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Synthesis and Properties of 5-Aminosalicyl-taurine as a Colon-specific Prodrug of 5-Aminosalicylic Acid

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5-Aminosalicylic acid (5-ASA) is an active ingredient of therapeutic agents used for Crohn's disease and ulcerative colitis. Because it is absorbed rapidly and extensively in the upper intestine, delivery of the agent specifically to the colon is necessary. We selected taurine as a colon-specific promoiety and designed 5-aminosalicyltaurine (5-ASA-Tau) as a new colon-specific prodrug of 5-aminosalicylic acid (5-ASA). It was expected that introduction of taurine would restrict the absorption of the prodrug and show additive effect to the anti-inflammatory action of 5-ASA after hydrolysis. 5-ASA-Tau was prepared in good yield by a simple synthetic route. The apparent partition coefficient of 5-ASA-Tau in 1-octanol/pH 6.8 phosphate buffer or $CHCl_3$/pH 6.8 phosphate buffer was 0.10 or 0.18, respectively, at 37°C. To determine the chemical and biochemical stability in the upper intestinal environment, 5-ASA-Tau was incubated in pH 1.2 and 6.8 buffer solutions, and with the homogenates of tissue and contents of stomach or small intestine of rats at 37°C. 5-ASA was not detected from any of the incubation medium with no change in the concentration of 5-ASA-Tau. On incubation of 5-ASA-Tau with the cecal and colonic contents of rats, the fraction of the dose released as 5-ASA was 45% and 20%, respectively, in 8 h. Considering low partition coefficient and stability in the upper intestine, 5-ASA-Tau might be nonabsorbable and stable in the upper intestine. After oral administration, it would be delivered to the colon in intact form and release 5-ASA and taurine. These results suggested 5-ASA-Tau as a promising colon-specific prodrug of 5-ASA.

Key words: 5-Aminosalicyltaurine, Colon-specific prodrug of 5-aminosalicylic acid, Inflammatory bowel disease, Colon-targeting

INTRODUCTION

Colon-specific delivery of orally administered drug is directed mainly to achieve efficient treatment of disease which develop at the colonic site and reduce side effect by restricting systemic absorption (Wilding *et al.*, 1994). The colon could also be utilized as the site of absorption for those drugs that are unstable in the upper intestine such as therapeutic peptides and proteins (Saffran *et al.*, 1986; 1992; Davis, 1990). Colonic targeting may be applicable to delay absorption to achieve desirable time-concentration for the treatment of disease such as asthma, gastric ulcer, or arthritis, which often has peak symptoms at bedtime.

5-ASA is an active ingredient of agents used for the long-term maintenance therapy to prevent relapses of Crohn's disease and ulcerative colitis (Podolsky, 1991; Crotty *et al.*, 1992). 5-ASA is absorbed rapidly and extensively in the upper intestine by the paracellular or carrier-mediated mechanism (Zhou *et al.*, 1999). Delivery of 5-ASA specifically to the colon is necessary to reduce side effect (Novis *et al.*,1988) and achieve efficient treatment of inflammatory bowl disease (IBD). Several prodrugs have been developed aiming at the delivery of 5-ASA specifically to the colon. (Brown *et al.* 1983; Kopeckova and Kopecek, 1990; Istran *et al.*, 1991). A colon-specific prodrug should be stable and non-absorbable in the upper intestine so that it could be delivered to the colon in intact form, and the linkage between drug and promoiety should be dissociated in the colon to liberate the active drug. In addition, the promoiety should not carry any adverse effect as exhibited in sulfasalazine, which is one of the most commonly prescribed colon-specific prodrug of 5-ASA. Previously, we adopted an amino acid as a colon-specific promoiety

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of 5-ASA based on the information that *N*-acyl amide bond derived from an aromatic carboxylic acid and an amino acid is stable in the upper intestine and hydrolyze by the amidase originated from microbes in the colon (Scheline, 1973). 5-ASA-amino acid conjugate should be free from adverse effects originated from the promoiety, because it is a natural amino acid. We prepared 5-aminosalicyl glycine (5-ASA-Gly) and 5-aminosalicyl-L-aspartic acid (5-ASA-Asp) and evaluated their *in vitro/in vivo* properties (Jung *et al.*, 2000; 2001). Amide bond of these compounds was stable in the upper intestinal environment and hydrolyzed when they were incubated with the cecal and colonic contents of rats. After oral administration of 5-ASA-Gly or 5-ASA-Asp, most of the prodrug was delivered to the large intestine and hydrolysed to release 5-ASA. The extend of prodrug conversion was affected by the nature of the amino acid. In the present study, we adopted taurine as a colon-specific promoiety expecting that introduction of taurine would increase the hydrophilicity and restrict the absorption of the prodrug. Considering that aminoalkylsulfonic acid is an isostere of an amino acid, it is expected that amide bond between taurine (2-aminoethanesulfonic acid) and 5-ASA would be stable in the upper intestine and dissociate by the enzymes of microbes in the colon to release 5-ASA and taurine. Because taurine is known to protect tissues from the damage in a variety of modes that share inflammation as a common pathogenic feature (Son *et al.*, 1998; Schuller-Levis *et al.*, 1994), we expect that the released taurine might exert additive effect to the anti-inflammatory action of 5-ASA. A simple synthetic route to prepare 5-ASA-Tau in good yield is introduced and *in vitro* properties desirable for a colon-specific prodrug were evaluated. In addition, the structural effect on the hydrolysis of *N*-aromatic acyl amide bond by the rat cecal contents was investigated when amino acid was substituted with aminoalkylsulfonic acid.

MATERIALS AND METHODS

Materials

5-Nitrosalicylic acid (5-NSA), 1,1'-carbonyldiimidazole (CDI) and 10% Pd/C, *N*-benzoylglycine, taurine and aminomethansulfonic acid were purchased from Sigma Chemical Co. (St. Louis, MO, USA) and *N*-benzoyl-β-alanine was received from Tokyo Kasei (Tokyo, Japan). They were used as received. Solvents for NMR and HPLC were obtained from Merck Inc (Damstadt, Germany). All other chemicals were reagent grade, commercially available products. IR spectra were recorded on a Bomem MB 100 FT-IR spectrophotometer (Bomem). ^{1}H-NMR spectra were taken on a Varian AS 500 spectrometer and the chemical shifts are in ppm downfield from tetramethylsilane. Elemental analysis was carried out by an Elemental Analyzer System (Profile HV-3). Melting points were taken on a Mel Tem II (Laboratory Devices, Holliston, MA, USA) and were uncorrected. A Parr 4562 pressure reactor (Parr Instrument Company, Moline, IL, USA) was used for catalytic hydrogenation. A Polytron PT 3100 homogenizer, an Eppendorf Centrifuge 5415C (Hamburg, Germany) and a Taitec microincubator M-36 (Japan) were used for the homogenization, centrifugation and incubation, respectively. TLCs were performed on Merck Kieselgel 60 F_{254}, and RP-8 F_{254s}. Open column chromatography was performed on Merck silica gel (70-230 mesh) column. The HPLC system consisted of Model 305, 306 pumps, a 117 variable UV detector, a Model 234 autoinjector, a Model 805 manometric module, and a Model 811C dynamic mixer from Gilson (Middleton, WI, USA).

Calibration of 5-ASA and 5-ASA-Tau in various biological specimens

Standard solutions of 5-ASA and 5-ASA-Tau in concentration of 0.5, 2.5, 5.0, or 10.0 ppm in various biological specimens were prepared by the processes reported previously (Jung *et al.*, 2000). Standard or blank solution (1 mL) was mixed on a vortex mixer for 2 min, centrifuged at 10,000 g for 5 min and filtered through a membrane filter (0.45 μm). The filtrate (20 μL) was injected on a LiChrospher RP-18 (250×4.6 mm, 5 μm) and eluted with the mobile phase at a flow rate of 0.7 mL/min and at a pressure of about 2000 psi. The mobile phase consisted of 25% methanol in 5 mM phosphate buffer (pH 6.0) containing 0.5 mM tetrabutylammonium chloride, which was filtered through 0.45 μm membrane filter before use. The eluate was monitored at 254 nm by an UV detector measuring the absorption with a sensitivity of AUFS 0.01. The Gilson 712 software was used for the data analysis. The retention time of 5-ASA or 5-ASA-Tau was 5.7 min or 8.2 min respectively. Calibration curves for 5-ASA and 5-ASA-Tau were constructed from the data of HPLC.

Preparation of 5-ASA-Tau

5-NSA (0.9 g, 5.0 mmol) was dissolved in 20 mL of dimethylformamide and added CDI (0.9 g, 5.5 mmol) in portions with stirring at 0°C for 1 h. The reaction mixture was added to a suspension of taurine (1.2 g, 9.8 mmol) and triethylamine (2.6 mL, 20 mmol) in 3 mL of distilled water and stirred mechanically for 24 h. The reaction mixture was filtered and the solvent was removed by flash evaporation. The residue (0.97 g) was loaded on a silica gel open column, eluted with $CHCl_3$/MeOH (6/4) and 5-nitrosalicyltaurine (5-NSA-Tau) was obtained (Mp: 177.2-179.5). 5-NSA-Tau (0.75 g, 2.6 mmol) dissolved in 20 mL of methanol and 200 mg of 10% Pd/C was placed in a Parr pressure reactor and hydrogenated at 50 psi for 1 h. The reaction mixture was filtered and the solvent was

removed by flash evaporation. The residue was added to excess ether and 5-ASA-Tau was obtained as precipitates (yield: 74%). mp 269-271°C (decomp.); IR (nujol) 1653 (C=O), 1166 (S=O), 1038 (S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.2 (t, 3H), 3.8 (t, 2H), 6.87.2 (m, 3H); Anal. Calcd for $C_9H_{12}N_2SO_5$: C, 41.54: H, 4.61; N, 10.77; S, 12.31. Found: C, 41.04; H, 4.98; N, 10.26; S, 12.72.

Preparation of *N*-benzoyltaurine

To the solution of 2-aminoethansulfonic acid (1.31 g, 10.5 mmol) in 10 mL of 1*N*-sodium hydroxide, was added benzoyl chloride (1.4 g, 10.0 mmol) and 3*N*-sodium hydroxide separately at such a rate that the solution is always slightly alkaline while stirring and cooling below 30 °C. After the addition was completed, the mixture was stirred for 2 h. It was then poured into a 100 mL beaker containing 3 mL of concentrated hydrochloric acid. The resulting precipitates were collected by suction filtration, washed with cold water, dried and recrystallized from ethanol-water. mp 251.3-253.8°C; IR (nujol) 1193, 1051 (S=O, symmetric, asymmetric), 1640 (amide I: C=O), 1537 (amide II: N-H), 1307 (amide III: C-N) cm^{-1}; ^{1}H-NMR (D_2O) δ 3.08 (t, 2H), 3.64 (t, 2H), 7.39 (t, 2H), 7.48 (t, 1H), 7.61 (d, 2H); Anal. Calcd for $C_9H_{11}SO_4N$: C, 47.12; H, 4.80; N, 6.11; S, 13.99. Found: C, 47.53; H, 4.62; N; 5.81; S, 13.64.

Preparation of *N*-benzoylaminomethanesulfonic acid

N-benzoylaminomethanesulfonic acid was prepared from benzoyl chloride and aminomethanesulfonic acid according to the procedure in the previous section. mp 260-305°C (decomp.); IR (nujol) 1187, 1047 (S=O, symmetric, asymmetric), 1649 (amide I: C=O), 1547 (amide II: N-H), 1297 (amide III: C-N) cm^{-1}; ^{1}H-NMR (D_2O) δ 4.49 (s, 2H), 7.42 (t, 2H), 7.53 (t, 1H), 7.70 (d, 2H); Anal. Calcd for $C_8H_9SO_4N$: C, 44.60; H, 4.18; N, 6.50; S, 14.90. Found: C, 44.78; H, 4.53; N, 6.87; S, 14.34.

Apparent partition coefficient

To a solution of 5-ASA-Tau (10 mL, 100 μg equivalent of 5-ASA/mL) in pH 6.8 isotonic phosphate buffer, was added 10 mL of 1-octanol or chloroform presaturated with pH 6.8 isotonic phosphate buffer. The mixture was shaken for 1 h and left for 3 h at 37°C. Concentration of 5-ASA-Tau in the aqueous phase was analyzed by HPLC as described previously. The apparent partition coefficients were calculated by employing the equation $(C_o\text{-}C_w)/C_w$, where C_o and C_w represent the initial and equilibrium concentration of the drug in aqueous phase, respectively.

pH stability

A Solution of 5-ASA-Tau (100 μg equivalent of 5-ASA/mL) in pH 1.2 hydrochloric acid buffer or in pH 6.8 phosphate buffer was incubated at 37°C for 10 h. At a predetermined time interval, a 20 μL portion of the solution was removed and the concentration of 5-ASA-Tau and 5-ASA was analyzed by HPLC as described previously.

Release of 5-ASA after incubation of 5-ASA-Tau with the homogenate of tissue and contents of stomach or small intestine of rats

A male Sprague-Dawley rat (200-250 g) was anesthetized by diethyl ether and a midline incision was made. Sections of stomach and small intestine were collected separately, homogenized and diluted to half concentration with isotonic acetate buffer (pH 4.5) for stomach and with isotonic phosphate buffer (pH 6.8) for small intestine. To each microtube, 0.8 mL of 5-ASA-Tau solution in pH 6.8 isotonic phosphate buffer (140 μg equivalent of 5-ASA/0.8 ml) and 0.2 g of the above homogenate were added, mixed and incubated under nitrogen at 37°C. At an appropriate time interval, a sample was taken out, centrifuged at 5,000 rpm for 3 min. Methanol (0.9 mL) was added to the supernatant (0.1 mL) to precipitate the protein, vortexed for 2 min and centrifuged for 5 min at 10,000×g. The amount of 5-ASA in a 20 μL portion of the supernatant was determined by HPLC as described previously.

Release of 5-ASA after incubation of 5-ASA-Tau with the cecal and colonic contents of rats

The cecal or colonic segment of the intestine was cut open and the contents were collected in a glove box, which was previously displaced by nitrogen. 5-ASA-Tau solution (140 μg equivalent of 5-ASA/0.9 mL) in pH 6.8 isotonic phosphate buffer (0.9 mL) and the gut contents (0.1 g) were placed in a microtube and incubated at 37°C. At an appropriate time interval, the amount of 5-ASA in the medium was determined by the same protocol as described in the previous section.

RESULTS AND DISCUSSION

Selection of an appropriate promoiety is a crucial step for the design of a colon-specific prodrug. A colon-specific promoiety should be able to impose such characteristics on a drug molecule that would limit the absorption in the upper intestine. It should be able to form chemical bonding with the drug molecule which would be stable in the upper intestine but dissociate in the large intestine. The promoiety should not hold any adverse biological effect. It should be of great value if some beneficial effect can be expected from the promoiety. Taurine is a free amino acid not incorporated into protein. It protects tissues from the damage in a variety of models that share inflammation as a common pathogenic feature. This has been well-docu-

mented in animal models of lung injury and chemically-induced inflammatory bowel disease (Gurujeyalakshmi *et al.*, 2000; Son *et al.*, 1998; Schuller-Levis *et al.*, 1994). Based on this information, we adopted taurine as a promoiety and designed 5-aminosalicyltaurine (5-ASA-Tau) as a colon-specific prodrug of 5-ASA. Introduction of taurine would enhance hydrophilicity of the compound and restrict the absorption. The amide bond is expected to be stable in the upper intestine to deliver the prodrug to the colon, where it would dissociate by the amidase of the microbial origin to release 5-ASA and taurine. The released taurine might exert additive effect to the anti-inflammatory action of 5-ASA.

Preparation of 5-aminosalicyltaurine (5-ASA-Tau)

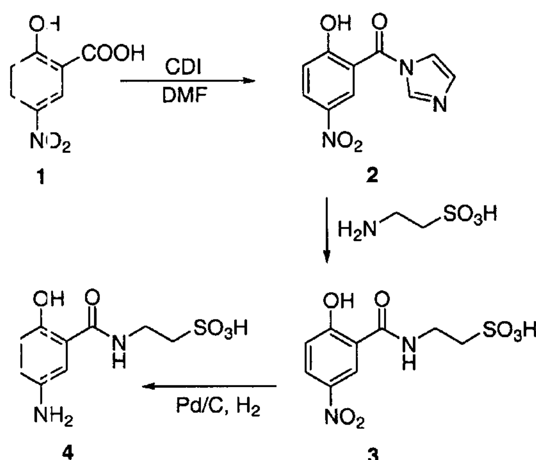
Synthesis of 5-ASA-Tau was achieved in two steps as shown in Scheme 1. 5-NSA was activated with CDI and reacted with taurine in the presence of triethylamine as catalyst to produce 5-NSA-Tau. 5-ASA-Tau was obtained by hydrogenation of 5-NSA-Tau in the presence of 10% Pd/C. The overall yield was 40-50% and reaction processes were relatively simple. Structure of 5-ASA-Tau was confirmed from the spectral data of IR and ^{1}H-NMR and results from the elemental analysis.

Preparation of *N*-benzoylaminoalkylsulfonic acid

N-Benzoyltaurine and *N*-benzoylaminomethanesulfonic acid were prepared adopting Schotten-Baumann technique. Structure of 5-ASA-Tau was confirmed from the spectral data of IR and ^{1}H-NMR and results from the elemental analysis.

Chemical stability and apparent partition coefficient

5-ASA-Tau was incubated in pH 1.2 or pH 6.8 buffer solution which represented pH of the stomach or small intestine, respectively. Neither the concentration of 5-ASA-Tau changed nor 5-ASA was detected during 10 h incubation period at 37. Apparent partition coefficient of 5-ASA-Tau in 1-octanol/phosphate buffer (pH 6.8) and $CHCl_3$/phosphate buffer (pH 6.8) at 37°C was 0.10 and 0.18, respectively. These results indicated that 5-ASA-Tau might be chemically stable during the transit through the upper intestine and absorption of 5-ASA-Tau by way of transcellular passive diffusion might be limited due to the low partition coefficient after oral administration of 5-ASA-Tau.



Scheme 1 Synthesis of 5-aminosalicyl-taurine

Incubation of 5-ASA-Tau with homogenates of various segments of gastrointestinal tract of rats

5-ASA-Tau was incubated with various segments of GI tract of rats at 37°C and the release profiles of 5-ASA were determined. On incubation with the homogenate of tissue and contents of stomach or small intestine, neither the concentration of 5-ASA-Tau changed nor 5-ASA was detected from the incubation medium, which indicated that the amide bond of the prodrug was stable against hydrolysis in the upper intestine. When 5-ASA-Tau was incubated with the cecal and colonic contents, hydrolysis of 5-ASA-Tau took place steadily until 8 h, when the fraction of the dose released as 5-ASA was 45% and 20%, respectively, in 8 h. The results are shown in Fig. 1.

Prodrug activation took place most readily in the rat cecum where the bacterial counts are high as in the human colon. Previously, we observed that the degree of prodrug conversion by the rat cecal contents was greatly

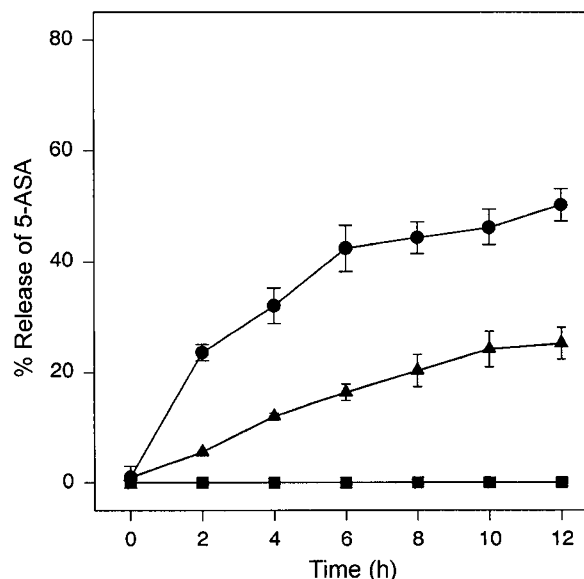


Fig. 1. Release profiles of 5-ASA during incubation of 5-ASA-Tau (equiv. to 140 μg of 5-ASA) with 1.0 mL of ten-fold dilution of ●; cecal contents, ▲ ; colonic contents, ■ ; stomach or small intestinal tissue/ contents of rats in pH 6.8 isotonic phosphate buffer at 37°C. Data are mean±S.E. (n=5).

affected by the nature of the amino acid. The extend of prodrug conversion by the rat cecal contents for 5-ASA-Gly, 5-ASA-Asp and 5-ASA-Tau decreases by substituting the amino acid from glycine to taurine and aspartic acid (Fig. 2).

Structurally, sulfonic acid moiety can be considered as an isostere of carboxylic acid group. We studied the

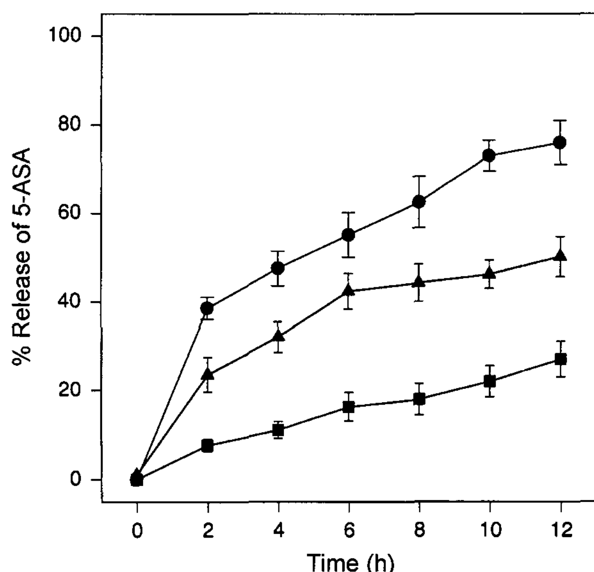


Fig. 2. Release profiles of 5-ASA during incubation of ●; 5-ASA-Gly, ▲; 5-ASA-Tau, ■ ; 5-ASA-Asp (equiv. to 140 μg of 5-ASA) in 1.0 mL of ten-fold dilution of cecal contents of rats in isotonic phosphate buffer (pH 6.8) at 37°C. Data are mean±S.E. (n=5).

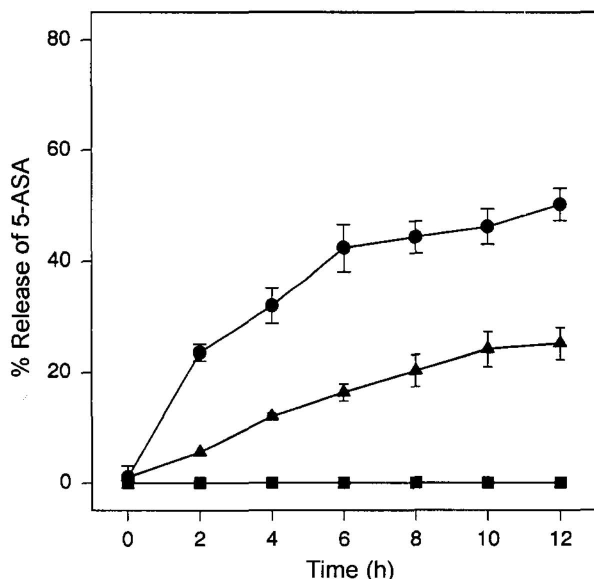


Fig. 3. Release profiles of benzoic acid during incubation of ●; *N*-benzoyl-glycine, ▼ ; *N*-benzoyl-taurine ▲ ; *N*-benzoyl-β-alanine, ■ ; *N*-benzoyl-aminomethanesulfonic acid (100 μg) in 1.0 mL of ten-fold dilution of cecal contents of rats in isotonic phosphate buffer (pH 6.8) at 37°C. Data are mean±S.E. (n=5).

structural effect on the hydrolysis of *N*-aromatic acyl amide bond by the rat cecal contents when amino acid was substituted with aminoalkylsulfonic acid. We incubated *N*-benzoylaminomethanesulfonic acid, *N*-benzoyl-2-aminoethanesulfonic acid (*N*-benzoyltaurine), *N*-benzoylglycine and *N*-benzoylalanine with the cecal contents of rats. The hydrolysis profiles are shown in Fig. 3.

N-Benzoylglycine and *N*-benzoyltaurine hydrolyzed to the extent of 94% and 85% of the dose, respectively, in 16 h. On the contrary, *N*-benzoylaminomethanesulfonic acid (a sulfonic acid analog of *N*-benzoylglycine) and *N*-benzoylalanine (a carboxylic acid analog of *N*-benzoyltaurine) did not hydrolyze appreciably. These results indicated that hydrolysis of *N*-acyl amide bond derived from an aromatic carboxylic acid and an amino acid by the rat cecal contents is mostly confined to the one which originated from natural amino acids or metabolites.

CONCLUSION

5-ASA-Tau was prepared in good yield by a simple synthetic route. Apparent partition coefficient was 0.10 in 1-octanol/pH 6.8 phosphate buffer at 37°C. It was stable on incubation with buffer solutions (pH 1.2 and pH 6.8) and the homogenate of the tissue and contents of the stomach and small intestine. On incubation with the cecal contents, the fraction of dose released as 5-ASA was 54% in 8 h. Considering these characteristics, 5-ASA-Tau might be nonabsorbable and stable in the upper intestine and delivered to the colon in intact form and release 5-ASA and taurine. The released taurine might exert additive effect to the anti-inflammatory action of 5-ASA. These results suggest 5-ASA-Tau as a promising colon-specific prodrug of 5-ASA.

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