

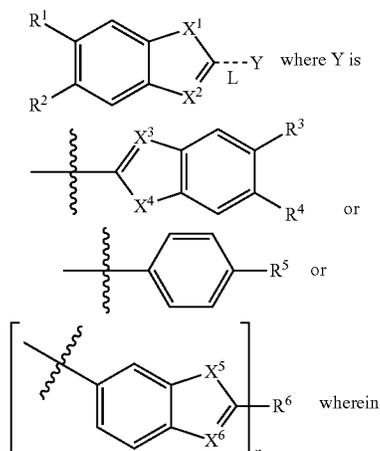
can last for months, and mechanical ventilation would be impractical if even a limited number of individuals were simultaneously intoxicated. See Meunier et al. (2003) *Mol Cell Neurosci* 22(4):454-466; and Eleopra et al. (1998) *Neurosci Lett* 256(3):135-138. Furthermore, antitoxin administration would preclude vaccinated individuals from any form of highly beneficial BoNT medical therapy.

**[0013]** Thus, a need exists for small molecule (non-peptidic) inhibitors of BoNT/A LC metalloprotease activity.

#### SUMMARY OF THE INVENTION

**[0014]** The present invention generally relates to compounds that inhibit BoNT/A LC metalloprotease activity.

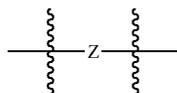
**[0015]** In some embodiments, the present invention provides a method of inhibiting the activity of the Botulinum neurotoxin A metalloprotease which comprises contacting Botulinum neurotoxin A metalloprotease with at least one compound having the following structural formula:



**[0016]**  $n$  is 1 or 2;

**[0017]**  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  are each independently N, S, O,  $SO_2$ ,  $CR^7$  or  $NR^8$  and at least one of  $X^1$  or  $X^2$  is N, S, O,  $SO_2$ , or  $NR^8$ ;

**[0018]**  $L$  is a linker which may be a direct bond or



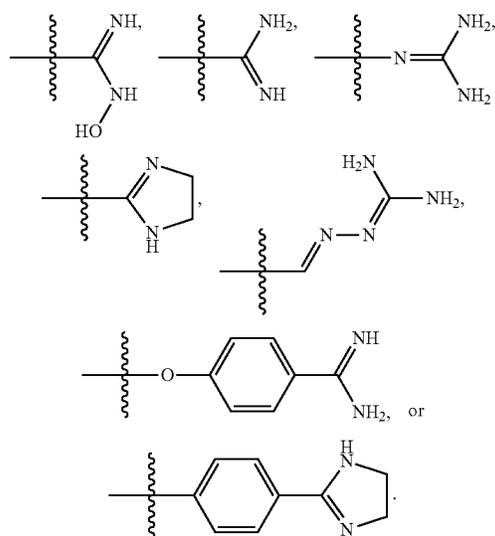
where  $Z$  is an optionally substituted alkyl, alkenyl, dialkenyl, trialkenyl, or aryl, or  $C(O)NH$ ; and

**[0019]**  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are each independently hydrogen, amino, amine with stabilized carbocations, carboxyl, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, cycloalkoxy, heteroaryloxy, alkoxy carbonyl, alkylamino, carbamoyl, alkylaminocarbonyl, alkylsulfhydryl, alkylhydroxymate; and

**[0020]**  $R^8$  is hydrogen, OH, a halogen, or an optionally substituted alkyl.

**[0021]** In some embodiments, at least one of  $R^1$ ,  $R^2$ ,  $R^3$ , or  $R^4$  is hydrogen, amidine, 2-imidazoline, amino, guanidine,

methyl, aminomethyl-hydroxamine, or methylamine-guanidine. In some embodiments,  $R^5$  is hydrogen, amidine, 2-imidazoline, amino, guanidine, methyl, aminomethyl-hydroxamine, methylamine-guanidine, 4-oxy-benzamidine, 1H-indole-6-carboxamide, or 1H-indole-5-carboxamide. In some embodiments,  $R^6$  is hydrogen, amidine, benzamidine, benzimidazole, imidazoline, guanidine, imidazole, oxazole, benzofuran-2-yl-imidazoline, benzofuran-2-yl-amidine, benzofuran-2-yl-guanidine, benzothiophene-2-yl-imidazoline, benzothiophene-2-yl-amidine, benzene-2-yl-amidine, benzofuran-2-yl-imidazole, or benzofuran-2-yl-oxazole. In some embodiments, at least one of  $X^1$  or  $X^2$  is N, NH, S, O,  $SO_2$ , CH,  $C-CH_3$ , C-phenyl, N-ethanol, N-chloroethyl, C-amino, C-(2-indole-6-imidazoline), C-(2-indole-6-amidine), C-(2-indole-5-imidazoline), or C-(2-indole-5-amidine). In some embodiments, at least one of  $X^3$ ,  $X^4$ ,  $X^5$ , or  $X^6$  is N, NH, S, O,  $SO_2$ , or CH. In some embodiments, at least one of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , or  $R^7$  is  $-H$ ,  $-CH_3$ ,  $-NH_2$ ,



In some embodiments,  $R^5$  is  $\sim NH_2$ ,

