Zinc and Copper Protease Inhibitors to Counter Bioterror

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Furin is an important human protease that is implicated in many pathogenic states, because it processes to maturity pro-toxins of a wide variety of bacteria {including *Bacillus anthracis* (Anthrax) and *Clostridium septicum* (causing fatal gas gangrene) bacteria}, and envelope glycoproteins of a wide variety of viruses {including the deadly Ebola, Avian Influenza (bird's flu), and HIV-1 viruses}(Thomas, *Nature Rev. Molec. Cell Biol.* **2002**, *3*, 753). Furin is present in most human cells and is accessible to drugs (especially when it operates outside the cell or in endosomes). For these reasons the inhibition of furin after exposure to a bioterror attack or an aggressive disease caused by an unknown pathogen may possibly prevent infection.

Furin inhibitors reported to date are peptide derivatives and proteins, which may not be suitable when cheap mass production and long storage periods are required. We report that small and stable M(chelate)Cl_2 (M is copper or zinc) inhibit furin. The most efficient inhibitors act at low micromolar concentrations, having the TTP as the tridentate chelate (TTP = 4'-[*p*-tolyl]-2,2':6',2"-terpyridine). Inhibition is irreversible, competitive with substrate, and affected by substituents on the terpyridine chelates. The free chelates are not inhibitors, and so are the bis-chelated compounds. Solvated Zn^{2+} is considerably less potent than some of its chelated compounds. However, solvated Cu^{2+} (k_{on} of 25000 ± 2500 s^{-1}) is more potent then Cu(TTP)Cl_2 (k_{on} = 140 ± 13 s^{-1}) and allows recovery of furin activity prior to a second inhibition phase. A mechanism involving coordination to the catalytic histidine is proposed for all inhibitors. Target selectivity between inhibitors of the proprotein convertases (of which furin is one) is uncommon, but is indicated here by the fact that our inhibitors are less potent towards Kex2 (the yeast homologue of furin).

M(TTP)Cl_2

(M = Zn, Cu)