

**BIFUNCTIONAL
ACETYLCHOLINESTERASE
REACTIVATORS**

PRIORITY OF INVENTION

This application claims priority under 35 U.S.C. §119 (e) from U.S. Provisional Patent Application No. 60/019,461, filed on Jun. 13, 1996, which is hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

Organophosphorous compounds are used in chemical weapons, including nerve agents such as methylphosphonofluoridic acid 1-methyl-ethyl ester (sarin), pinacolyl methylphosphono fluoridate (soman), and methylphosphonothioic acid S-[2-[bis(1-methylethyl)amino]ethyl]O-ethyl ester (VX), and in insecticides such as phosphoric acid diethyl 4-nitrophenyl ester (paraoxon), diethyl-p-nitrophenyl mono thiophosphate (parathion) and phosphorothioic acid O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) O,O-diethyl ester (coumaphos). Exposure to even small amounts of a nerve agent can be fatal. In humans, the mechanism of organophosphate poisoning involves reaction with a serine hydroxyl group in the active site of a key enzyme acetylcholinesterase ("AChE") producing an inactive and phosphorylated enzyme. The classical therapeutic approach for reactivating an inactive phosphorylated enzyme is treatment with nucleophilic oximes, which react with phosphorylated AChE and release the active enzyme. See I. B. Wilson; S. A. Ginsburg *Biochem. Biophys. Acta*, 1955, 18, 168-170.

Oximes such as pyridinium aldoxime methochloride ("PAM") have been used to treat the actions of some organophosphates, however, they are not effective for other organophosphates such as soman (J. H. Fleisher et al. *J. Pharmacol. Exp. Ther.* 1967, 156, 345-351). Derivatives of 1-methylpyridinium-aldoxime iodides have also been used as reactivators of AChE (E. J. Poziomek et al. *J. Org. Chem.* 1958, 23, 714-717). Such oximes are structurally analogous to the AChE inhibitor 9-amino-1,2,3,4-tetrahydroacridine ("THA"), which has been shown to bind to both a catalytic binding site and a peripheral binding site of AChE (See FIG. 2) (Y.-P. Pang et al. *J. Biol. Chem.* 1996, 271, 23646-23649).

The effectiveness of an oxime AChE reactivator depends on the intrinsic equilibrium constant for the equilibrium illustrated in FIG. 1. Reactivation is effective only when enzyme dephosphorylation is faster than oxime dephosphorylation. There is currently a need for effective reactivators of AChE.

SUMMARY OF THE INVENTION

The invention comprises novel compounds which are AChE reactivators, useful as antidotes for organophosphate poisoning. According to the invention there is provided a compound of the invention which is a compound of formula I:



wherein

Ar¹ and Ar² are each independently (a) a monocyclic heteroaromatic ring containing five or six ring atoms, attached to R¹ via a ring nitrogen, wherein said ring optionally comprises one, two or three additional heteroatoms, each independently selected from the group consisting of non-peroxide oxygen, sulfur, and N(X); (b) a benz- or

benzo-derivative of said ring; or (c) an ortho-fused bicyclic heterocycle comprising a propylene, trimethylene, or tetramethylene diradical fused to said heteroaromatic ring; wherein

Ar¹ and Ar² are each substituted on a ring carbon atom with a radical of formula —CHNOH; and Ar¹ and Ar² are optionally substituted with one, two, or three additional substituents selected from the group consisting of (C₁-C₆) alkyl, (C₁-C₆)alkoxy, phenyl, and benzyl;

X is absent or is H, O, (C₁-C₄)alkyl, phenyl or benzyl; and R¹ is an unbranched (C₇)-, (C₈)-, or (C₉)alkylene chain, optionally substituted with one, two, or three substituents selected from the group consisting of (C₁-C₃)alkoxy, hydroxy, oxo, and halo; or

R¹ is an unbranched (C₂-C₁₀)alkylene chain comprising at least one, i.e. 1, 2, or 3, divalent radicals selected from the group consisting of —OC(=O)—, —NHC(=O)—, —NHC(=O)C(=O)NH—, —OCH₂C=CCH₂O—, 1,4-phenylene, 1,3-phenylene, 1,2-phenylene, 1,4-cyclohexadiyl, 1,3-cyclohexadiyl, and 1,3-cyclopentadiyl; or a pharmaceutically acceptable salt thereof.

Compounds of the invention have activity as reactivators of AChE, and therefore may be useful to counter or attenuate the toxic effects of chemical agents which act on the cholinergic system. Accordingly, the invention includes a method comprising attenuating the effects on a mammal caused by exposure to a chemical agent that covalently inhibits AChE, by administering to said mammal (such as for example a human) an effective amount of a compound of formula I; or a pharmaceutically acceptable salt thereof. The compound may be administered either prior to exposure or after exposure to said chemical agent.

Compounds of the invention may also be useful to counter or attenuate the toxic effects of chemical agents which act on the cholinergic system when administered in combination with atropine (Poziomek et al. *J. Org. Chem.* 1958, 23, 714-717) and/or other antimuscarinic or antinicotinic agents such as carbaphens (U.S. Pat. No. 5,026,897). Accordingly, the invention includes a method comprising attenuating the effects on a mammal caused by exposure to a chemical agent that covalently inhibits AChE, by administering to said mammal (such as for example a human) an effective amount of a compound of formula I; or a pharmaceutically acceptable salt thereof, in combination with atropine and/or another antimuscarinic or antinicotinic agent. Compounds of the invention may be administered with said antimuscarinic or said antinicotinic agent simultaneously as a single dose, simultaneously in individual doses, or sequentially; each therapeutic agent may be administered prior to exposure or after exposure to said chemical agent.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the equilibrium equation for oxime reactivation of AChE.

FIG. 2 shows the catalytic and peripheral binding sites of AChE.

FIG. 3 shows compounds exemplified herein.

DETAILED DESCRIPTION OF THE
INVENTION

In the following detailed description, reference is made to the accompanying figures which from a part hereof, wherein specific embodiments of the invention may be illustrated. It is to be understood that other embodiments may be utilized and structural changes may be made without departing from the scope of the present invention.