MODULATORS OF ALPHA-1 ANTITRYPSIN

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 63/004,636, filed April 3, 2020, the contents of which are incorporated by reference herein in their entirety.

[0002] The disclosure provides compounds that are capable of modulating alpha-1 antitrypsin (AAT) activity and methods of treating alpha-1 antitrypsin deficiency (AATD) by administering one or more such compounds.

[0003] AATD is a genetic disorder characterized by low circulating levels of AAT. While treatments for AATD exist, there is currently no cure. AAT is produced primarily in liver cells and secreted into the blood, but it is also made by other cell types including lung epithelial cells and certain white blood cells. AAT inhibits several serine proteases secreted by inflammatory cells (most notably neutrophil elastase [NE], proteinase 3, and cathepsin G) and thus protects organs such as the lung from protease-induced damage, especially during periods of inflammation.

[0004] The mutation most commonly associated with AATD involves a substitution of lysine for glutamic acid (E342K) in the SERPINA1 gene that encodes the AAT protein. This mutation, known as the Z mutation or the Z allele, leads to misfolding of the translated protein, which is therefore not secreted into the bloodstream and can polymerize within the producing cell. Consequently, circulating AAT levels in individuals homozygous for the Z allele (*PiZZ*) are markedly reduced; only approximately 15% of mutant Z-AAT protein folds correctly and is secreted by the cell. An additional consequence of the Z mutation is that the secreted Z-AAT has reduced activity compared to wild-type protein, with 40% to 80% of normal antiprotease activity (American thoracic society/European respiratory society, Am J Respir Crit Care Med. 2003;168(7):818-900; and Ogushi et al. J Clin Invest. 1987;80(5):1366-74).

[0005] The accumulation of polymerized Z-AAT protein within hepatocytes results in a gain-of-function cytotoxicity that can result in cirrhosis or liver cancer later in life and neonatal liver disease in 12% of patients. This accumulation may spontaneously remit but can be fatal in a small number of children. The deficiency of circulating AAT results in unregulated protease activity that degrades lung tissue over time, resulting in emphysema, a form of chronic obstructive pulmonary disease (COPD). This effect is severe in *PiZZ* individuals and typically manifests in middle age, resulting in a decline in quality of life and shortened lifespan (mean 68 years of age) (Tanash et al. Int J Chron Obstruct Pulm Dis. 2016;11:1663-9). The effect is more pronounced in *PiZZ* individuals who smoke, resulting in an even further shortened lifespan (58