyridine (5 eq), THF, room temperature, 15 min, 76%; (f) HCl (gas), THF, room temperature, 4 h, 95%; (g) CH_3COCl (large excess), THF, room temperature, 4 h, 86%; (h) same conditions as c, 80%.

Scheme 2[a]

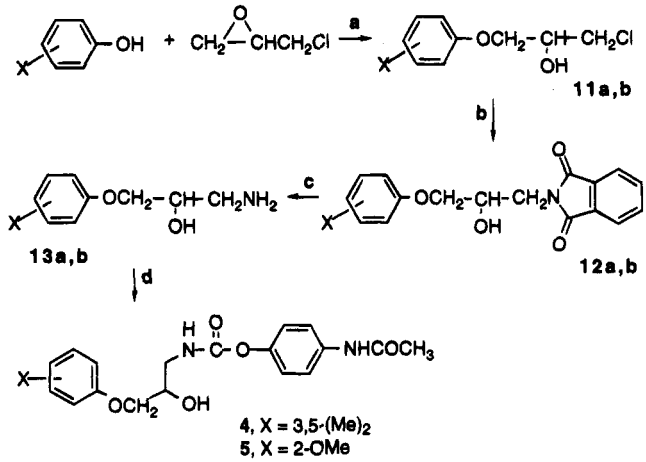


[a] (a) THF, pyridine (1 eq), 2 °C, 4 h, 93%; (b) 5-chloro-2-hydroxyaniline (2 eq), pyridine (1 eq), THF–H_2O (1/19, v/v), room temperature, 2 h, 81%.

that of the aminal, especially with **10b** where chloral hydrate was the sole byproduct. Consequently, the overall yield of the carbamate **1m** reaches more than 80%.

4-Acetamidophenyl *N*-(4-benzoyl-2-hydroxyphenyl)-carbamate (**2**) and 4-acetamidophenyl *N*-(5-benzoyl-2-hydroxyphenyl)carbamate (**3**) were prepared by coupling respectively 4-benzoyl- and 5-benzoyl-2-hydroxyanilines with 4-acetamidophenyl 1,2,2,2-tetrachloroethyl carbonate (**10b**) using the same experimental conditions as for

Scheme 3[a]



[a] (a) Piperidine chlorohydrate, 100 °C, 6 h, 71%; (b) potassium phthalimide, reflux (DMF), 24 h, 70%; (c) hydrazine hydrate, reflux (MeOH), 2 h, 93%; (d) **10b** (1 eq), DMAP (1 eq), THF–H_2O (1/19, v/v), room temperature, 4 h.

1m. 4-Benzoyl-2-hydroxyaniline was obtained from acylation of 2(3*H*)-benzoxazolone using benzoic acid as reagent and polyphosphoric acid as solvent and catalyst leading to 6-benzoylbenzoxazolone[28] followed by ring opening in alkaline media,[29] while 5-benzoyl-2-hydroxyaniline was prepared from 2-aminophenol in a three-step process according to the procedure of Henichart.[29]

Similarly, 4-acetamidophenyl *N*-[3-(3,5-dimethylphenoxy)-2-hydroxypropyl]carbamate (**4**) and 4-acetamidophenyl *N*-[3-(2-methoxyphenoxy)-2-hydroxypropyl]carbamate (**5**) were prepared by coupling the corresponding 2-hydroxyamines with carbonate **10b** (Scheme 3). First, 1-(aryloxy)-3-chloropropan-2-ols were prepared by the procedure of Stephenson[30] by condensation of the appropriate phenol with 1-chloro-2,3-epoxypropane, and 2-hydroxyamines were further obtained according to Gabriel's method[31] by reaction of the chlorohydrins with potassium phthalimide and subsequent deprotection of the amine group by hydrazinolysis.

Results and Discussion

Stability Studies and Mechanisms. Model A: Prodrugs 1 and Mutual Prodrugs 1m, 2, and 3. The stability of trichloroethyl and 4-acetamidophenyl *N*-(5-chloro-2-hydroxyphenyl)carbamates (**1g,m**, respectively) and 4-acetamidophenyl *N*-(5-benzoyl-2-hydroxyphenyl)-carbamate (**3**) was extensively investigated in aqueous media from pH 6 to 11 at 25 °C. For the other prodrugs **1** and 4-acetamidophenyl *N*-(4-benzoyl-2-hydroxyphenyl)carbamate (**2**), the study was limited at pH 7.4 and within the pH range 10–11. At all the pH values studied, active benzoxazolones and alcohols or phenols (ROH) were quantitatively formed. This was confirmed by HPLC analysis and/or by comparing UV spectra of the products obtained at the end of kinetic runs (10 half-lives) with those of a synthetic mixture of authentic samples of the corresponding benzoxazolone and ROH. In the case of the mutual prodrugs **1m**, **2**, and **3**, acetaminophen and the active benzoxazolones, chlorzoxazone and 6-benzoyl- and 5-benzoylbenzoxazolones, respectively, were quantitatively identified as the products of hydrolysis. The formation of the corresponding

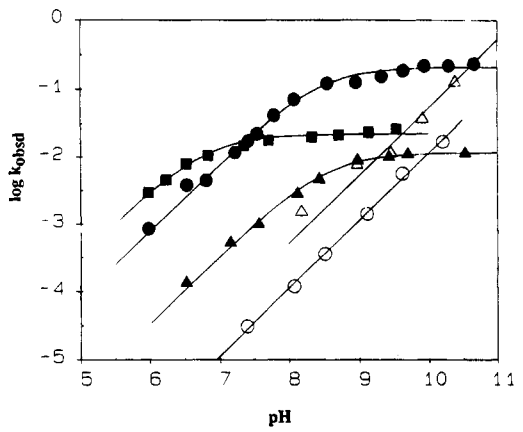
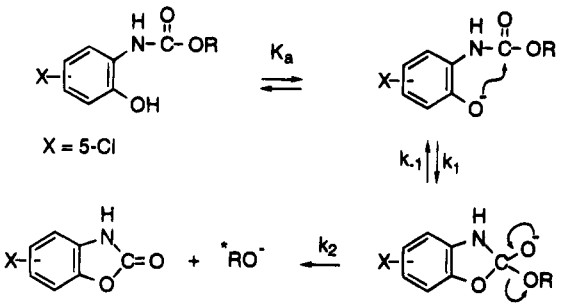


Figure 1. Plots of log k_{obsd} vs pH for the hydrolysis of prodrug **1g** (▲), mutual prodrugs **1m** (●), **2** (■), and **5** (○), and *O*-methyl derivative **14** (△). All kinetics were carried out at 25 °C and ionic strenght μ = 0.5 M with KCl except for **5** (T = 37 °C, μ = 1.0 M).

Scheme 4[a]



[a] An asterisk indicates that acetaminophen is liberated when R = 4-AcNHC$_6$H$_4$.

substituted 2-hydroxyaniline resulting from the possible nucleophilic attack of hydroxide ion on the carbonyl group of the carbamate ester of prodrugs **1**–**3** was not detected among the products of the reaction. Hydrolyses of carbamates **1**–**3** were monitored spectrophotometrically in aqueous NaOH and buffered solutions (carbonate, borax, Tris, phosphate). For all buffers examined, significant buffer catalysis was not observed. The plots log k_{obsd} vs pH for hydrolyses of **1g,m** and **3** are presented in Figure 1, and the corresponding data are collected in Table S1. They are characterized by two distinct regions: a linear increase of log k_{obsd} with pH followed by a plateau beyond pH 9. The observed behavior is fitted by eq 1, where $k_p = k_1k_2/(k_2 + k_{-1})$ is the rate constant (k_{obsd}) of the pH-independent region

$$k_{obsd} = k_1k_2K_a/(k_2 + k_{-1})(K_a + a_H) \quad (1)$$

and K_a is the acidic dissociation constant of the hydroxyl function of the prodrugs. The theoretical curves of Figure 1 were obtained using the following constants: $k_p = 1.14 \times 10^{-2}$ s^{-1}, $K_a = 2.92 \times 10^{-9}$ for **1g**; $k_p = 2.05 \times 10^{-1}$ s^{-1}, $K_a = 3.82 \times 10^{-9}$ for **1m**, and $k_p = 2.21 \times 10^{-2}$ s^{-1}, $K_a = 1.50 \times 10^{-7}$ for **3**.

In agreement with the pH–rate profiles of **1g,m** and **3**, the mechanism of formation of the active benzoxazolones does involve an intramolecular nucleophilic attack of the phenolate ion on the carbonyl group (step k_1) followed by the expelling (step k_2) of the leaving group trichloroethanol for **1g** and acetaminophen for **1m** and **3** (Scheme 4). However, an elimination–addition mechanism (E1cB) involving rate-determining isocyanate formation followed by a spontaneous ring closure reaction yielding to the corresponding benzoxazolones could also be considered. According to the literature, an E1cB mechanism occurs for the hydrolysis of aryl *N*-phenylcarbamates[6] and therefore for 4-acetamidophenyl *N*-(5-chloro-2-methoxyphenyl)carbamate (**14**), for which the *O*-methyl substituent precludes any intramolecular nucleophilic participation. The pH–rate profile for this compound (Figure 1) shows a linear increase of log k_{obsd} vs pH with no pH-independent region (up to the investigated pH 10.5), meaning that the apparent kinetic pK_a of the NH carbamate function is, as expected,[32] >10.5. Substitution of the methoxy group by the ionizable OH substituent leads to the mutual prodrug **1m** for which a pH-independent region is observed from pH 9. Thus, the apparent kinetic pK_a's obtained from the pH–rate profiles of prodrugs **1g,m** and **3** (8.53, 8.42, and 6.82, respectively) are more in agreement with the expected pK_a value of the phenolic function present in the molecule rather than the carbamate function. Second-order rate constants (k_{OH}) for compounds **1m** and **14** were determined at 25 °C (Table 2) from the linear plots of k_{obsd} vs [OH$^-$] in the pH-dependent regions; $k_{OH} = k_{obsd}/[OH^-]$. The much greater k_{OH} value obtained for **1m** compared with **14** (k_{OH}(**1m**)/k_{OH}(**14**) = 130 ± 7) strongly argues in favor of an intramolecular nucleophilic participation of the phenoxide ion in the hydrolysis of the mutual prodrug **1m** as depicted in Scheme 4.

The pH-independent rate constants (k_p) at 25 °C and the cyclization half-lives ($t_{1/2}$) at pH 7.4 and 37 °C of prodrugs **1** giving chlorzoxazone are reported in Table 1. The Brönsted-type relationship log k_p vs pK_a of ROH,

Table 2. Bimolecular Rate Constants (k_{OH}) and Half-Lives of Prodrugs and *O*-Methyl Derivatives **14** and **15** in Phosphate Buffer (pH 7.40) and Human and Rat Plasma

		$t_{1/2}$, min, 37 °C		
		pH 7.4	pH 7.4, plasma	
compd	k_{OH}, M^{-1} s^{-1}, 25 °C; m = 0.5	phosphate buffer	human	rat
1m	(6.6 ± 0.1) × 10^4	7.1 s; 36 s[c]	66 s[c]	50 s[c]
14	(5.1 ± 0.2) × 10^2			
1f		42.4	105.1	53.8
1g		3.2	10.1	7.5
2		5.8 s	60 s[c]	14 s[c]
3		14 s; 46 s[c]	10.2[c]	2.9[c]
4		416[a]	45	62
5	10.5 ± 0.4[a]	371[a]	59	58
$CH_3NHCO_2C_6H_4$-4-NHAc	11.5 ± 0.3[b]			
15		502[a]	134	153

[a] μ = 1.0 (KCl). [b] From data of ref 35. μ = 1.0 (KCl) and 25 °C. [c] 25 °C.

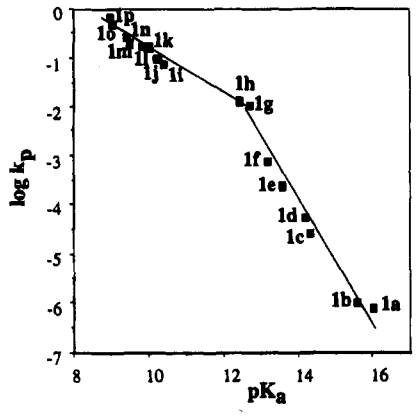


Figure 2. Brönsted relationship for the cyclization reaction of alkyl and aryl *N*-(5-chloro-2-hydroxyphenyl)carbamates **1** to chlorzoxazone (experimental conditions: pH 10–11 carbonate buffer, 25 °C).

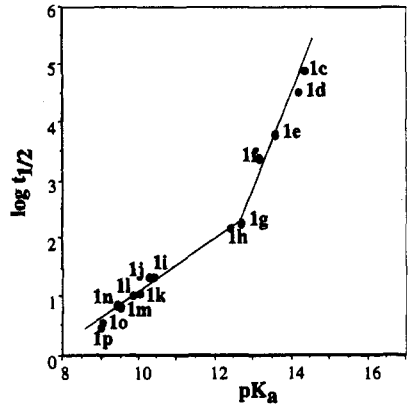


Figure 3. Brönsted relationship for the liberation of chlorzoxazone from alkyl and aryl *N*-(5-chloro-2-hydroxyphenyl)-carbamate prodrugs **1** (experimental conditions: pH 7.40 phosphate buffer, 37 °C). Linear regression equations relevant to these data are log $t_{1/2}$ = 0.46pK_a(ROH) − 3.55 (r = 0.991, s = 0.02) for aryl and trihalogenoethyl esters and log $t_{1/2}$ = 1.46pK_a(ROH) −16.03 (r = 0.988, s = 0.12) for alkyl esters. Half-lives values for prodrugs **1a** ($t_{1/2}$ = 73 days) and **1b** ($t_{1/2}$ = 290 days) have been extrapolated from the latter equation using the pK_a values of methanol and ethanol, respectively.

the conjugate acid of the leaving group, shows two distinct linear portions (Figure 2). Prodrugs **1** which release poor leaving groups (RO^-), such as EtO^-, MeO^-, CH_3-C≡C-CH_2O^-, H-C≡C-CH_2O^-, $Cl_2CHCH_2O^-$, and $ClCH_2CH_2O^-$, fall on a straight line, log k_p = −1.23pK_a + 13.29 (r = 0.988, s = 0.07), while those with better leaving groups, *i.e.*, phenolate ions, possess a lower Brönsted sensitivity, log k_p = −0.45 pK_a + 3.70 (r = 0.987, s = 0.02). The Brönsted relationship breaks into two straight lines in the region corresponding to the pK_a of trichloroethanol (prodrug **1g**) and trifluoroethanol (prodrug **1h**). The most probable explanation for the change in linearity observed in Figure 2 lies in the change in the rate-determining step (k_1 or k_2, Scheme 4) that occurs for the cyclization process with change in the leaving ability of the leaving group as measured by its pK_a value.

The Brönsted β value (β = −0.45) obtained from prodrugs **1i–p** corresponds to the β values ranging from −0.23 to −0.47[34] for reactions which are known to involve the bimolecular nucleophilic attack of hydroxide ion on the carbonyl center of carbamates as the rate-determining step (B_{Ac2} mechanism). According to these data, the rate-determining step for the hydrolysis of prodrugs **1** possessing a good leaving group (**1i–p**) is more likely to be the nucleophilic attack of the phenolate ion leading to the formation of the tetrahedric intermediate anion (step k_1, Scheme 4) rather than its subsequent decomposition (step k_2) into chlorzoxazone. Therefore, for these prodrugs, the rate law for the liberation of the muscle relaxant obeys eq 2 ($k_2 \gg k_{-1}$ in eq 1), where $k_{obsd} = k_1 = k_p$ when $a_H \ll K_a$.

$$k_{obsd} = k_1 K_a/(K_a + a_H) \qquad (2)$$

On the contrary, the β value (β = −1.23) obtained from prodrugs **1a–h** possessing worse leaving groups is more in agreement with the fact that the decomposition of the tetrahedric intermediate (step k_2) is rate-determining. A greater sensitivity of k_{obsd} with changing pK_a of the leaving ROH is expected for this step. Indeed, the E1cB hydrolysis of *N*-phenylcarbamates, for which the expelling step of the leaving group ROH (simultaneously with isocyanate formation) is rate-determining, shows higher β values (from −1.10 to −1.38)[6,34] than the corresponding B_{Ac2} mechanism discussed above. For prodrugs **1a–h**, the rate law for drug delivery obeys eq 3 ($k_2 \ll k_{-1}$ in eq 1), where $k_{obsd} = k_1k_2/k_{-1} = k_p$ when $a_H \ll K_a$.

$$k_{obsd} = k_1 k_2 K_a/k_{-1}(K_a + a_H) \qquad (3)$$

Thus, the mechanism of Scheme 4 allows an explanation of the break observed in the two Brönsted-type relationships, log k_p vs pK_a(ROH) (Figure 2) and log $t_{1/2}$ vs pK_a(ROH) (Figure 3), and accounts for the greater aqueous reactivity of prodrug **1m** compared with **14** for which the *O*-methyl substituent precludes any intramolecular nucleophilic participation.

Half-lives of prodrugs **1f,g,m**, **2**, and **3** were determined at 25 or 37 °C in human and rat plasma by HPLC analysis (Table 2). In every case, active benzoxazolones (accompanied with acetaminophen for **1m**, **2**, and **3**) were quantitatively generated. The rates of liberation in human plasma (25 or 37 °C) compared with buffered aqueous medium (pH 7.4, 25 or 37 °C) are not faster but in fact slightly slower by a factor of 2–3 for prodrugs **1**. This apparent stabilizing effect of human and rat plasma could be due to binding of the carbamate prodrugs to plasma proteins, resulting in partial inhibition of the cyclization mechanism. Table 2 data show that the formation of chlorzoxazone from prodrugs **1** bearing poor (**1f**) or good (**1m**) leaving groups is barely dependent on the presence of enzymes. This observation is in agreement with a preeminent chemical regeneration of chlorzoxazone prior to a possible enzyme-mediated conversion of the prodrugs. Analogous results were obtained with similar drug delivery systems involving cyclization process.[14a,15,16]

Carbamate prodrugs **1–3** appear to satisfy the classic requirements for cyclization-activated prodrugs: the formation of the active drug is not related to enzymatic cleavage but rather depends solely upon a predictable intramolecular cyclization–elimination reaction. Thus, the pH dependence and the Brönsted-type relationships of the critical cyclization steps (k_1 or k_2) can be advantageously used in the design of practical prodrugs.

Model B: Mutual Prodrugs 4 and 5. The stability of 4-acetamidophenyl *N*-[3-(2-methoxyphenoxy)-2-hy-

droxypropyl]carbamate (**5**) was determined in aqueous media from pH 7.4 to 11 at 37 °C. For prodrug **4** the study was limited to aqueous media at pH 7.4 and 37 °C. Product analyses carried out by analytic HPLC at the end of kinetic runs show that the two active drugs, acetaminophen and mephenoxalone, were quantitatively regenerated from their mutual prodrug **5** over the whole pH range investigated. Hydrolysis of carbamate **5** was monitored by UV spectrophotometry in aqueous NaOH and alkaline-buffered solutions (carbonate, borax, Tris, phosphate). Buffer catalysis was not observed for any of the buffers examined. The pH–rate profile (Figure 1) for hydrolysis of **5** shows a linear increase of log k_{obsd} against pH with a slope of 1. The rate law for disappearance of the mutual prodrug **5** is indicated in eq 4 for within this pH range. K_a is taken as the ionization constant of the prodrug and k_1 as the pH-independent rate constant (k_{obsd}) that would be observed in the case $K_a \gg a_H$ in eq 4.

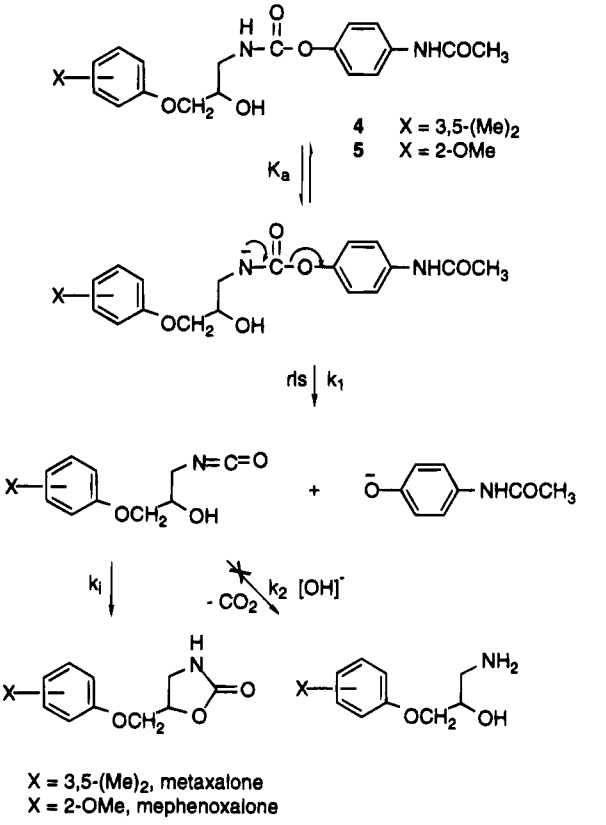
$$k_{obsd} = k_1 K_a/(a_H + K_a) \qquad (4)$$

Product analyses carried out by analytic HPLC at the end of kinetic runs (10 half-lives) from pH 7.4 to 12.3 show the absence of the amino alcohol **13b**, *i.e.*, 1-amino-3-(2-methoxyphenoxy)-2-propanol. The possible nucleophilic attack of a hydroxide ion on the carbonyl moiety of the neutral carbamate ester is therefore ruled out. This woud have been a B_{Ac2} mechanism leading to the same pH–rate profile but giving a quantitative formation of amino alcohol **13b** and acetaminophen.

In agreement with the pH–rate profile and the products formed, an intramolecular nucleophilic attack by the neighboring alkoxide ion at the carbamate carbonyl with expulsion of acetaminophen and ring closure yielding to the oxazolidinone could be considered. The second-order rate constant (k_{OH}) for **5** was determined from the linear plot of k_{obsd} vs [OH^-] using six concentrations of OH^- (from 5×10^{-3} to 0.1 M). In the same experimental conditions (25 °C, ionic strength made up to 1.0 M with KCl), it was found to be identical with the one obtained by interpolation of the plot log k_{OH} vs pK_a(ArOH) given by Williams[35] for the hydrolysis of aryl *N*-methylcarbamates ($CH_3NHCOOAr$) using the pK_a value of acetaminophen (Table 2). Thus $k_{OH} = 10.5 \pm 0.4$ M^{-1} s^{-1} for **5**, and according to the equation log $k_{OH} = -1.1pK_a + 11.5$, obtained from the data given by Williams,[35] $k_{OH} = 11.5 \pm 0.3$ M^{-1} s^{-1} for 4-acetamidophenyl *N*-methylcarbamate. Thus the similarity in the second-order rate constants (k_{OH}) indicates that the reaction of the mutual prodrug **5** must involve the rate-limiting formation of an isocyanate intermediate (Scheme 5) as in the case of aryl carbamates.[6] Therefore, the neighboring nucleophile alkoxide ion of prodrugs **4** and **5** related to model B is not involved in the rate-limiting step of the hydrolysis reaction as opposed to prodrugs **1–3** related to model A. Fife observed the same behavior with 4-nitrophenyl *N*-[2-(hydroxymethyl)phenyl]carbamate for which an E1cB elimination mechanism operates independently of the presence of a powerful intramolecular nucleophile hydroxymethyl group in the vicinity of the carbamate carbonyl.[36]

Thus, it is likely that the apparent hydroxide ion catalysis seen in the hydrolysis of **5** (Figure 1) is not due to the preequilibrium ionization of the neighboring

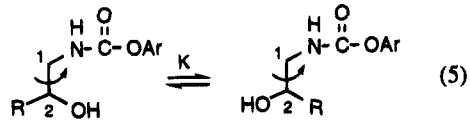
Scheme 5. Model B: Mutual Prodrugs **4** and **5**



hydroxyl group but rather to the NH carbamate moiety whose pK_a value should be close to that of phenyl *N*-methylcarbamate estimated to 17.1.[35] In eq 4, k_1 is the rate constant for the decomposition of the conjugate base of the carbamate and K_a is the dissociation constant of the NH bond of the carbamate group. Then, as depicted in Scheme 5, the isocyanate intermediate formed in the rate-limiting step (k_1) cyclizes—at any pH—with great ease yielding a quantitative generation of oxazolidinone (step k_i). Consequently, even at high hydroxide ion concentrations, *the intramolecular reaction k_i is the exclusive pathway for trapping of the intermediate isocyanate*: the conceivable hydroxide ion-promoted trapping (step k_2[OH^-], Scheme 5) does not compete with k_i (k_2[OH^-] $\ll k_i$), and formation of amino alcohol **13b** at 10 half-lives was not ever observed.[37]

It is noteworthy that in aqueous media models A and B both operate as drug delivery systems. The mechanisms by which the active benzoxazolones compared to the active oxazolidinones are delivered are different and inherent in the specificity of the two models. In both models A and B, the hydroxyl and carbamate ester reacting groups are held together by a covalent chain. The particularity of each model is based on the flexibility of that chain and on the ionization constant of the hydroxyl group. In model B, the much greater pK_a value for the hydroxyl group compared to the phenolic one in model A implies that there will be only a small amount of the active alcoholate fraction at the physiological pH 7.4. In addition, the chain in model B is flexible enough that the reacting groups are not forced together in an energetically unfavorable manner that might induce an intramolecular reaction (like in model A) by strain or some related destabilization mechanism. Thus, (2-hydroxyalkyl)carbamate molecules related to

model B are free to rotate about the C_1-C_2 bond (eq 5)



(5)

and probably mainly exist in aqueous solution in conformations in which the reacting groups are separated from each other. The E1cB mechanism which is known to operate in the hydrolysis of aryl *N*-alkylcarbamates is then maintained for prodrugs related to model B. Because there is no competition, even at high pH, between internal and external trappings (k_i and $k_2[OH^-]$, Scheme 5), model B proves to be, in aqueous medium, an original oxazolidinone delivery system.

Half-lives at 37 °C of prodrugs **4** and **5** in rat and human plasma were determined conveniently by HPLC analysis (Table 2). It was found that both **4** and **5** released quantitatively acetaminophen and the corresponding active oxazolidinones with $t_{1/2}$ in human plasma of 45 min for **4** and 59 min for **5**. Table 2 data show that the rates of liberation in human and rat plasma compared with buffered aqueous medium (pH 7.4 and 37 °C) are faster by a factor of 6–9. As opposed to model A, the rates of hydrolysis of prodrugs **4** and **5** related to model B clearly exhibit a catalytic role of the plasma. This enhanced reactivity is probably due to the presence in the plasma of various enzymes like esterases capable of carrying out the necessary activation of the corresponding prodrugs.[38-40] The potential mechanisms by which acetaminophen and the active oxazolidinones are released in plasma could involve one of the two following processes: (i) a hydrolytic cleavage of the carbamate ester mediated by enzymatic catalysis or (ii) a ring closure reaction promoted by the presence of certain enzymes (enzymatic cyclization).[41]

In order to discriminate between these two possibilities, we have determined the aqueous and plasma half-lives of the O-methylated analog of prodrug **5** (compound **15**, Chart 1), for which the cyclization process is excluded. Examination of Table 2 shows that compound **15** hydrolyses in plasma media faster than in aqueous medium. The extent of plasma catalysis observed at pH 7.4 and 37 °C for **15** ($t_{1/2}$(phosphate buffer)/$t_{1/2}$(human plasma) = 3.8) allows discarding of the enzymatic cyclization as the major process of catalysis for **4** and **5** and therefore, rather, argues in favor of an enzymatic cleavage of the carbamate ester. The quantitative formations of the cyclic metaxalone and mephenoxalone observed from plasma hydrolysis of prodrugs **4** and **5**, respectively, are then explained if we consider that *the carbamate substrates undergo a covalent transformation yielding to the very unstable 2-hydroxypropyl isocyanate intermediates which rapidly and quantitatively cyclize to the corresponding oxazolidinones.*

The product analysis carried out by HPLC at the end of kinetic runs of **15** in aqueous solutions (pH 7.4 phosphate buffer) allowed the identification of quantitative formations of acetaminophen and 3-(2-methoxyphenoxy)-2-methoxypropylamine (**16**). At the end of the reaction, identification of the latter was further confirmed, after subsequent isolation, by ^1H and ^{13}C NMR spectroscopy (see the Experimental Section). As opposed to aqueous medium, 2-methoxypropylamine **16** was not detected among the products of plasma hydrolysis of **15**. Only the expected theoretical amount of acetaminophen was observed. It was also confirmed that authentic samples of 2-methoxypropylamine **16** in solution in human or rat plasma (in the same experimental conditions as kinetic runs) could be quantitatively extracted using the experimental procedure described in the Experimental Section. Thus, the quantitative extraction of an authentic sample of **16** from plasma media leads to the conclusion that if **16** is not detected at the end of plasma hydrolysis of **15**, then it is not formed. Indeed, once generated, the powerful electrophilic 2-methoxypropyl isocyanate intermediate unable to cyclize might then induce a subsequent covalent linkage with the enzyme catalysts. This would explain the remarkable absence of **16** among the products of plasma hydrolysis, the covalently linked (2-methoxypropyl)amino moiety being eliminated during the deproteinization procedure carried out prior to HPLC injection (see the Experimental Section).

Conclusions

We have demonstrated in both aqueous and plasma media the efficiency of a novel drug delivery system based on masked active benzoxazolones (model A) and oxazolidinones (model B). The mutual prodrugs **4** and **5** (model B) affording acetaminophen together with the oxazolidinone drugs metaxalone and mephenoxalone, respectively, have cyclization rates that are likely to be adequate for therapeutic use. Although acetaminophen and the active benzoxazolones appear to be delivered rather rapidly from mutual prodrugs **1m**, **2**, and **3** related to model A, liberation half-lives in the region of 1 h seem nevertheless possible by means of a subsequent derivatization of the hydroxyl group (in progress) according to the pro-prodrug approach.[2]

Models A and B are related to a cyclization-activated prodrug system. The triggering mechanism of model A involves a classic ring closure reaction proceeding spontaneously at pH 7.4 and similarly being independent of the action of enzymes, whereas model B involves an original mechanism of liberation with both an enzymatic process and a spontaneous ring closure reaction.[42]

The carbamate bond in model B is probably hydrolyzed by means of plasma hydrolases (*e.g.*, cholinesterases) to produce a 2-hydroxypropyl isocyanate intermediate which spontaneously cyclizes to the corresponding oxazolidinone drugs. If there is no neighboring nucleophile on the molecule (as in the compound **15**), then the electrophilic isocyanate formed during the plasma-catalyzed process cannot cyclize and, hence, appears free to react with any external nucleophiles present in the vicinity (*e.g.*, serine or cysteine residues of enzymes). This is supported by the observation that the (2-methoxypropyl)amino moiety of **15** was never detected among the products of plasma hydrolysis of **15**. It is then concluded (i) that a carbamate function can be *enzymatically* transformed into a potent electrophile, *i.e.*, an isocyanate, and (ii) that this characteristic might be related to the enzyme–inhibitor activity of various substrates bearing carbamoyl groups.[43] These observations, as a whole, indicate that the carbamate functionality could play a key role in the design of both new prodrugs and enzyme inhibitors in the very near future.

Experimental Section

Chemistry. Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed by Analytic Service, University Paul Sabatier, and the results obtained were reported only by symbols of the elements. The data are within ±0.4% of the theoretical values. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer using TMS as internal standard. IR spectra were obtained on a Perkin-Elmer 883 spectrometer.

General Synthesis of Aryl and Alkyl *N*-(5-Chloro-2-hydroxyphenyl)carbamates 1: Preparation of 3-Acetamidophenyl Chloroformate. Phosgene in toluene (7.62 g, 77 mmol) was added to 3-acetamidophenol (7.79 g, 50 mmol) dissolved in anhydrous ethyl acetate (200 mL), cooled to 0–5 °C, and stirred under argon. *N,N*-Dimethylaniline (6.05 g, 50 mmol) in ethyl acetate (5 mL) was then added dropwise, and stirring was continued for 1 h. The temperature was then raised to 40 °C in order to expel phosgene which was trapped with a NaOH solution. The reaction mixture was cooled at room temperature and filtered off. The organic layer was washed with 0.1 M HCl, dried over $MgSO_4$, and evaporated *in vacuo*. Recrystallization of the residue from chloroform gave chloroformate as white needles (9.0 g, 90%): IR (KBr) 3400, 1790, 1672 cm^{-1}.

The other chloroformates (previously listed) were obtained similarly and identified from the $\nu_{C=O}$ band in the 1780–1790 cm^{-1} range. They were used in the following steps without purification.

Synthesis of 3-Acetamidophenyl *N*-(2-Hydroxy-5-chlorophenyl)carbamate (1n). 3-Acetamidophenyl chloroformate (1.06 g, 5 mmol) in diethyl ether (10 mL) was slowly added to a solution of 5-chloro-2-hydroxyaniline (1.48 g, 10 mmol) in 20 mL of diethyl ether warmed to reflux, and the solution was then stirred for 4 h. The reaction mixture was filtered to remove the chlorohydrate salt, and the filtrate was washed with 3 M HCl. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to afford **1n** (1.56 g, 98%): mp 218 °C; IR (KBr) 3308, 1710, 1652 cm^{-1}; ^{13}C NMR (DMSO-d_6) δ 23.95 (CH_3), 106.08–154.21 (aryl-C), 157.46 (NH*C*(O)O), 166.09 (NH*C*(O)). Anal. ($C_{15}H_{13}ClN_2O_4$) C, H, N.

The other carbamates **1** were synthesized according to the same procedure with good yields (>70%) and show the same spectral properties as **1n** (Table 1).

Synthesis of Chlorzacetamol (1m) by a Five-Step Process: *tert*-Butyl *N*-(4-Hydroxyphenyl)carbamate (6). A solution of di-*tert*-butyl dicarbonate (14.63 g, 65 mmol) in anhydrous THF (60 mL) was added dropwise to 4-aminophenol (7.1 g, 65 mmol) in THF (350 mL) at 6 °C. The mixture was stirred and refluxed at room temperature for 24 h. After removing THF *in vacuo*, the brown solid obtained was redissolved in ethyl acetate. The organic layer was washed three times with water and dried over $MgSO_4$, and the solvent was removed *in vacuo* to afford 12.6 g (93%) of **6** as a powder: mp 144–145 °C; IR (KBr) 3400, 3363, 1696 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.46 (s, 9H, CH_3), 6.75 (d, 2H, ArH, J = 8.93 Hz), 7.34 (d, 2H, ArH, J = 8.93 Hz), 7.96 (s, 1H, OH), 8.16 (s, 1H, NH). Anal. ($C_{11}H_{15}NO_3$) C, H, N.

4-[(*tert*-Butoxycarbonyl)amino]phenyl Chloroformate (7). The synthesis of **7** was carried out as previously described for 3-acetamidophenyl chloroformate. Extractive workup afforded 12.6 g (93%) of a solid: mp 137 °C; IR (CCl_3) 3441, 1782, 1728 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.49 (s, 9H, CH_3), 7.27 (d, 2H, ArH, J = 9.62 Hz), 7.65 (d, 2H, ArH, J = 9.62 Hz), 8.53 (s, 1H, NH). Anal. ($C_{12}H_{14}ClNO_4$) C, H, N.

Path A: 4-[(*tert*-Butoxycarbonyl)amino]phenyl *N*-(5-Chloro-2-hydroxyphenyl)carbamate (1l). Via the same procedure used for the preparation of **1n**, condensation of 5-chloro-2-hydroxyaniline (1.48 g, 10 mmol) with **7** (1.35 g, 5 mmol) followed by the same extractive workup gave 1.60 g (85%) of a solid material: mp 184 °C; IR (KBr) 3413, 3305, 2981, 1735, 1690 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.49 (s, 9H, CH_3), 6.94 (m, 2H, ArH), 7.15 (d, 2H, ArH, J = 8.81 Hz), 7.59 (d, 2H, ArH, J = 8.81 Hz), 7.99 (s, 1H, ArH), 8.16 (s, 1H, OH), 8.40 (s, 1H, NH), 8.66 (s, 1H, NH). Anal. ($C_{18}H_{19}ClN_2O_5$) C, H, N.

4-Aminophenyl *N*-(5-Chloro-2-hydroxyphenyl)carbamate (1i). To a solution of **1l** (1 g, 2.64 mmol) in THF (25 mL) was added a solution of 99% formic acid (30 mL, 800 mmol) and 1 M hydrochloric acid (3.2 mL, 800 mmol) dissolved in THF. The mixture was stirred at room temperature for 24 h. Evaporation of the solvent gave 0.7 g (84%) of a crude residue which was washed with ether and filtered: mp 223 °C; IR (KBr) 3408, 3095–2622, 1731 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.96 (m, 2H, ArH), 7.34 (d, 2H, ArH, J = 8.75 Hz), 7.45 (d, 2H, ArH, J = 8.75 Hz), 7.63 (m, 1H, ArH), 9.23 and 9.82 (5H br m and s, OH, NH and NH^{3+}). Anal. ($C_{13}H_{11}ClN_2O_3$) C, H, N.

4-Acetamidophenyl *N*-(5-Chloro-2-hydroxyphenyl)carbamate (1m). A solution of **1i** (2.0 g, 6.35 mmol) and pyridine (2.5 g, 31.7 mmol) in THF (10 mL) was stirred at room temperature as acetic anhydride (0.86 g, 8.07 mmol) was added dropwise (the reaction is exothermic). After 15 min, the solvent was removed and the residue was redissolved in AcOEt/THF mixture (v/v: 9/1). The organic layer was washed twice with HCl 1M and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was filtered and washed with ether to afford **1m** (1.54 g, 76%) as a powder: mp 194 °C; IR (KBr) 3400, 3327, 3400–3200, 1724, 1647, 1605, 1529, 1502 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.04 (d, 3H, CH_3), 6.87 (d, 1H, ArH, J = 8.63 Hz), 7.00 (dd, 1H, ArH, J = 8.63, 2.6 Hz), 7.13 (d, 2H, ArH, J = 8.95 Hz), 7.60 (d, 2H, ArH, J = 8.95 Hz), 7.64 (d, 1H, ArH, J = 2.6 Hz), 9.08 (s, 1H, OH), 9.99 (s, 1H, NH), 10.15 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.84 (CH_3), 116.38–147.38 (Ar-*C*), 152.21 (NH*C*(O)O), 166.12 (NH*C*=O). Anal. ($C_{15}H_{13}ClNO_4$) C, H, N.

Path B: 4-Aminophenyl Chloroformate (8). A solution of 4-[(*tert*-butoxycarbonyl)amino]phenyl chloroformate (**7**) (2 g, 7.38 mmol) in THF (55 mL) was saturated with HCl gas by slow bubbling for 4 h. The chlorohydrate salt was filtered, washed with ether, and quickly dried *in vacuo* to give 1.46 g (95%) of an irritant powder which was further stored under argon at −30 °C: IR (KBr) 2896, 2596, 1781, 1500 cm^{-1}. Anal. ($C_7H_6ClNO_2$·HCl) C, H, N.

4-Acetamidophenyl Chloroformate (9). To a solution of 150 mg (0.72 mmol) of **8** in THF (30 mL) was added acetyl chloride (10 mL, large excess). The mixture was then stirred at room temperature for 4 h. After removal of the solvent, the residue was washed with petroleum ether to afford 132 mg (96%) of **9** as gray crystals: IR (KBr) 3300, 1774, 1666 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 24.49 (CH_3), 120.95–147.64 (Ar-*C*), 149.80 (Cl-*C*=O), 168.88 (NH-*C*=O).

The synthesis of the mutual prodrug **1m** was then carried out by condensation of 5-chloro-2-hydroxyaniline with **9** according to the procedure previously described for **1l,n**.

Synthesis in a Two-Step Process of Chlorzacetamol (1m): 4-Acetamidophenyl 1-Chloroethyl Carbonate (10a). A mixture of 4-hydroxyacetanilide (7.71 g, 50 mmol) and pyridine (4.43 g, 55 mmol) dissolved in tetrahydrofuran (100 mL) was added dropwise to a solution of 1-chloroethyl chloroformate (8.75 g, 60 mmol) in THF (4 mL) and cooled to 2 °C. The reaction mixture was stirred at room temperature for 4 h. The precipitate obtained was filtered off, and the filtrate was concentrated by removal of the solvent. The residue was redissolved in dichloromethane. The organic layer was washed with 1 M HCl, dried over $MgSO_4$, and evaporated *in vacuo* to afford the crude carbonate. The residue was recrystallized (diethyl ether) to give 11.6 g (90%) of **10a** as crystals: mp 124 °C; IR (KBr) 3261, 1779, 1661 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 24.24 (CH_3 amide), 25.22 (CH_3CH), 85.06 (*C*H), 121.27–146.92 (Ar-*C*), 151.65 (O-*C*=O), 169.10 (NH*C*=O).

4-Acetamidophenyl 1,2,2,2-Tetrachloroethyl Carbonate (10b). The carbonate **10b** was obtained in 93% yield by coupling 1,2,2,2-tetrachloroethyl chloroformate with 4-hydroxyacetanilide using the same procedure described for **10a:** mp 125 °C; IR (KBr) 3264, 1780, 1662 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 24.34 (CH_3), 91.25 (*C*H), 121.08–146.77 (Ar-*C*), 150.69 (O-*C*=O), 169.09 (NH*C*=O).

4-Acetamidophenyl *N*-(5-Chloro-2-hydroxyphenyl)-carbamate (1m). Pyridine (0.29 g, 3.8 mmol) was added dropwise at room temperature to a mixture of 5-chloro-2-hydroxyaniline (1.12 g, 7.6 mmol) and **10b** (1.37 g, 3.8 mmol) dissolved in THF (28 mL) and water (1.5 mL). The reaction

mixture was stirred for 1.5 h. After removal of the solvent, the residue was dissolved in diethyl ether/THF (v/v: 9/1). The organic layer was washed three times with 3 M HCl, dried over $MgSO_4$, and evaporated *in vacuo*. The crude product was washed with ether to afford 0.98 g (81%) of the mutual prodrug **1m**.

Synthesis of 4-Acetamidophenyl *N*-(4-Benzoyl-2-hydroxyphenyl)carbamate (2). 6-Benzoylbenzoxazolone was prepared by treating 2(3*H*)-benzoxazolone and benzoic acid with polyphosphoric acid (PPA) according to the method of Hénichart *et al.*[28]

4-Benzoyl-2-hydroxyaniline. 6-Benzoylbenzoxazolone (6 g, 25 mmol) dissolved in a 2.5 M NaOH solution (50 mL) was refluxed for 4 h. After cooling, the solution was acidified with 3 M HCl, and the mixture was stirred for 1 h. Ethyl acetate was added to the reaction mixture, and the aqueous layer was neutralized with $NaHCO_3$. The residue when washed with petroleum ether afforded 5.22 g (98%) of substituted phenol: mp 160 °C (lit.[29] mp 164 °C); IR (KBr) 3490, 3396, 3303, 1643, 1584, 1558 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.5 (s, 2H, NH_2), 6.63 (d, 1H, ArH, J = 8.2 Hz), 7.10 (dd, 1H, ArH, J = 8.2, 1.9 Hz), 7.23 (d, 1H, ArH, J = 1.9 Hz), 7.49–7.72 (m, 5H, ArH), 9.4 (s, 1H, OH).

4-Acetamidophenyl *N*-(4-Benzoyl-2-hydroxyphenyl)carbamate (2). The prodrug **2** was obtained in 60% yield by coupling 4-benzoyl-2-hydroxyaniline with carbonate **10b** using the same procedure described for **1m**: mp 179 °C; IR (KBr) 3600–3200, 3420, 3350, 1756, 1660, 1635, 1599, 1502 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.06 (s, 3H, CH_3), 7.13–7.86 (m, 12H, ArH), 9.03 (s, 1H, OH), 9.96 (s, 1H, NH), 10.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.83 (*C*H_3), 115.89–147.42 (Ar-*C*), 151.99 (NH*C*(O)O), 168.21 (NH*C*(O)-), 194.69 (C_6H_5*C*(O)-). Anal. ($C_{22}H_{18}N_2O_5$) C, H, N.

Synthesis of 4-Acetamidophenyl *N*-(5-Benzoyl-2-hydroxyphenyl)carbamate (3). 5-Benzoyl-2-hydroxyaniline was obtained in a three-step process by acetylation of 2-aminophenol followed by benzoylation on the aromatic ring using $AlCl_3$ in DMF and deprotecting the amino group by refluxing in concentrated hydrochloric acid according to the procedure of Henichart.[29]

4-Acetamidophenyl *N*-(5-Benzoyl-2-hydroxyphenyl)carbamate (3). The prodrug **3** was obtained in 60% yield by coupling 5-benzoyl-2-hydroxyaniline with carbonate **10b:** mp 190 °C; IR (KBr) 3432, 3297, 1757, 1664, 1635, 1594, 1536, 1496 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.04 (s, 3H, CH_3), 6.97–7.73 (m, 11H, ArH), 8.11 (d, 1H, ArH_6), 9.10 (s, 1H, OH), 9.94 (s, 1H, NH), 10.88 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.63 (*C*H_3), 114.96–152.37 (Ar-*C*), 153.00 (NH*C*(O)O), 168.13 (NH*C*=O), 194.14 (*C*=O). Anal. ($C_{22}H_{18}N_2O_5$) C, H, N.

Synthesis of 4-Acetamidophenyl *N*-[3-(3,5-Dimethylphenoxy)-2-hydroxypropyl]carbamate (4): 3-Chloro-1-(3,5-dimethylphenoxy)-2-propanol (11a). To a solution of 3,5-dimethylphenol (10.38 g, 85 mmol) dissolved in epichlorohydrin (20 mL, 255 mmol) was added piperidine hydrochloride (0.17 g, 1.4 mmol), and the reaction mixture was stirred at 100 °C for 6 h. The mixture was evaporated *in vacuo*. The oily residue was dissolved in an equal volume of chloroform, and the organic layer was acidified with 10 M HCl (5 mL), washed with water (3 × 20 mL), and dried over $MgSO_4$. The resulting residue was purified by column chromatography on silica gel (ether/petroleum ether, 7/3, v/v) to afford 12.91 g (71%) of **11a** as an oil: IR (neat) 3401, 2923, 1595, 1463, 1173, 831, 753 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 21.46 (*C*H_3), 46.01 (*C*H_2Cl), 66.38 (*C*H_2O), 69.97 (*C*HOH), 112.38–158.30 (Ar-*C*).

3-(3,5-Dimethylphenoxy)-1-phthalimido-2-propanol (12a). Potassium phthalimide (7.40 g, 40 mmol) and **11a** (4.29 g, 20 mmol) were dissolved in DMF (40 mL), and the mixture was stirred and refluxed for 2 h. Then, chloroform was added to the reaction mixture, and the latter was washed with water. The organic layer was washed with 0.2 M NaOH in order to eliminate phthalimide and washed again with water (3 × 30 mL) and then dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the oil was purified by column chromatography on silica gel (ether/dichloromethane, 1/9, v/v) to afford 5.2 g (80%) of **12a** as white crystals: mp 84–86 °C; IR (KBr) 3416, 2924, 1767, 1699, 1593, 1467, 1390, 1174, 831, 715 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 21.45 (*C*H_3), 41.34 (*C*H_2N), 68.83 (*C*HOH), 69.65 (*C*H_2O), 112.43–158.46 (Ar*C*), 168.78 (*C*O phthalimide).

1-Amino-3-(3,5-dimethylphenoxy)-2-propanol (13a). 12a (1 g, 3 mmol) and 0.31 g (6.2 mmol) of hydrazine hydrate were dissolved in methanol (15 mL), and the mixture was refluxed and stirred for 1.5 h. The solution was acidified with cold 10% aqueous HCl up to pH 3. The mixture was cooled to 0 °C, and the precipitate was filtered off. The filtrate was made alkaline (pH 11) with 1% aqueous NaOH, and chloroform was added. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to afford 0.54 g (93%) of **13a** as white crystals: mp 84 °C; IR ($CDCl_3$) 3598, 3392, 3006, 2927, 1594, 1457, 1159, 833 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 21.42 (*C*H_3), 44.24 (*C*H_2N), 70.05 (*C*H_2O), 70.52 (*C*HOH), 112.30–158.67 (Ar-*C*).

4-Acetamidophenyl *N*-[3-(3,5-Dimethylphenoxy)-2-hydroxypropyl]carbamate (4). The prodrug **4** was obtained in 72% yield by coupling **13a** with carbonate **10b** according to the procedure described for **1m** for which (*N*,*N*-dimethylamino)pyridine (DMAP) was used instead of pyridine: mp 128 °C; IR (KBr) 3354, 3070, 1707, 1663, 1609, 1545, 1504, 1161, 830 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.03 (s, 3H, $CH_3C(O)$), 2.22 (s, 6H, CH_3 arom), 3.04–3.44 (m, 3H, CH, CH_2N), 3.84–3.94 (m, 2H, CH_2O), 5.1 (br s, 1H, OH), 6.55 (s with shoulder, 3H, ArH arom), 7.02 (d, 2H, ArH, J = 7.5 Hz), 7.53 (d, 2H, ArH, J = 7.5 Hz), 7.74 (t, 1H, NH), 9.96 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 20.95 (A_rCH_3), 23.79 (CH_3*C*=O), 43.93 (*C*H_2N), 67.70 (*C*HOH), 69.86 (*C*H_2O), 112.13–158.53 (Ar*C*), 154.89 (NH-*C*(O)O), 166.02 (CH_3*C*=O). Anal. ($C_{20}H_{24}N_2O_5$) C, H, N.

Synthesis of 4-Acetamidophenyl *N*-[3-(2-Methoxyphenoxy)-2-hydroxypropyl]carbamate (5). The prodrug **5** was prepared in 55% yield by coupling **13b** with carbonate **10b** according to the same procedure used for **4**.

3-Chloro-1-(2-methoxyphenoxy)-2-propanol (11b): yield 66%; oil purified by silica gel chromatography (petroleum ether/ethyl acetate/dichloromethane, 10/1/4, v/v/v); IR (neat) 3449, 2939, 1593, 1504, 1457, 1255, 1179, 746 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 45.64 (CH_2Cl), 55.89 (CH_3O), 69.95 (CHOH), 71.19 (CH_2O), 112.11–149.96 (ArC).

3-(2-Methoxyphenoxy)-1-phthalimido-2-propanol (12b): yield 88%; mp 85 °C; IR (KBr) 3459, 2946, 1711, 1593, 1461, 1384 cm^{-1}; ^{13}C NMR ($CDCl_3$) 40.98 (*C*H_2N), 55.86 (*C*H_3O), 68.64 (*C*HOH), 72.63 (*C*H_2O), 112.12–150.10 (Ar*C*), 168.68 (*C*=O).

1-Amino-3-(2-methoxyphenoxy)-2-propanol (13b): yield 73%; mp 89 °C; IR ($CDCl_3$) 3600, 3455, 3400, 3006, 2943, 1593, 1501, 1252, 1178 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 44.13 (*C*H_2N), 55.78 (*C*H_3O), 70.46 (*C*HOH), 72.20 (*C*H_2O), 111.85–149.54 (Ar*C*).

4-Acetamidophenyl *N*-[3-(2-methoxyphenoxy)-2-hydroxypropyl]carbamate (5): mp 142 °C; IR (KBr) 3500–3200, 1710, 1669 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.03 (s, 3H, $CH_3C(O)$), 3.21–3.35 (m, 3H, CH_2, CH), 3.76 (s, 3H, OMe), 3.92 (m, 2H, CH_2O), 5.1 (m, 1H, OH), 6.92 (m, 4H, aromatic H), 6.95–7.65 (m, 5H, aromatic H, NH), 9.88 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.79 (CH_3*C*O), 44.20 (NCH_2), 55.44 (OCH_3), 67.74 (*C*HOH), 69.67 (*C*H_2O), 112.37–158.55 (Ar*C*), 154.71 (NH*C*(O)O), 168.04 (NH*C*O). Anal. ($C_{19}H_{22}N_2O_6$) C, H, N.

Synthesis of 4-Acetamidophenyl *N*-(5-Chloro-2-methoxyphenyl)carbamate (14): 5-Chloro-2-methoxyphenyl Isocyanate. Phosgene in toluene (14.84 g, 0.15 mol) was added dropwise to 5-chloro-2-methoxyaniline (15.7 g, 0.1 mol) dissolved in anhydrous toluene (70 mL), cooled to 0–5 °C, and stirred under argon. The mixture was refluxed at room temperature for 4 h. Careful removal of the toluene by distillation resulted in isolation of the isocyanate as a white solid (15.6 g, 85%): IR (KBr) 2271 cm^{-1}.

The carbamate was obtained by reacting 4-hydroxyacetanilide (6.55 g, 42.5 mmol) dissolved in anhydrous acetone (60 mL) with isocyanate (7.8 g, 42.5 mmol) in anhydrous acetone (25 mL) added dropwise in the presence of triethylamine (1.6 g, 15.3 mmol) as catalyst. The mixture was refluxed for 12 h and the solvent removed under vacuum. Recrystallization of the crude solid from acetone gave **14** (9.95 g, 70%): mp 167 °C; IR (KBr) 3425, 1745, 1668 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.04 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 7.05–7.83 (m, 7H, ArH), 9.23 (s, 1H, NH), 9.95 (s, 1H, NH). Anal. ($C_{16}H_{15}ClN_2O_4$) C, H, N.

Synthesis of 4-Acetamidophenyl *N*-[3-(2-Methoxyphenoxy)-2-methoxypropyl]carbamate (15). Mutual prodrug **5** (100 mg, 1 mmol) dissolved in dichloromethane (3 mL) was stirred under nitrogen and trimethyloxonium tetrafluoroborate (59.7 mg, 1.5 mmol) added. The reaction mixture was refluxed and stirred for 5 h and then washed twice with water. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give an oily residue. Chromatography on silica gel (eluant: ethyl acetate) gave the title compound (77.6 mg, 20%) as an oil: ^{1}H NMR ($CDCl_3$), δ 2.10 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 3.67 (m, 2H, CH_2O), 3.85 (s, 3H, OCH_3), 4.14 (m, 3H, CH_2, CH), 6.36 (m, 1H, NH carb), 6.91 (m, 4H, ArH), 7.02 (d, 2H, ArH, J = 9.04 Hz), 7.37 (d, 2H, ArH, J = 9.04 Hz), 7.63 (m, 1H, NHC=O); ^{13}C NMR ($CDCl_3$) δ 24.33 (CH_3C=O), 42.29 (CH_2N), 55.72 (CH_3OAr), 57.81 (CH_3O), 70.39 (CH_2-O), 77.17 (CHO), 111.7–149.69 (Ar-*C*), 155.47 (NH*C*(O)O), 168.57 (NH*C*=O). Anal. ($C_{20}H_{24}N_2O_6$) C, H, N.

Isolation of 3-(2-Methoxyphenoxy)-2-methoxypropylamine (16). Compound **15** (15 mg, 0.039 mmol) dissolved in acetonitrile was hydrolyzed at 37 °C in 1.5 mL of pH 7.4 phosphate buffer solution for 4 days (>10 half-lives). The reaction mixture was acidified with 1 M HCl in order to decarboxylate the carbamic acid salt formed. The free amine was then obtained after basification with NaOH and the aqueous layer washed five times with dichloromethane. The combined organic layers were washed three times with water, dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel (eluant: dichloromethane/methanol, 9/1) gave the title compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3H, CH_3O), 3.69 (m, 2H, CH_2-N), 3.84 (s, 3H, CH_3-OAr), 4.08 (d, 2H, CH_2O), 4.17 (m, 1H, CH), 6.90 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 41.46 (CH_2N), 55.88 (CH_3OAr), 57.85 (CH_3O), 70.02 (CH_2O), 78.13 (CH), 111.98, 113.92, 120.98, 122.09, 148.08, 149.65 (Ar*C*).

Kinetic Measurements. Nonenzymatic hydrolysis of carbamate prodrugs was followed spectrophotometrically using a Perkin Elmer Lambda 7 spectrophotometer set up at the appropriate wavelength. Reactions were initiated by mixing 30 μL of the dry acetonitrile or dioxane solution containing carbamate into 3 mL of aqueous buffer affording initial concentrations of 10^{-4}–(5×10^{-5}) M. The cuvettes were thermostated by means of an attached water bath. Reaction solutions were made up with KCl to ionic strength 0.5 M (prodrugs **1**–**3**) or 1.0 M (prodrugs **4** and **5**). The kinetics of the disappearance of the starting prodrugs (or formation of the corresponding drugs) were cleanly first-order for between 4 and 5 half-lives of reaction. The rate constants (k_{obsd}) were obtained from the plots of $\ln(OD_t - OD_\infty)$ or $\ln(OD_\infty - OD_t)$ vs time depending on the wavelength used and/or the use of a commercially available fitting program. The half-lives ($t_{1/2}$) were obtained from the equation $k_{obsd} = 0.693/t_{1/2}$. The pH of the solution in the cell was measured before and after reaction on a Tacussel pH meter (TT processor 2) using a XCIII combination electrode with calibration against standard buffer solutions at the appropriate temperature.

Determination of prodrug half-lives in human and rat plasma was achieved by means of HPLC technique. The conversion of the prodrugs to drugs in 0.05 M phosphate buffer, pH 7.40, containing 80% plasma obtained from human subjects or rats was studied at 37 or 25 °C depending on the stability of the prodrugs. The reactions were initiated by adding 35 μL of the acetonitrile or dioxane solution containing the carbamate prodrug into 500 μL of the preequilibrated plasma solutions to give an initial concentration of about 0.04 mg/mL. At appropriate intervals, 100 μL samples were withdrawn and added to 150 μL of 0.05 M HCl methanolic solution in order to stop the reaction and deproteinize the plasma. After mixing and centrifugation, 20 μL of the clear supernatant was injected on an HPLC column and analyzed. The reversed-phase column (μBondapack C18 Waters column: 30 × 4.6 mm, particle size 10 μm) was eluted at a constant temperature of 30 °C (Four Lisa Eurosas) with a gradient mobile phase: for prodrugs **1**, 55% 0.025 M KH_2PO_4/CH_3COONa (1.1, v/v, pH 4)–45% CH_3OH to 40% 0.025 M KH_2PO_4/CH_3COONa–60% CH_3OH over 13 min, flow rate 1 mL/min; for prodrugs **2**–**5**, 88% 0.005 M Pic reagent B5 (Waters; pH 3.5)–12% CH_3CN to 55% Pic reagent B5–45% CH_3CN over 15 min, flow rate 1 mL/min. The column effluent was monitored by the means of a photodiode array detector (Waters 990) at the appropriate wavelength. These conditions allowed the separation and quantification in the increasing order of elution times of (i) acetaminophen (246 nm), chlorzoxazone (282 nm), and mutual prodrug **1m** (246 nm), respectively, from prodrugs **1** study; (ii) acetaminophen (246 nm), 6-benzoylbenzoxazolone (300 nm) or 5-benzoylbenzoxazolone (250 nm), and prodrugs **2** (246 nm) or **3** (250 nm), respectively, from prodrugs **2** and **3** studies; and (iii) acetaminophen (246 nm), amino alcohol **13b** (273 nm), 2-methoxypropylamine **16** (273 nm), mephenoxalone (273 nm), and prodrug **5** (273 nm) or compound **15** (240 nm), respectively, from prodrug **5** and compound **15** studies.

Quantitation of drugs was done from measurements of the peak area in relation to those of corresponding standards chromatographed under the same conditions. First-order rate constants were calculated from the slopes of linear plots of $\ln(C_\infty - C_t)$ vs time, where C_∞ and C_t are the drug concentrations at infinity (*i.e.*, after 8–10 half-lives) and time t, respectively, or $\ln(C_t)$ vs time, where C_t is the prodrug concentration at time t.

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Supporting Information Available: pH–rate profile data and second-order rate constant (k_{OH}) values for prodrugs **1g**,**m**, **3**, and **5** and compound **14** (2 pages). Ordering information is given on any current masthead page.

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