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Design, synthesis, and evaluation of L-cystine diamides as L-cystine crystallization inhibitors for cystinuria

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ABSTRACT

To overcome the chemical and metabolic stability issues of L-cystine dimethyl ester (CDME) and L-cystine methyl ester (CME), a series of L-cystine diamides with or without N^{α}-methylation was designed, synthesized, and evaluated for their inhibitory activity of L-cystine crystallization. L-Cystine diamides **2a**–**i** without N^{α}-methylation were found to be potent inhibitors of L-cystine crystallization while N^{α}-methylation of L-cystine diamides resulted in derivatives **3b**–**i** devoid of any inhibitory activity of L-cystine crystallization. Computational modeling indicates that N^{α}-methylation leads to significant decrease in binding of the L-cystine diamides to L-cystine crystal surface. Among the L-cystine diamides **2a**–**i**, L-cystine bismorpholide (CDMOR, LH707, **2g**) and L-cystine bis(*N*′-methylpiperazide) (CDNMP, LH708, **2h**) are the most potent inhibitors of L-cystine crystallization.

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Cystinuria is an inherited disease caused by a defect in the reabsorption of cystine and dibasic amino acids in the renal proximal tubule.[1–3] The transporter responsible for the reabsorption is a heterodimer consisting of rBAT and $b^{0,+}$ AT subunits. Mutations in either of the two subunits can result in abnormal transport of L-cystine and other dibasic amino acids from the luminal fluid of the renal proximal tubule and intestines, leading to elevated concentrations of these amino acids in the urine of affected individuals causing cystinuria.[4] While dibasic amino acids such as lysine, ornithine, and arginine are completely soluble in urine, L-cystine has limited aqueous solubility, leading to its crystallization in urine and formation of L-cystine stones in the patient's kidney, ureter, and bladder. Even though the incidence of L-cystine stones is much lower than that of calcium oxalate stones, L-cystine stones are larger, occur at a young age, recur more frequently, and are more likely to cause chronic kidney disease.[5]

Clinical treatment of cystinuria has not changed over the last 30 years. Current approaches are aimed at reducing the concentration of free L-cystine in urine and increasing its solubility.[6] A high fluid intake of around 4–5 L a day and urine alkalinization with citrate or bicarbonate salts can suppress but may not completely prevent stone formation. For severe cases, drug therapy can be used, utilizing the chemical reaction of D-penicillamine or α-mercaptopropionylglycine with L-cystine to generate more soluble mixed disulfides.[5,7] These drugs have side effects including loss of taste, fever, proteinuria, serum sickness-type reactions, and even frank nephritic syndrome.[7]

Following a study by Ward and co-workers that L-cystine dimethyl ester (CDME) and L-cystine methyl ester (CME), can bind to L-cystine crystal surfaces, acting as molecular imposters to slow down the crystallization of L-cystine,[8] we recently reported the discovery of two novel L-cystine diamides that have been shown to be more effective than CDME as tailored L-cystine crystal growth inhibitors and with significantly better stability and *in vivo* activity profile.[9] Herein, we present the design, synthesis, and evaluation of a small focused library of L-cystine diamides for the initial structure-activity relationship study that led to the discovery of the two potent inhibitors of L-cystine crystallization.

Design principle

CDME (**1**) is a dimethyl ester. Esters are known to be unstable *in vivo* and susceptible to esterase-mediated hydrolysis. For this reason, esters are commonly used prodrug forms and are readily converted *in vivo* to their precursor carboxylic acids.[10,11] Upon

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hydrolysis, CDME would be converted to L-cystine, the amino acid that is already in high concentration and causes stone formation in cystinuria patients. These concerns about CDME (**1**) prompted us to design the more stable amide derivatives of L-cystine.

As shown in Fig. 1, a series of amide modification on the two α-carboxylates of L-cystine were designed to derive the various diamides (**2**), while a small methyl group was introduced to obtain a series of *N,N′*-dimethyl L-cystine diamide derivatives **3** to explore the effect of substitution at the α-amino groups of L-cystine on their ability to inhibit L-cystine crystallization. A total of 16 L-cystine derivatives were designed.

Chemical synthesis

As shown in Scheme 1, L-cystine diamides (**2a–i**) were readily synthesized through the amidation of Boc-protected L-cystine **6** using activated OSu or OBt ester and subsequent deprotection of Boc using 50% TFA in CH_2Cl_2 or 4 equiv. of 4 N HCl in dioxane, as we reported previously.[9] Amidation using activated esters was found to give better reaction yields and fewer side products. The overall yields of the three step sequence ranged from 10% to 50%.

Several conditions were initially explored to directly methylate L-cystine but failed to obtain *N,N′*-dimethyl L-cystine. Later, we first obtained *N*-methyl L-cysteine through Na/NH_3 reduction of L-thiazolidine-4-carboxylic acid (**4**) and then air oxidized the *N*-methyl cysteine in the presence of catalytic iron (III) chloride to afford the desired *N,N′*-dimethyl L-cystine **5**.[12,13] Protection of the secondary amine with Boc anhydride afforded **7**, which was activated through its activated ester and formed amides with a series of amines. The target *N,N′*-dimethyl L-cystine diamides **3b–i** were obtained in 10–30% overall yield upon final Boc deprotection.

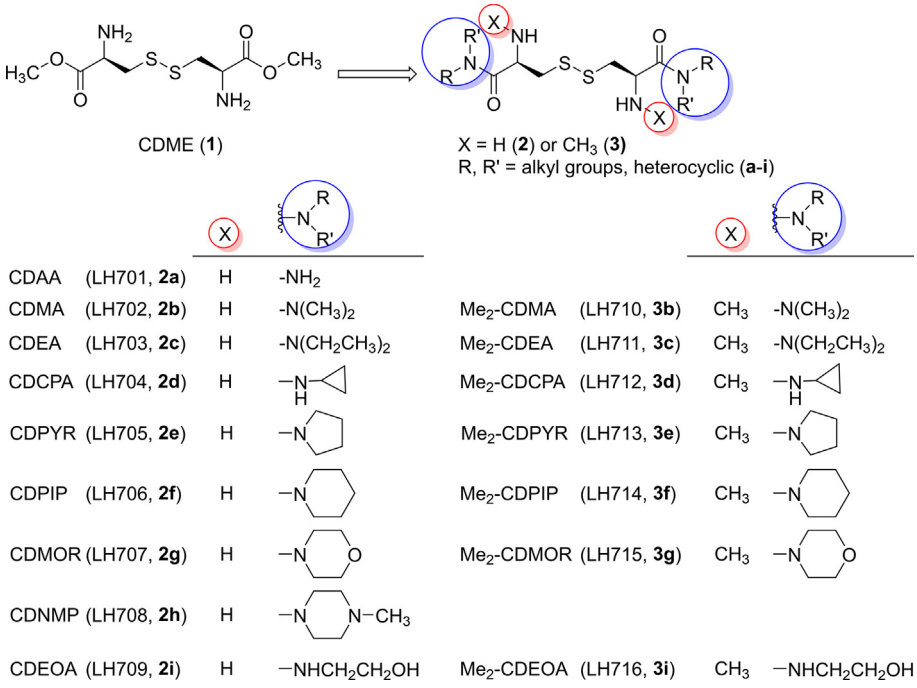
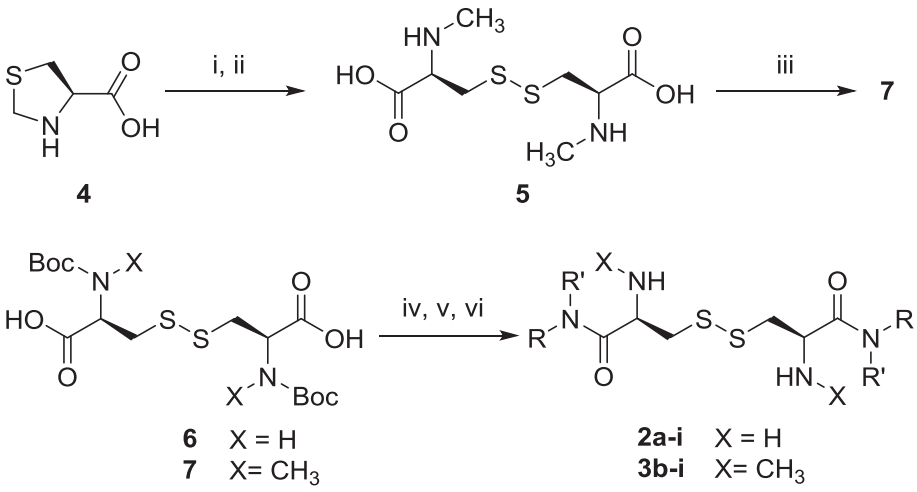


Fig. 1. Design of L-cystine diamides (**2** and **3**).



Scheme 1. Synthesis of L-cystine diamides (**2a–i**) and *N,N′*-dimethyl L-cystine diamides (**3b–i**) from Boc-L-cystine (**6**) or L-thiazolidine-4-carboxylic acid (**4**). Reaction conditions: i) Na, NH_3 liquid; ii) air, $FeCl_3$, pH 9; iii) $(Boc)_2O$; iv) HOAt, EDC, DIEA; v) HNRR'; vi) 4 N HCl/dioxane.

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