

**COMPOUNDS HAVING BOTH POTENT
CALCIUM ANTAGONIST AND ANTIOXIDANT
ACTIVITY AND USE THEREOF AS
CYTOPROTECTIVE AGENTS**

BACKGROUND OF INVENTION

1. Field of the Invention

The present invention is directed to the provision of compounds having potent calcium antagonist and anti-oxidant activity, and to the use of those compounds as cellular protective agents. The invention is further directed to the provision of methods for synthesizing the compounds of the invention and to compounds formed as intermediates during the synthesis. The invention is particularly directed to the use of the compounds of the present invention to prevent or reduce cellular damage associated with ophthalmic diseases or injuries.

2. Discussion of Related Art

In a biological system under stress induced by trauma, ischemia-reperfusion, depletion of natural defenses, inflammation, light damage (especially laser or intense operating room light), or degenerative conditions, damage occurs which can result in an increase in cellular free calcium and/or an increase in oxidative damage. Both these changes are components of the common pathway of cell death. The result of these changes is the initiation of a cascade of cellular destruction, loss of cellular function and ultimately cell loss. The loss of critical cellular components can result in organ damage and loss of organ function. Loss of function can be caused by an acute insult or may be the result of the cumulative effects of chronic insult. The following texts may be referred to for further details concerning these phenomena:

Prog. Neuro-Psychopharmacol. and Biol. Psych., volume 17, pages 21-70 (1993);

Age, volume 16, pages 23-30 (1993);

Chem. Res. Tox., volume 32, pages 2-18 (1993); and

Ann. Neurol., volume 32, pages S33-42 (1992).

Calcium flux is a necessary part of normal cell function. The level of intracellular free calcium is highly regulated. Both receptor-operated and voltage-sensitive channels control cell signaling and stimulus response. Multiple voltage-sensitive calcium channels have been identified. These include the N, T, P, and L channels. The following publications may be referred to for further background concerning the regulation of intracellular free calcium levels:

Med. Res. Review, volume 9, pages 123-80 (1989);

Pharmacol. Review, volume 38(4), pages 321-416 (1986);

Cardiovasc. Drugs and Therapy, volume 6, pages 35-39 (1992);

Science, volume 235, pages 46-52 (1987);

Chem.-Biol. Interactions, pages 1-23 (1991); and

Biochemical Pharmacol., volume 43(1), pages 39-46 (1992).

Over-stimulation of the cell or cellular system or the defective regulation of intracellular free calcium can result in increased intracellular free calcium levels. This can lead to the initiation of a chain of biochemical processes which can lead to cell death. Agents that modulate increases in intracellular free calcium concentration can moderate the deleterious effects of over-stimulation or defective regulation. See *PNAS*, volume 89, pages 435-39 (1992), and references cited above. In addition, a compound that acts as a calcium antagonist can provide

an additional beneficial effect by improving blood flow, reducing ischemic insult and facilitating repair. See *Naunyn-Schmiedeberg's Acta Pharmacol.*, volume 335, pages 680-685 (1987). As utilized herein, the term "calcium antagonists" refers to organic molecules which inhibit increases in intracellular free calcium concentrations.

Agents that act as antioxidants can protect against oxidative damage associated with cellular stress. Such protection has been the subject of numerous scientific publications, including the following:

Arch. Pharmacol., volume 325, pages 129-146 (1992);

Free Rad. Biol. Med., volume 6, pages 209-224;

Free Rad. Biol. Med., volume 11, pages 215-232 (1991);

Eur. J. Pharmacol., volume 210, pages 85-90 (1992);

J. Photochem., Photobiol. Biol., volume 8, pages 211-224 (1991);

Pharmacol. and Tox., volume 70, pages 271-277 (1992); and

Medicinal Res. Rev., volume 13(2), pages 161-182 (1993).

The combined use of two or more compounds having calcium antagonist and antioxidant activity, respectively, is discussed in *Experimental Eye Research*, volume 5, pages 71-78 (1993). The provision of compounds having both calcium antagonist and antioxidant activity is discussed in the following patent publications:

EP 267 155A and WO 89/05803 A1.

One compound known to have calcium antagonist activity, flunarizine, has also been reported to have free radical scavenging activity. See:

Arch. int. Pharmacodyn., volume 272, pages 283-295 (1984);

Eur. J. Pharmacol., volume 204, pages 315-322 (1991); and

Meth. and Find Exp. Clin. Pharmacol., volume 11(10), pages 607-612 (1989).

In addition, other classes of calcium antagonists have been reported to have antioxidant activity. See:

Free Rad. Biol. and Med., volume 12, pages 183-187 (1992);

Res. Commun. in Chem. Path. and Pharmacol., volume 76(3), pages 367-370 (1992);

J. Mol. Cell Cardiol., volume 22, pages 1199-1208 (1990);

Circulation Res., volume 66(5), pages 1449-1452 (1990);

J. Cardiovas. Pharmacol., volume 18(Suppl. 1) pages S6-S10 (1991);

Basic Res. in Cardiology, volume 87, pages 148-160 (1992);

Free Rad. Res. Comms., volume 15(2), pages 91-100 (1991); and

Biochem. Pharmacol., volume 37(21), page 4197 (1988).

However, in most cases the antioxidant effect reported is weak and not clinically relevant. This is pointed out in *Biochem. Pharmacol.*, volume 42(4), pages 735-743 (1991), and *Biochem. Pharmacol.*, 38(20), pages 3601-3610 (1989). In addition, it is believed that a number of the effects attributed to the free radical scavenging effect of flunarizine might actually be an effect of its calcium antagonist activity since this activity was poorly understood in the early 1980's.

The present invention is directed to the provision of new compounds that have both potent calcium antago-