Synthesis of a Novel L-Cystine Crystallization Inhibitor for the Treatment of Cystinuria

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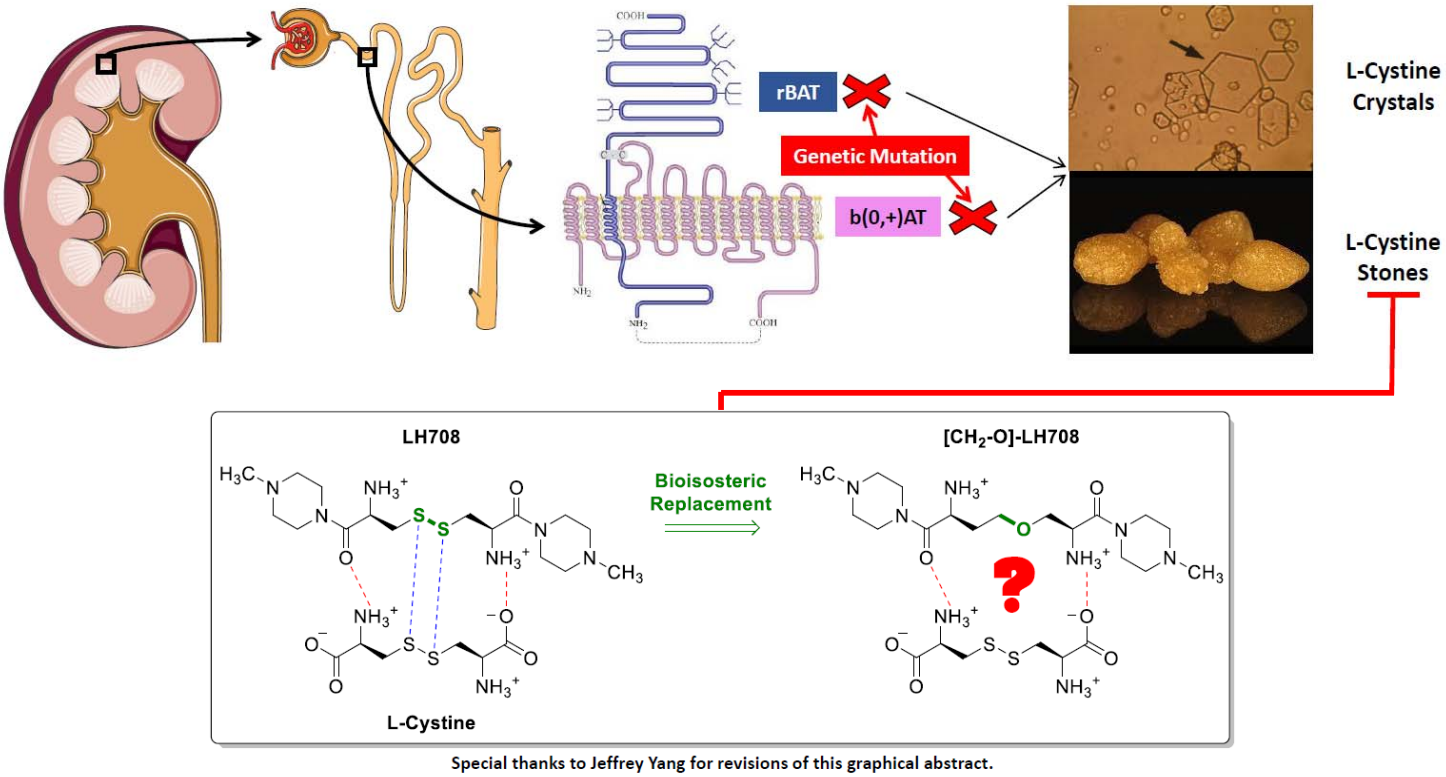
Cystinuria is a genetic disorder that results in defects in the amino acid transport proteins, rBAT and b(0,+)AT, responsible for the reabsorption of L-cystine from the renal tubules. L-Cystine, which is poorly soluble in urine, accumulates and forms crystals that amass into stones. These stones can become stuck at certain locations in the urinary tract, resulting in unbearable flank pain, hematuria, frequent urinary tract infections, tissue damage, and ultimately acute or chronic renal failure. Current treatments for cystinuria include dietary modifications, urinary alkalinization, thiol-binding medications, and surgery. However, these treatments are not ideal for several reasons: inadequate patient compliance, poor safety profile, and high likelihood of stone recurrence. In 2010, two potential lead compounds, L-cystine methyl ester (L-CME) and L-cystine dimethyl ester (L-CDME), were reported to reduce crystal growth rate by binding and sterically hindering the attachment of additional L-cystine to the surface. Our lab has sought to improve the binding and stability of these L-cystine crystal growth inhibitors. After much work by colleagues in our lab, L-cystine bis(N′-methylpiperazide), or LH708, was found to be the most potent in inhibiting L-cystine crystallization and exhibited significantly better stability. In the current study, we were interested in determining if the disulfide functionality in the L-cystine analogs was necessary for binding to the crystal surface. Using the principle of bioisosteric replacement, the disulfide was replaced with a methyleneoxy moiety. A seven-step synthesis was designed to obtain [CH2-O]-LH708. Several steps required optimization to improve yields. Once [CH2-O]-LH708 is successfully synthesized, additional studies will be performed to determine the inhibitory activity of this novel analog. Supported by NIH R25ES020721 and R01DK112782.



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