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α-(1*H*-Imidazol-1-yl)alkyl (IMIDA) carboxylic acid esters as prodrugs of carboxylic acid containing drugs

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Abstract—Synthesis of α-(1*H*-imidazol-1-yl)alkyl (IMIDA) carboxylic acid esters have been reported in 2–3 simple steps. α-(1*H*-Imidazol-1-yl)alkyl (IMIDA) carboxylic acid esters were found to be chemically labile and thus serve as novel prodrugs of carboxylic acids.
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The ionization and poor lipid solubility of carboxylic acid containing drugs compromises their permeability across biological membranes like skin. Prodrugs, which are biologically inactive derivatives of a drug and which hydrolyze in vivo to the pharmacologically active drug molecule, are useful in breaching biological barriers. Various prodrug ester based approaches utilizing a simple alkyl group in the ester promoiety have been used in the past to improve the lipid solubility and hence theoretically the permeability of carboxylic acids across the skin.[1,2] However it is now clear that water solubility is also important in increasing permeability.[2–7] On the other hand, it is not always possible to improve the water solubility of carboxylic acids without introducing an ionized dialkylamino$(CH_2)_n$ group (pK_a 8–10)[8–10] or polar group[3,4] in the ester promoiety, which may decrease the lipid solubility of the derivative compared to a simple alkyl ester. In order to explore the possibility of incorporating lower pK_a amines, which would be less highly ionized but still polar and more water soluble than a simple alkyl ester,[11] into the ester promoiety, we have synthesized α-(1*H*-imidazol-1-yl)alkyl (IMIDA) carboxylic acid esters and measured their hydrolysis in aqueous buffers and in vitro hairless mouse skins.

We have synthesized two types of IMIDA ester prodrugs where A, the alkyl spacer between Drug-CO_2 and N_1 in imidazole, is $–CH_2$ or $–CHCH_3$. The synthesis of α-(1*H*-imidazol-1-yl)methyl (A = $–CH_2$) carboxylic acid esters was achieved in two steps. Imidazole was first converted to 1-hydroxymethylimidazole then coupled to the parent carboxylic acid in the next step. 1-Hydroxymethylimidazole was synthesized by heating paraformaldehyde, imidazole and catalytic amounts of triethylamine at 80 °C with constant stirring for 5 min till all the solid residue had completely melted to a colorless viscous liquid. The contents in the flask were then allowed to cool to room temperature. 1-Hydroxymethylimidazole was isolated as a low melting white solid in excellent yields.[12] Previous reports on the synthesis of 1-hydroxymethylimidazole have used the reaction of formaldehyde with imidazole at 120–130 °C in a sealed tube for 15 h to give a crude mixture of products which included 1,2-(dihydroxymethyl)imidazole, 2,4,5-(trihydroxymethyl)imidazole, and 1-hydroxymethylimidazole. 1-Hydroxymethylimidazole was isolated as its picrate salt from those crude reaction mixtures in poor yields.[13] On the other hand, the present simple and regioselective route gives 1-hydroxymethylimidazole in high yields.

The parent carboxylic acid was then reacted with carbonyldiimidazole (CDI) in methylene chloride (DCM) for 4 h at room temperature and the intermediate was coupled to 1-hydroxymethylimidazole. The reaction was allowed to run overnight and the product (Table 1, **1**–**7**) isolated by either crystallization or column chromatography in good yields (Scheme 1).[14] Reaction of salicyclic acid with CDI and 1-hydroxymethylimidazole gave several products and poor yield of the desired

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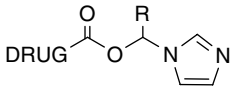
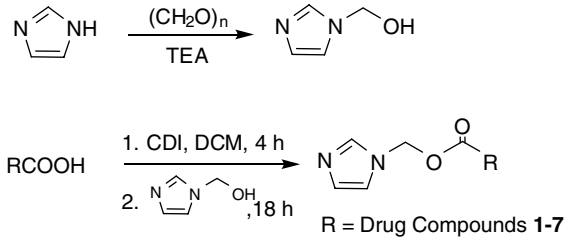
Table 1. Compounds synthesized with their respective rates of hydrolysis in pH 7.1 buffer at 39 °C



Compd	Drug	R	Yield (%)	Log k[17] (s^{-1})	$t_{1/2}$ (min)
1	Naproxen	H	94	−4.35	257.79
2	Indomethacin	H	66	−4.29	224.22
3	Salicyclic acid	H	33	—[a]	—[a]
4	Ibuprofen	H	66	—[a]	—[a]
5	Nalidixic acid	H	20	—	>24 h
6	*p*-Nitrobenzoic acid	H	80	−4.28	220.08
7	Niflumic acid	H	74	−4.43	310.87
8	Naproxen	CH_3	22	−3.79	72.59
9	Ibuprofen	CH_3	50	—[a]	—[a]

[a] Not determined.



Scheme 1.

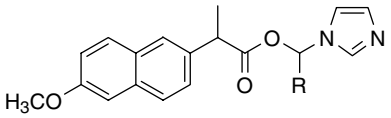
product. Reaction of 2-acetoxybenzoic acid (aspirin) with CDI and 1-hydroxymethylimidazole gave cleaner reaction mixtures and the desired product (**3**) was obtained by simple crystallization. Apparently the acetate group was deprotected in situ by the generation of imidazole which catalyzed the hydrolysis of the phenolic ester moiety.

Synthesis of α-(1*H*-imidazol-1-yl)ethyl (A = –$CHCH_3$) carboxylic acid esters (**8** and **9**) was carried out in three steps. The parent carboxylic acid was first converted to the acid chloride by reacting it with thionyl chloride. The corresponding acid chloride was next converted to α-(acyloxy)ethyl iodide by reacting it with paraldehyde, $AlCl_3$, NaI in dry methylene chloride.[15,16] The desired alkylating agent was used in the next step without any purification. Alkylation of imidazole with α-(acyloxy)-ethyl iodide in the presence of K_2CO_3 and in acetone gave the desired product in moderate yields (Scheme 2).[15]

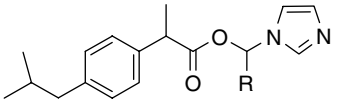
To exhibit pharmacological activity these prodrugs must hydrolyze to the parent molecule. Hydrolysis studies[17] were carried out in pH 7.1 buffers at 39 °C for **1**, **2** and **5**–**8**. The prodrugs hydrolyzed to the parent drug exhibiting pseudo unimolecular first order kinetics and $t_{1/2}$ values ranged from 72 min to greater than 24 h. The topical delivery of **1** and **7** was also investigated in in vitro diffusion cell experiments from hairless mouse skin.[18] Compound **1** hydrolyzed completely to naproxen and about 37% of **7** hydrolyzed to niflumic acid on passage of the prodrug through mouse skin.

In conclusion, a novel synthesis of 1-hydroxymethylimidazole and of IMIDA (A = –CH_2 and –$CHCH_3$) carboxylic acid esters has been reported. IMIDA esters of carboxylic acids represent novel class of carboxylic acid prodrugs which hydrolyze chemically to yield the parent carboxylic acid. Since this type of delivery system does not rely on enzymes to generate the active princi-

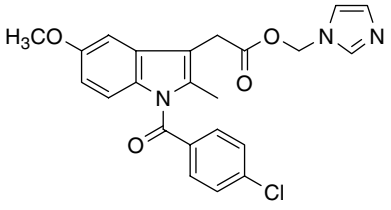
Representative prodrug structures



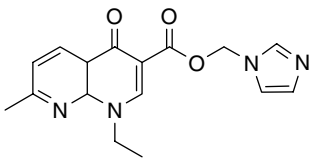
1, R = H, Naproxen prodrug
8, R = Me, Naproxen prodrug



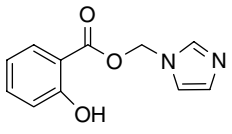
4, R = H, Ibuprofen prodrug
9, R = Me, Ibuprofen prodrug



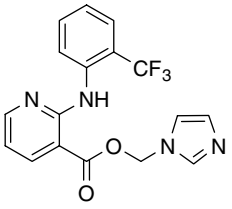
2, Indomethacin prodrug



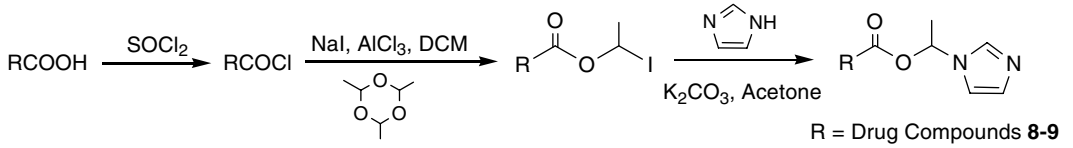
5, Nalidixic acid prodrug



3, Salicylic acid prodrug



7, Niflumic acid prodrug



Scheme 2.

ple, they are not prone to biological variability in tissues and cells which affects the therapeutic efficiency of enzyme dependent prodrugs. We are currently investigating the mechanism of hydrolysis and topical delivery of these prodrugs.

Acknowledgment

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12. *1-Hydroxymethylimidazole*: Imidazole (3 g, 44 mmol), paraformaldehyde (1.46 g, 49 mmol), and 2–3 drops of triethylamine were heated with stirring in an oil bath at 80 °C till the solid completely melted to give a viscous residue. The contents were then cooled to room temperature and allowed to solidify to a white solid. Yield = 85%, mp = 36–38 °C. ^{1}H NMR ($CDCl_3$): δ 7.37 (s, 1H), 7.06 (s, 1H), 6.91 (s, 1H), 5.4 (s, 2H).
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14. *Protocol for esterification*: To 4 mmol of carboxylic acid drug was added CDI (1,1′-carbonyldiimidazole) (1.1 equiv) in 20 ml dry DCM and the contents were stirred for 4 h. 1-Hydroxymethylimidazole (1.1 equiv) was then added and contents were stirred overnight at room temperature. The reaction was worked up by diluting the reaction mixture to 200 ml with DCM and washing quickly with 5 ml of cold 0.05 N HCl and then with 5 ml of brine. The organic layer was dried over Na_2SO_4 and concentrated to give a solid/oily residue depending on the drug being used. The crude mixture was purified by recrystallization or column chromatography. The characterization of **1** follows: recrystallization using methylene chloride–petroleum ether, yield = 94%, mp = 119–121 °C. ^{1}H NMR ($CDCl_3$): δ 7.66 (q, 3H), 7.53 (s, 1H), 7.27 (s, 1H), 7.15 (d, 1H), 7.13 (d, 1H), 7.1 (d, 1H), 7.02 (d, 1H), 5.89–5.75 (2d, 2H), 3.9 (s, 3H), 3.84 (q, 1H), 1.54 (d, 3H). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.33; H, 5.85; N, 9.03. Found: C, 69.19; H, 5.87; N, 8.85.
15. *Protocol for synthesis of* **8**: This compound was made in three steps. Naproxen was first converted to its acid chloride by reacting 2 g naproxen (1 equiv) with 2.5 ml thionyl chloride (3.5 equiv) in 10 ml benzene under reflux conditions at 80 °C for 2 h. The reaction mixture was concentrated under vacuum to give a yellow solid. Yield = 97%, ^{1}H NMR ($CDCl_3$): δ 7.75 (m, 3H), 7.34–7.36 (2d, 1H), 7.18–7.12 (3d, 2H), 4.22 (q, 1H), 3.9 (s, 3H), 1.7 (d, 3H). Naproxoyl chloride was next converted to the α-(acyloxy)ethyl iodide. NaI (1.2 equiv) and paraldehyde (3.36 equiv) were stirred at 0 °C under N_2 in dry DCM (25 ml) covered with an Al foil to which naproxoyl chloride (1 equiv), $AlCl_3$ (0.03 equiv), and I_2 (0.007 equiv) were then added. The dark orange colored reaction mixture was stirred overnight at room temperature. The suspension was filtered and the residue thoroughly washed with 50 ml DCM. The filtrate was subsequently washed with 10% sodium thiosulfate solution (10 ml) and water (3 × 5 ml). The CH_2Cl_2 solution was dried over Na_2SO_4 for an hour and filtered. The α-(acyloxy)ethyl iodide solution was concentrated using a rotavapor under vacuum at 40 °C to give an oil. Crude yield = 50%. ^{1}H NMR ($CDCl_3$): δ 7.75 (m, 3H), 7.34–7.36 (2d, 1H), 7.18–7.12 (3d, 2H), 6.8 (qq, 1H), 4.22 (q, 1H), 2.15 (2d, 3H), 3.9 (s,3H), 1.7 (d, 3H). Alkylation of imidazole with the α-(acyloxy)ethyl iodide gave **8**. Imidazole (1 equiv), K_2CO_3 (1 equiv), and alkylating agent (1 equiv) in dry acetone (25 ml) were stirred at room temperature overnight. The suspension was filtered and the filtrate was concentrated to an oil. The filtrate was washed with water (3 × 5 ml). The CH_2Cl_2 solution was dried over Na_2SO_4 for an hour and filtered. The solution was concentrated using a rotavapor under vacuum at 40 °C to give **8** as an oil. The resulting material was purified by column chromatography using 20% ethyl acetate–hexane as the eluent to an oil. Yield = 50%. ^{1}H NMR ($CDCl_3$): δ 7.9 (2d, 1H), 7.3–7.6 (m, 5H), 7–6.8 (m, 3H), 6.67 (qq, 1H), 3.99 (2s, 3H), 3.9 (2q, 1H), 1.7–1.8 (2d, 3H), 1.65 (d, 3H).
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17. The rates of hydrolysis in aqueous buffers were determined by UV spectroscopy. An aliquot (100 μl) of a stock solution of compound dissolved in acetonitrile was added to 2.9 ml of buffer in a cuvette such that the final concentration was about 10^{-5} M. Half-lives were calculated from the plot of $\log(A_\infty - A_t)$ or $\log(-(A_\infty - A_t))$ versus time.
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