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Design, synthesis, and bioavailability evaluation of coumarin-based prodrug of meptazinol

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Abstract—Based on the known coumarin-based prodrug system, a new meptazinol (*Z*)-3-[2-(propionyloxy) phenyl]-2-propenoic ester (**3**) was designed and synthesized as prodrug to minimize the first-pass effect of meptazinol (**1**) and improve the oral bioavailability. The prodrug (**3**) showed a 4-fold increase in oral bioavailability over the parent drug meptazinol in rats.

Acting as a mixed agonist/antagonist opioid analgesic, meptazinol ((±)-3-(3-ethyl-1-methyl-hexahydro-1*H*-azepin-3-yl) phenol, **1**) has been marketed by Wyeth for the treatment of moderate to severe pain since 1983[1] and included in the British Pharmacopoeia in 1998.[2] Unlike other typical opiates, meptazinol showed less respiratory depression and lower addictive potential.[3–5] However, the clinical uses of meptazinol were still restricted by its low oral bioavailability (8.69%).[6] Similar to some drugs with phenol groups, meptazinol was easily metabolized by enzymes in liver and caused serious first-pass effect. New clinical applications, pharmacophores, and analgesic mechanism of meptazinol were reported recently[7–10] both from Qiu's group and other researchers.

As part of a continuing effort in our laboratory to develop novel meptazinol prodrugs as potential therapeutic agents, Qiu and co-workers recently reported the synthesis of three benzoyl esters (**I**–**III**) as meptazinol prodrugs. Among these three esters, analogue **III** showed enhanced bioavailability presumably due to an enhanced lipophilicity and metabolic stability.[11] A coumarin-based esterase-sensitive prodrug system and its application for the preparation of prodrugs of amines and cyclic prodrugs of peptides[12–28] have been reported recently. The design utilized an esterase-triggering intramolecular lactonization of *cis*-coumarinic acid to release the parent drug and coumarin.[29–31] The major outstanding advantage of the prodrug system is that the hydrolysate coumarin has been found to be relatively nontoxic in many clinical and laboratory studies.

It was of considerable interest to apply the coumarin-based prodrug system for masking the phenol group of meptazinol (**1**) for protection against the enzyme metabolism. Among the several previously reported carboxylated phenyl propenoic acid as masked coumarin carriers, the propionyloxy group-substituted phenyl propenoic acid (**2**) was specifically chosen as our carrier molecule simply because it could be prepared mostly efficiently among all the known acetyl, *iso*-propionyl, and *tert*-butyryl coumarin carriers as described in the literature[13] and the corresponding results of esterase kinetics indicated that variations of the steric bulkiness of the acyl group did not significantly affect the rate of the release of the parent drug. Therefore, we designed and synthesized meptazinol (*Z*)-3-[2-(propionyloxy)phenyl]-2-propenoic ester (**3**) as a potential prodrug to explore this potential. Coumarin was converted into (*Z*)-3-[2-(propionyloxy)phenyl]-2-propenoic acid (**2**) in six steps using a modification of literature procedures[13] with the total productivity of 20.4% (Fig. 1). The spectrum of (**2**) has confirmed a *Z*-configuration of double bond based on a *J* value of 12.2 Hz,[32] which matched well with the data reported in Ref. 13.

Coupling of meptazinol (**1**) with (*Z*)-3-[2-(propionyloxy)phenyl]-2-propenoic acid (**2**) was accomplished in the presence of 1,3-dicyclohexyl carbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to give the

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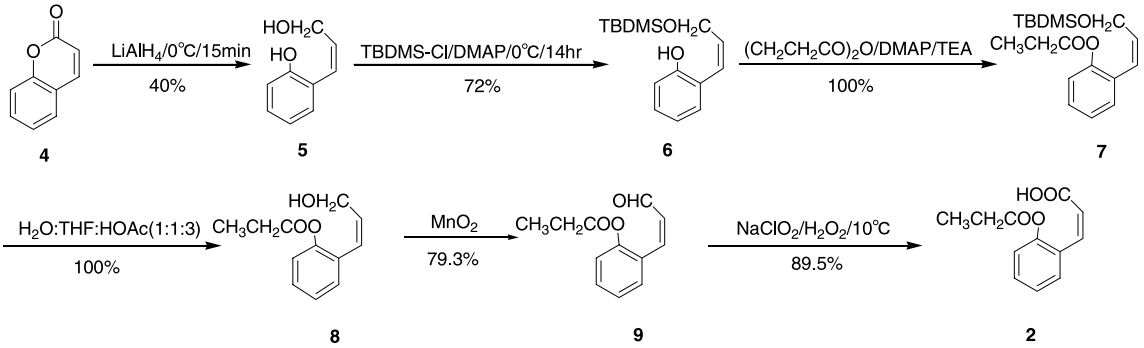

Figure 1. Synthesis of the carrier molecule (**2**). TBDMS, *tert*-butyldimethyl silyl; DMAP, 4-dimethylaminopyridine.

phenol ester (**3**) in 69% yield.[33] The synthetic route is outlined below (Fig. 2). The structures of the base and hydrochloride of this prodrug were determined by NMR, IR, and HR-ESI.[34]

As suggested by Franklin et al.[35] a good correlation was observed between meptazinol's analgesic potency and its plasma concentration. Thus in our hand, oral bioavailability, which in turn indicated the bioactivity, of the prodrug and of the parent drug was measured in rats, respectively.

The bioavailability evaluation was designed as a three-way cross-over study. Six rats were divided into three groups randomly and evenly. During each period, there is a 7 days' wash-out time. The routes of administration in each period for each rat were listed in Table 1.

As known to us, the prodrug can be hydrolyzed to meptazinol by the plasma esterase in vitro after the blood sample is collected, which can result in the concentration of meptazinol determined to be higher than the actual concentration. To prevent the above case occurring, the esterase inhibitor $Na_2S_2O_5$ was quantitatively added to the plasma sample immediately after blood sample was collected and centrifuged.[36] The HPLC system was optimized on Frost.[37]

Listed in Table 2 are the area under curve (AUC) and absolute bioavailability (F%) of meptazinol via intravenous (iv) versus intragastric (ig) administration as well as that of the meptazinol prodrug via ig administration. The corresponding mean plasma meptazinol concentration–time curves are shown in Figure 3.

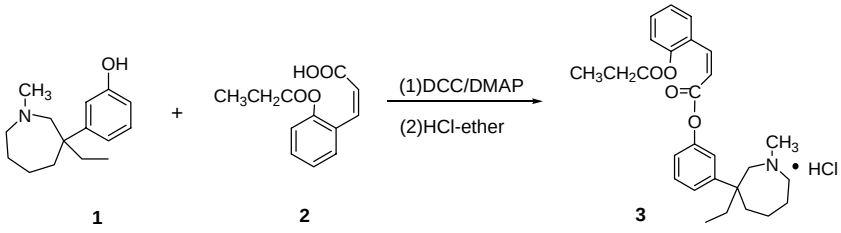

Figure 2. Synthetic route of the meptazinol prodrug (**3**).

Table 1. The routes of administration in each period for each rat

No	1	2	3	4	5	6
Period I	A	A	B	B	C	C
Period II	B	B	C	C	A	A
Period III	C	C	A	A	B	B

A, iv 29.7 μmol/kg meptazinol; B, ig 92.8 μmol/kg meptazinol; C, ig 92.8 μmol/kg prodrug.

Table 2. AUC and absolute bioavailability of meptazinol and prodrug

(n = 6)	Meptazinol (iv) 29.7 μmol/kg		Meptazinol (ig) 92.8 μmol/kg		Prodrug (ig) 92.8 μmol/kg	
	Mean	SD	Mean	SD	Mean	SD
$AUC_{0\rightarrow10}$ (ng h/ml)	1985.53	533.82	712.63	118.69	2631.78	1385.30
F%[a]			12.12	3.57	51.75	32.99

[a] $F\% = (AUC_{0\rightarrow10\ (ig)}/92.8)/(AUC_{0\rightarrow10\ (iv)}/29.7)$.

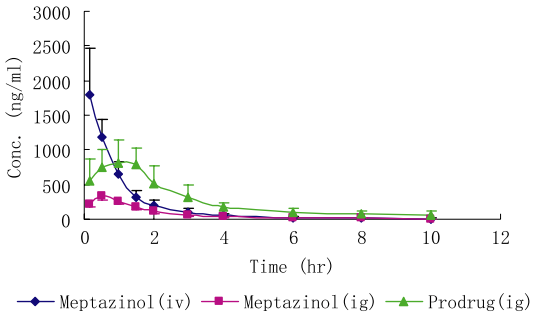

Figure 3. Mean plasma meptazinol concentration–time curves after iv and ig administration of meptazinol and ig administration of prodrug in rats.

The absolute bioavailability of meptazinol prodrug (**3**) via ig administration was 51.75% ± 32.99% ($n = 6$). This indicated a more than 4-fold increase over the value obtained for meptazinol, 12.12% ± 3.57%. Based on the two sides t-test ($P < 0.01$), differences in the values of $AUC_{0\rightarrow10}$ and F% between the two groups suggested great statistical significance.

propionyloxy)phenyl]-2-propenoic meptazinol ester hydrochloride (**3**), was designed and synthesized to minimize the first-pass effect of meptazinol and enhance the oral bioavailability. Biological evaluation data indicated that there was a 4-fold increase in oral bioavailability of this prodrug compared to the parent drug meptazinol. This coumarin-based prodrug showed a superior oral bioavailability to the earlier reported meptazinol benzoyl esters.[11] These results highlight the potential of using coumarin-based esterase-sensitive system as a prodrug template for other drug molecules besides meptazinol.

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32. Spectral data of the carrier molecule (**2**): ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1H), 7.36 (t, 1H), 7.22 (t, 1H), 7.08 (d, 1H), 7.00 (d, 1H, $J = 12.2$ Hz), 6.05 (d, 1H, $J = 12.2$ Hz), 2.58 (q, 2H, $J = 7.6$ Hz), 1.25 (t, 3H, $J = 7.6$ Hz).
33. Synthesis of (*Z*)-3-[2-(propionyloxy)phenyl]-2-propenoic meptazinol ester hydrochloride (**3**). A solution of **2** (0.73 g, 3.32 mmol) in dry CH_2Cl_2 (15 ml) was added DCC (0.75 g, 3.64 mmol) at 0 °C. After stirring for 10 min, this was followed by the addition of **1** (0.70 g, 3.00 mmol) in dry CH_2Cl_2 (40 ml) and DMAP (0.07 g, 0.57 mmol). After stirring at 0 °C for 2 h and at room temperature for 4 h, the solution was cooled below −20 °C for 30 min and filtered. The filtrate was acidified to pH 7.0 using 2.5% acetic acid, then extracted with CH_2Cl_2 (5 ml). The combined organic layer was dried over $MgSO_4$ and evaporated to give a brown oil (1.54 g). The oil was chromatographed on a silica gel column to afford the prodrug base as a yellow oil (0.90 g, 68.9%). To a solution of the base (0.02 g) in dry ether (4 ml) was added HCl–ether (0.3 ml) to modulate pH to 4. The solution was concentrated and dried at room temperature to afford hydrochloride **3** as a yellow solid (0.02 g, 92.3%).
34. Spectral data of the prodrug base and its hydrochloride (**3**): Spectral data of the prodrug base: ^{1}H NMR ($CDCl_3$)

δ 7.60 (dd, 1H, J_1 = 7.53 Hz, J_2 = 1.37 Hz), 7.34 (dt, 1H, J_1 = 7.53 Hz, J_2 = 1.37 Hz), 7.27 (m, 1H), 7.22 (dt, 1H, J_1 = 7.52 Hz, J_2 = 1.02 Hz), 7.14 (m, 1H), 7.10 (dd, 1H, J_1 = 8.20 Hz, J_2 = 1.02 Hz), 7.07 (d, 1H, J = 12.3 Hz, *cis*- = CH × 1), 6.94–6.90 (m, 2H), 6.22 (d, 1H, J = 12.3 Hz, *cis*- = CH × 1), 2.90 (m, 1H, NCH_2), 2.72–2.65 (m, 2H, NCH_2), 2.60 (q, 2H, J = 7.52 Hz, $COCH_2CH_3$), 2.54–2.48 (m, 1H, NCH_2), 2.44 (s, 3H, N-CH_3), 2.13–1.52 (m, 8H, CH_2 × 4), 1.28 (t, 3H, J = 7.52 Hz, $COCH_2CH_3$), 0.60 (t, 3H, J = 7.52 Hz, CH_2CH_3). Spectral data of the prodrug hydrochloride (**3**): ^{1}H NMR (DMSO-d_6): δ 10.18 (br s, ≈1/2 H, N^+–H, D_2O exchange), 8.63 (br s, ≈1/2 H, N^+–H, D_2O exchange), 7.60 (t, 1H, J = 7.42 Hz, Ar-H), 7.45–7.38 (m, 2H, Ar-H × 2), 7.31–7.00 (m, 6H, Ar-H × 5, *cis*- = CH × 1), 6.32 (dd, H, J_1 = 4.3 Hz, J_2 = 12.1 Hz; *cis*- = CH × 1), 3.94–3.09 (m, 4H, $NHCH_2$ × 2), 2.82 (m, 3H, N-CH_3), 2.59 (q, 2H, J = 7.42 Hz, $COCH_2CH_3$), 2.83–1.40 (m, 8H, CH_2 × 4), 1.13 (t, 3H, J = 7.42 Hz, $COCH_2CH_3$), 0.49 (m, 3H, CH_2CH_3). ^{13}C NMR (DMSO-d_6): δ 171.2 (C═O), 162.8 (C═O), 149.6, 147.3, 144.8, 143.3, 138.4, 129.5, 128.9, 127.4, 124.9, 123.7 & 123.3, 121.9, 120.8, 119.7, 119.3, 66.0 & 62.8, 59.3 & 57.7, 47.1 & 46.3, 44.2 & 43.8, 36.0 & 35.3, 33.5 & 33.0, 26.9, 26.4 & 24.8, 20.7, 9.1, 8.3. HR-ESI $[M+1]^+$ calcd for $C_{27}H_{34}NO_4$ 436.24823, found 436.24848. FT-IR: 3404 (γ_{N+H}), 2937, 1758 ($\gamma_{C=O}$), 1606 (γ_{phenyl}), 1458, 1131 (γ_{C-O-C}), 950, 761,702.

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