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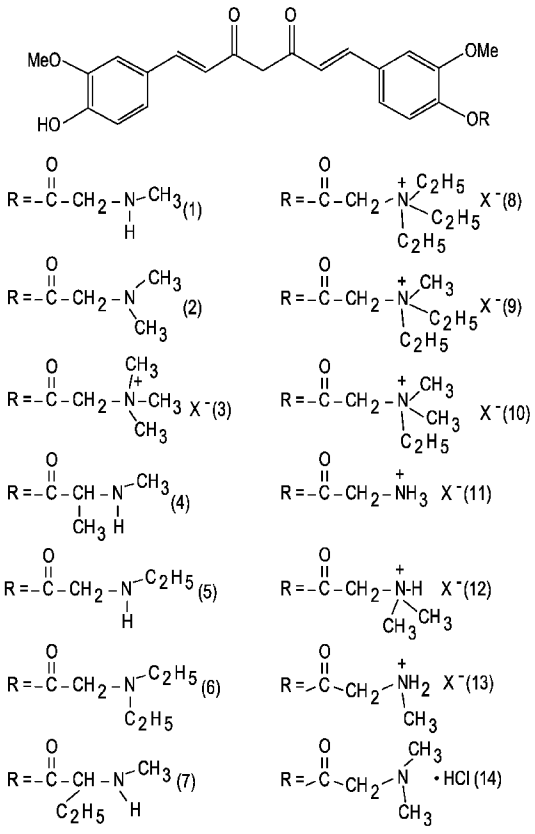
(54) **Title:** INTRANASALLY ADMINISTERING CURCUMIN IN A BOLUS OF HELIUM GAS TO TREAT ALZHEIMER'S DISEASE

FIG. 1A



(57) **Abstract:** Intranasally administering curcumin prodrugs and curcumin hybrids in a bolus of helium gas to the brain to treat Alzheimer's Disease.

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Intranasally Administering Curcumin In a Bolus of Helium Gas to Treat Alzheimer's Disease

RELATED APPLICATIONS

This application is a continuation-in-part of US Patent Application No. 11/534,384, filed Sept. 22, 2006, entitled "Intranasally Administering Curcumin to the Brain to Treat Alzheimer's Disease" (Docket No. COD -5140), the specification of which is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

In Alzheimer's Disease (AD), the abnormal cleavage of beta amyloid protein precursor from the intracellular membrane often produces a protein Aβ 1-42 which is incompletely removed by normal clearance processes. It has been reported that soluble beta amyloid oligomers are highly neurotoxic. Moreover, over time, this soluble protein assemblage is deposited as a beta amyloid protein Aβ plaque within brain tissue, leading to the local destruction of neurons. The Aβ plaque deposition is also believed to provoke an inflammatory response by microglia and macrophages, which recognize the plaque as a foreign body. These cells are believed to respond to the plaque deposition by releasing pro-inflammatory cytokines and reactive oxygen species (ROS). Although the inflammatory response may be provoked in an effort to clear the brain tissue of the detrimental plaque, it is now believed that this inflammation also injures local neuronal tissue, thereby exacerbating AD. Soluble oligomers of beta amyloid or "ADDLs" are a neurotoxic species implicated in AD pathogenesis. Yang, J. Biol. Chem., 280,7, Feb. 18.,2005, 5892-5901.

In the book "The Memory Cure" (2003,McGraw-Hill, NY, NY), Dr. Majid Fotuhi writes: "Pharmaceutical companies in search of magic drugs to treat Alzheimer's Disease need to pay close attention to curcumin."

It has been reported that 0.1 – 1.0 μM curcumin inhibits the *in vitro* formation of amyloid beta oligomers, and blocks the *in vitro* toxicity of $A\beta_{1-42}$ oligomers in differentiated neuroblastoma cells. Yang, J. Biol. Chem., 280,7, Feb. 18.,2005, 5892-5901. Curcumin also reduced the amount of soluble beta amyloid by 43% when provided in the diet of Alzheimer's Transgenic mice in a low dose of 160 ppm. Lim, J. Neurosci., 2001, Nov. 1, 21(21) 8370-7.

It appears that curcumin also benefically reduces deposits of beta amyloid. In middle aged female Sprague-Dawley rats, 500 ppm dietary curcumin reduced amyloid beta deposits induced by beta amyloid infusion by about 80%. Frautschy, Neurobiol. Aging, 22, 2001, 993-1005. Curcumin also reduced beta amyloid plaque burden by about 30-40% when provided in the diet of Alzheimer's Transgenic mice in a low dose of 160 ppm. Lim, J. Neurosci., 2001, Nov. 1, 21(21) 8370-7. This is advantageous because it is believed that the oxidative and inflammatory damage caused by AD is linked to microglial response to amyloid beta deposits.

In addition to its beneficial action against soluble beta amyloid, curcumin has considerable anti-oxidative properties and also inhibits the expression of pro-inflammatory cytokines. . Frank, Ann. Clin. Psychiatry, 2005, Oct.-Dec. 17,4,269-86, and Cole, Neurobiol. Aging, 26S(2005) S133-S136.

Because curcumin is able to effectively act against many targets of AD, it has been hypothesized that the 4.4 fold lower incidence of AD in the Indian population between the ages of 70 and 79 is due to the high dietary consumption of curcumin. Lim, J. Neuroscience, Nov.1, 2001, 21(21) 8370-77. In those aged 80 years and older, age-adjusted Alzheimer's prevalence in India is roughly one-quarter the rates in the United States (4% versus 15.7%). Frautschy, Neurobiol. Aging, 22, 2001, 993-1005. Curcumin has been identified in review articles as one of the most promising candidates for long term AD study. Frank, Ann. Clin. Psychiatry, 2005, Oct.-Dec. 17,4,269-86, and Cole, Neurobiol. Aging, 26S(2005) S133-S136. Curcumin is currently the subject of an FDA approved IND clinical trial at the UCLA Alzheimer Center in the treatment of mild to moderate AD patients. Cole, Neurobiol. Aging, 26S(2005) S133-S136.

Because the above-mentioned *in vivo* effects of curcumin upon AD symptoms were achieved by providing curcumin in the diet, it appears that curcumin is effectively

able to cross the blood brain barrier. As curcumin is highly lipophilic, it is expected to easily cross the blood brain barrier. Frautschy, Neurobiol. Aging, 22, 2001, 993-1005. Indeed, it has been reported that *in vivo* studies show that curcumin injected peripherally into aged Tg mice crossed the blood brain barrier and bound amyloid plaques. Yang, J. Biol. Chem., 280, 7, Feb. 18. 2005, 5892-5901.

SUMMARY OF THE INVENTION

Despite the beneficial effects of curcumin, the present inventors have noted that there are many bioavailability problems associated with the oral delivery of curcumin.

First, because curcumin does not easily penetrate the human digestive tract and is subject to intestine-based metabolism and rejection, less than 1% of oral curcumin enters the plasma. Second, the small amount of curcumin that enters the bloodstream is rapidly metabolized by the liver and kidney. Therefore, although curcumin is highly lipophilic (and so easily crosses the blood brain barrier), only very small amounts of orally administered curcumin are registered in the serum and in the brain tissue. One study found that ingesting up to 3.6 g of curcumin per day produced a plasma curcumin level in the range of only about 10 nM. Sharma, Clin. Cancer Res., 2004, Oct. 15, 10(20) 6847-54. A second study found that ingesting up to 6-8 g of curcumin per day produced a peak serum level in the range of about 0.51 – 1.77 μM.. Third, it has been reported that high oral doses of curcumin in the range of 4,000-8,000 mg/day cause problems such as headache, rash and diarrhea, likely produced by metabolites of curcumin. Accordingly, it appears that the above cited plasma curcumin concentrations (10 nM - 1.77 μM) represent the practical upper limit of oral dosing of curcumin. Yang, supra, concludes that higher >(5 μM) concentrations of curcumin are not likely to occur in the brain with oral dosing. In fact, Wang reports that injection of 30 mg/kg of curcumin results in a peak curcumin concentration in brain tissue of only about 0.15 ng/mg, which is about 0.40 uM.

It appears that, in the brain tissue concentration range about 1 uM, some but not all of the beneficial therapeutic qualities of curcumin are realized. For example, it has been reported that 0.1 – 1.0 μM curcumin inhibits the *in vitro* formation of amyloid beta oligomers, and blocks the *in vitro* toxicity of $A\beta_{1-42}$ oligomers in differentiated

neuroblastoma cells. Yang, J. Biol. Chem., 280,7, Feb. 18.,2005, 5892-5901. However, there also appear to be a number of AD-related therapeutic qualities of curcumin that are only realized at higher curcumin concentrations. For example, Yang reports that whereas 0.25 – 4 uM concentrations of curcumin only minimally prevent the formation of toxic beta amyloid oligomer formation in vitro, 16-64 uM concentrations of curcumin completely prevent the formation of toxic beta amyloid oligomer formation. Yang also notes that curcumin has the pontential to inhibit copper binding of beta amyloid, but concludes that it is not clear whether curcumin's avidity for copper and potential concentration in the brain will be enough to directly alter CNS beta amyloid metal binding.

The present invention relates to the intranasal administration of a formulation comprising an effective amount of curcumin. In particular, the present invention relates to the intranasal administration of a formulation comprising an effective amount of curcumin to the olfactory mucosa across the cribriform plate and into the brain in order to treat a neurodegenerative disease, such as AD.

The objective of the present invention is to improve curcumin brain bioavailability by administering curcumin via the nasal route in order to deliver curcumin through the olfactory mucosa and to the brain, and to reduce the dose required for its beneficial effect. As curcumin is highly lipophilic, it will easily pass through the olfactory mucosa located high in the nasal cavity, and enter olfactory neurons and thereby the brain. This mode of delivery will also pass less curcumin into the circulation, and so will result in lower plasma concentrations of metabolites of curcumin, and therefore fewer side effects. Intranasal delivery will improve drug bioavailability to the brain by passive diffusion through the olfactory mucosa, thereby avoiding extensive hepatic first-pass metabolism which significantly lowers the plasma and brain concentrations of curcumin administered orally. Therefore, small doses of curcumin can be administered which will result in fewer side effects, and the drug will be more tolerable and more effective. Lipophilic drugs such as curcumin generally achieve higher brain levels after intranasal administration than after oral or intravenous administration. Therefore, the nasal route of administration of curcumin may help to enhance the effectiveness of curcumin in the brain (the site of action). Additionally, as curcumin is heavily

metabolized by the liver, administration by the nasal route may help to reduce drug interactions with other drugs that are also extensively metabolized by the liver. Lastly, because intranasally administered curcumin will passively diffuse through the olfactory mucosa and into the olfactory bulb, which is connected to the hippocampus and amygdala through the limbic system, it is believed that intranasal administration of curcumin will preferentially deposit in the hippocampus and amygdala portions of the brain. These regions are believed to be origination sites of Alzheimer's Disease.

Therefore, in accordance with the present invention, there is provided a method for administering curcumin to a brain of a mammal, comprising:

a) applying a pharmaceutical composition comprising curcumin to an upper third of a nasal cavity of the mammal, wherein the curcumin is absorbed through an olfactory mucosa and transported to the brain of the mammal.

DESCRIPTION OF THE FIGURES

FIGS. 1a through 1c disclose novel curcumin prodrugs of the present invention **(1) – (30)**.

FIG. 1d discloses preferred curcumin analogs (**31**) – (**34**) that are candidate parent compounds for making prodrugs thereof.

FIGS. 2-16 disclose various curcumin derivatives that are hybrids of curcumin and various other natural polyphenols. Each of these derivatives is a triphenolic compound, wherein the intermediate diketone structure of curcumin is replaced with a phenolic group. The resulting compound retains the spacing between the two phenols of curcumin, and also possesses the biphenolic spacing of the additional polyphenol.

FIG. 2 discloses the structures of curcumin, resveratrol, and two curcumin-resveratrol hybrids. Note how each of the hybrids retains the interphenolic spacing of each of curcumin and reveratrol.

FIG. 3 discloses a method of making the curcumin-resveratrol I hybrid.

FIG. 4 discloses a method of making the curcumin-resveratrol II hybrid.

FIG. 5 discloses a method of making a curcumin-resveratrol hybrid having three hydroxyl groups in each of the central phenolic group and lateral phenolic groups.

FIG. 6 discloses curcumin, resveratrol and a hybrid thereof, wherein all of the phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a dihydroxyl central phenolic group.

FIG. 7 discloses a method of making the curcumin-resveratrol hybrid of FIG. 6.

FIG. 8 is similar to the hybrid of FIG. 6, but wherein the methoxy groups of the base curcumin molecule are retained.

FIG. 9 discloses curcumin, oxyresveratrol and a hybrid thereof, wherein all of the hydroxyls/phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a trihydroxyl central phenolic group.

FIG. 10 discloses curcumin, piceatannol and a hybrid thereof, wherein all of the hydroxyls/phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a trihydroxyl central phenolic group.

FIG. 11 discloses a method of making a curcumin-resveratrol hybrid,wherein all of the hydroxyls/phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a dihydroxyl central phenolic group.

FIG.12 discloses curcumin, BDMC, resveratrol and curcumin hybrids thereof, wherein all of the phenolics of the natural compounds are represented in the hybrid, providing

hydroxyl demethoxy lateral phenolic groups and a hydroxy or dihydroxyl central phenolic group.

FIG. 13 provides a method of making the compound of FIG. 12 that has hydroxyl demethoxy lateral phenolic groups and a hydroxy central phenolic group.

FIG. 14 provides a method of making the compound of FIG. 12 that has hydroxyl demethoxy lateral phenolic groups and a dihydroxy central phenolic group.

FIG.15 discloses curcumin, fistein and hybrids thereof, wherein all of the phenolics of the natural compounds are represented in the hybrid, providing dihydroxyl phenolic groups and a hydroxy central phenolic group in the positions common with the two natural compounds.

FIG. 16 provides a method of making the compound of FIG. 15.

DETAILED DESCRIPTION OF THE INVENTION

As used herein curcumin is also known as diferuloylmethane or (E,E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5,-dione. Curcumin may be derived from a natural source, the perennial herb Curcuma longa L., which is a member of the Zingiberaceae family. The spice turmeric is extracted from the rhizomes of Curcuma longa L. and has long been associated with traditional-medicine treatments used in Hindu and Chinese medicine. Turmeric was administered orally or topically in these traditional treatment methods.

In some embodiments, curcumin is intranasally administered so that it produces a brain tissue concentration of at least 0.1 μM, more preferably at least 1 μM, more preferably at least 5 μM, more preferably at least 20 μM.

Without wishing to be tied to a theory, it is believed that a daily intranasal dose of at least about 0.2 mg/kg would be sufficient to produce the above-cited brain tissue

concentrations. More preferably, the dose is at least 1 mg/kg, more preferably at least 10 mg/kg.

It is believed that applying a pharmaceutical composition comprising curcumin at the above cited levels to an upper third of a nasal cavity of the mammal, wherein the curcumin is absorbed through an olfactory mucosa and transported to the brain of the mammal, will result in attainment of these higher levels of curcumin in brain tissue.

It is known that the more lipophlilic a molecule, the greater its propensity to cross the olfactory mucosa and the blood brain barrier. In this respect, it has been reported that the octanol:water partition coefficient of curcumin (log_{10} PC) is 3.29. Therefore, curcumin is very lipophilic, and so should easily cross the olfactory mucosa and the blood brain barrier by passive diffusion.

It is further known that the blood brain barrier contains the p-glycoprotein (P-gp) transporter which effluxes a number of important molecules such as drugs. Accordingly, the behaviour of these pumps towards curcumin is pertinent to the question of whether curcumin will cross the olfactory mucosa and the blood brain barrier. Since it has been reported that curcumin lowers the expression of P-gp (Holland, Biochem. Pharmacol. 2006 , Apr.14, 71(8) 1146-54), it is believed that curcumin antagonizes these P-gp pumps. In addition to its ability to lower the expression of P-gp, it has been suggested that curcumin is able to modulate the function of hepatic P-gp. In both freshly-plated hepatocytes, containing low levels of Pgp, and 72 hour-cultured hepatocytes, containing high levels of Pgp, the Rhodamine-123 (R-123) efflux, which represents a specific functional test for Pgp-mediated transport, was inhibited by curcumin in a dose-dependent manner. (Romiti N, Tongiani R, Cervelli F, Chieli E. Effects of curcumin on P-glycoprotein in primary cultures of rat hepatocytes. Life Sci. 1998;62: 2349-58.).

Because the octanol:water partition coefficient of curcumin (log_{10} PC) is 3.29 and curcumin has been shown to antagonize P-gp, it is believed that curcumin will easily cross the blood brain barrier. In this respect, it is helpful to compare these qualities of curcumin to those of hydroxyzine. It has been reported by Kandimalla, Int'l. J. Pharmaceutics, 302(2005) 133-144, that hydroxyzine · HCl has a molecular weight of 447.8, an octanol:water partition coefficient of log Doct/pH 7.4 of only 2.37 - 2.87, and has the ability to inhibit P-gp. According to Kandimalla, "the lipophilicity of

(hydroxyzine), coupled with (its) ability to inhibit P-gp, enable(s) (it) to freely permeate across the olfactory mucosa." Because curcumin has an even lower molecular weight than hydroxyzine, has a significantly higher lipophilicity, and is able to lower both the function and expression of p-gp, it is reasonably concluded that curcumin should be able to pass through the olfactory mucosa and the blood brain barrier even easier than hydroxyzine.

Since curcumin (MW=368) and carbamazepine (MW=236) have similar molecular weights and are each highly lipophilic, the effects of intranasal carbamazepine upon carbamazepine brain concentration are highly instructive. Barakat, J. Pharm. Pharmacol., 2006, Jan. 58(1) 63-72 reports that peak brain tissue concentrations of carbamazepine attained by intranasal dosing (12 ug/g) were about four times higher than those attained by oral dosing:

Route	**Carbamazepine Dose (mg/kg)**	**Carbamazepine Peak Brain Tissue (ug/g)**	**~uM**
Intranasal	0.2	12	48
Intravenous	8.0	4	16
Oral	16	3	12

Therefore, if curcumin enters the brain in molar amounts similar to carbamazepine (as is reasonably expected), then the resulting concentrations may be sufficient to both completely prevent toxic oligomer formation and effect Aβ metal binding. If even higher dosages of curcumin are used above 0.2 mg/kg, then the resultant brain tissue concentration would be expected to be even higher.

The dose of curcumin can be combined with a mucoadhesive to enhance its contact with the olfactory mucosa. In some embodiments, the mucoadhesive is selected from the group consisting of a hydrophilic polymer, a hydrogel and a thermoplastic polymer. Preferred hydrophilic polymers include cellulose-based polymers (such as methylcellulose, hydroxyethyl cellulose, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose), a carbomer chitosan and plant gum.

In some embodiments, the mucoadhesive is a water-soluble high molecular weight cellulose polymer. High molecular weight cellulose polymer refers to a cellulose polymer having an average molecular weight of at least about 25,000, preferably at least about 65,000, and more preferably at least about 85,000. The exact molecular weight cellulose polymer used will generally depend upon the desired release profile. For example, polymers having an average molecular weight of about 25,000 are useful in a controlled-release composition having a time release period of up to about 8 hours, while polymers having an average molecular weight of about 85,000 are useful in a controlled-release composition having a time released period of up to about 18 hours. Even higher molecular weight cellulose polymers are contemplated for use in compositions having longer release periods. For example, polymers having an average molecular weight of 180,000 or higher are useful in a controlled-release composition having a time release period of 20 hours or longer.

The controlled-release carrier layer preferably consists of a water-soluble cellulose polymer, preferably a high molecular weight cellulose polymer, selected from the group consisting of hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), carboxy methyl cellulose (CMC), and mixtures thereof. Of these, the most preferred water-soluble cellulose polymer is HPMC. Preferably the HPMC is a high molecular weight HPMC, with the specific molecular weight selected to provide the desired release profile.

The HPMC is preferably a high molecular weight HPMC, having an average molecular weight of at least about 25,000, more preferably at least about 65,000 and most preferably at least about 85,000. The HPMC preferably consists of fine particulates having a particle size such that not less than 80% of the HPMC particles pass through an 80 mesh screen. The HPMC can be included in an amount of from about 4 to about 24 wt %, preferably from about 6 to about 16 wt % and more preferably from about 8 to about 12 wt %, based upon total weight of the composition.

Hydrogels can also be used to deliver the curcumin to the olfactory mucosa. A "hydrogel" is a substance formed when an organic polymer (natural or synthetic) is set or solidified to create a three- dimensional open-lattice structure that entraps molecules of water or other solution to form a gel. The solidification can occur, e.g., by aggregation,

coagulation, hydrophobic interactions, or cross-linking. The hydrogels employed in this invention rapidly solidify to keep the curcumin at the application site, thereby eliminating undesired migration from the site. The hydrogels are also biocompatible, e.g., not toxic, to cells suspended in the hydrogel. A "hydrogel-inducer composition" is a suspension of a hydrogel containing desired curcumin. The hydrogel-inducer composition forms a uniform distribution of inducer with a well-defined and precisely controllable density. Moreover, the hydrogel can support very large densities of inducers. In addition, the hydrogel allows diffusion of nutrients and waste products to, and away from, the inducer, which promotes tissue growth.

Hydrogels suitable for use in the present invention include water-containing gels, i.e., polymers characterized by hydrophilicity and insolubility in water. See, for instance, "Hydrogels", pages 458-459 in Concise Encyclopedia of Polymer Science and Engineering, Eds. Mark et al., Wiley and Sons, 1990, the disclosure of which is incorporated herein by reference.

In a preferred embodiment, the hydrogel is a fine, powdery synthetic hydrogel. Suitable hydrogels exhibit an optimal combination of such properties as compatibility with the matrix polymer of choice, and biocompatability. The hydrogel can include any of the following: polysaccharides, proteins, polyphosphazenes, poly(oxyethylene)-poly(oxypropylene) block polymers, poly(oxyethylene)-poly(oxypropylene) block polymers of ethylene diamine, poly(acrylic acids), poly(methacrylic acids), copolymers of acrylic acid and methacrylic acid, poly(vinyl acetate), and sulfonated polymers. Other preferred hydrogels include poly(acrylic acid co acrylamide) copolymer, carrageenan, sodium alginate, guar gum and modified guar gum.

In general, these polymers are at least partially soluble in aqueous solutions, e.g., water, or aqueous alcohol solutions that have charged side groups, or a monovalent ionic salt thereof. There are many examples of polymers with acidic side groups that can be reacted with cations, e.g., poly(phosphazenes), poly(acrylic acids), and poly(methacrylic acids). Examples of acidic groups include carboxylic acid groups, sulfonic acid groups, and halogenated (preferably fluorinated) alcohol groups. Examples of polymers with basic side groups that can react with anions are poly(vinyl amines), poly(vinyl pyridine), and poly(vinyl imidazole).

Preferred thermoplastic polymers include PVA, polyamide, polycarbonate, polyalkylene glycol, polyvinyl ether, polyvinyl ether, and polyvinyl halides, polymethacrylic acid, polymethylmethacrylic acid, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and sodium carboxymethylcellulose, ethylene glycol copolymers.

Other polymers that may be suitable for use as a mucoadhesive include aliphatic polyesters, poly(amino acids), copoly(ether-esters), polyalkylenes oxalates, polyamides, tyrosine derived polycarbonates, poly(iminocarbonates), polyorthoesters, polyoxaesters, polyamidoesters, polyoxaesters containing amine groups, poly(anhydrides), polyphosphazenes, biomolecules (i.e., biopolymers such as collagen, elastin, bioabsorbable starches, etc.) and blends thereof. For the purpose of this invention aliphatic polyesters include, but are not limited to, homopolymers and copolymers of lactide (which includes lactic acid, D-,L- and meso lactide), glycolide (including glycolic acid), ε-caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene carbonate, δ-valerolactone, β-butyrolactone, χ-butyrolactone, ε-decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one, 2,5-diketomorpholine, pivalolactone, χ,χ-diethylpropiolactone, ethylene carbonate, ethylene oxalate, 3-methyl-1,4-dioxane-2,5-dione, 3,3-diethyl-1,4-dioxan-2,5-dione, 6,8-dioxabicycloctane-7-one and polymer blends thereof. Poly(iminocarbonates), for the purpose of this invention, are understood to include those polymers as described by Kemnitzer and Kohn, in the Handbook of Biodegradable Polymers, edited by Domb, et. al., Hardwood Academic Press, pp. 251-272 (1997). Copoly(ether-esters), for the purpose of this invention, are understood to include those copolyester-ethers as described in the Journal of Biomaterials Research, Vol. 22, pages 993-1009, 1988 by Cohn and Younes, and in Polymer Preprints (ACS Division of Polymer Chemistry), Vol. 30(1), page 498, 1989 by Cohn (e.g. PEO/PLA). Polyalkylene oxalates, for the purpose of this invention, include those described in U.S. Patent Numbers 4,208,511; 4,141,087; 4,130,639; 4,140,678; 4,105,034; and 4,205,399. Polyphosphazenes, co-, ter- and higher order mixed monomer-based polymers made from L-lactide, D,L-lactide, lactic acid, glycolide, glycolic acid, para-dioxanone, trimethylene

carbonate and ε-caprolactone such as are described by Allcock in The Encyclopedia of Polymer Science, Vol. 13, pages 31-41, Wiley Intersciences, John Wiley & Sons, 1988 and by Vandorpe, et al in the Handbook of Biodegradable Polymers, edited by Domb, et al, Hardwood Academic Press, pp. 161-182 (1997). Polyanhydrides include those derived from diacids of the form HOOC-C_6H_4 –O-$(CH_2)_m$-O-C_6H_4-COOH, where m is an integer in the range of from 2 to 8, and copolymers thereof with aliphatic alpha-omega diacids of up to 12 carbons. Polyoxaesters, polyoxaamides and polyoxaesters containing amines and/or amido groups are described in one or more of the following U.S. Patent Nos. 5,464,929; 5,595,751; 5,597,579; 5,607,687; 5,618,552; 5,620,698; 5,645,850; 5,648,088; 5,698,213; 5,700,583; and 5,859,150. Polyorthoesters such as those described by Heller in Handbook of Biodegradable Polymers, edited by Domb, et al, Hardwood Academic Press, pp. 99-118 (1997).

In some embodiments, the mucoadhseive is selected from the group consisting of poly(lactic acid) ("PLA") and poly(glycolic acid)("PGA"), and copolymers thereof.

In some embodiments, the mucoadhesive formulation includes a penetration enhancer such as sodium glycocholate, sodium taurocholate, L-lysophosphotidyl choline, DMSO and a protease inhibitor.

In some embodiments, the curcumin is tagged with a molecule that binds specifically with the olfactory mucosa, such as an odorant.

In some embodiments, the pharmaceutical composition comprising curcumin includes a pharmaceutically-acceptable carrier, a lipophilic micelle, a liposome, or a combination thereof. Preferably, the lipophilic micelle or liposome comprises a ganglioside, a phosphatidylcholine, a phosphatidylserine, or a combination thereof.

In some embodiments, the pharmaceutical composition comprises a substance having an affinity for a receptor site on a neuron.

According to particular methods of intranasal delivery, it can be desirable to prolong the residence time of the pharmaceutical composition in the nasal cavity (e.g., in the olfactory region and/or in the sinus region), for example, to enhance absorption. Thus, the pharmaceutical composition can optionally be formulated with a bioadhesive polymer, a gum (e.g., xanthan gum), chitosan (e.g., highly purified cationic

polysaccharide), pectin (or any carbohydrate that thickens like a gel or emulsifies when applied to nasal mucosa), a microsphere (e.g., starch, albumin, dextran, cyclodextrin), gelatin, a liposome, carbamer, polyvinyl alcohol, alginate, acacia, chitosans and/or cellulose (e.g., methyl or propyl; hydroxyl or carboxy; carboxymethyl or hydroxylpropyl), which are agents that enhance residence time in the nasal cavity. As a further approach, increasing the viscosity of the dosage formulation can also provide a means of prolonging contact of agent with olfactory epithelium. The pharmaceutical composition can be formulated as a nasal emulsion, ointment or gel, which offer advantages for local application because of their viscosity.

The pharmaceutical composition can also optionally include an absorption enhancer, such as an agent that inhibits enzyme activity, reduces mucous viscosity or elasticity, decreases mucociliary clearance effects, opens tight junctions, and/or solubilizes the active compound. Chemical enhancers are known in the art and include chelating agents (e.g., EDTA), fatty acids, bile acid salts, surfactants, and/or preservatives. Enhancers for penetration can be particularly useful when formulating compounds that exhibit poor membrane permeability, lack of lipophilicity, and/or are degraded by aminopeptidases. The concentration of the absorption enhancer in the pharmaceutical composition will vary depending upon the agent selected and the formulation.

To extend shelf life, preservatives can optionally be added to the pharmaceutical composition. Suitable preservatives include but are not limited to benzyl alcohol, parabens, thimerosal, chlorobutanol and benzalkonium chloride, and combinations of the foregoing. The concentration of the preservative will vary depending upon the preservative used, the compound being formulated, the formulation, and the like. In some representative embodiments, the preservative is present in an amount of 2% by weight or less.

The pharmaceutical composition can optionally contain an odorant, e.g., as described in EP 0 504 263 B1 to provide a sensation of odor, to aid in inhalation of the composition so as to promote delivery to the olfactory epithelium and/or to trigger transport by the olfactory neurons.

In some embodiments, the curcumin is delivered in a pharmaceutical composition selected from the group consisting of a liquid, a powder, a spray, a nose drop, a gel, an ointment, or a combination thereof.

In some embodiments, the curcumin is delivered in a pharmaceutical composition comprising piperine.

In some embodiments, the method of the present invention includes applying the pharmaceutical composition to an olfactory area in the upper third of the nasal cavity, such as the olfactory mucosa. In some embodiments, the method of the present invention includes applying the pharmaceutical composition to a roof of a nasal cavity. In some embodiments, the method of the present invention includes applying the pharmaceutical composition by employing a tube, a catheter, a syringe, a packtail, a pledget, a submucosal infusion, an intranasal spray container, or a combination thereof.

For delivery, there is provided a standard nose drops squeezable spray container with a long thin semi-flexible tube attached to the distal end. The outer diameter of the tube is less than a millimeter, preferably less than 0.5 mm, more preferably less than 0. 25 mm. The exit hole of the tube is preferably located on the peripheral wall near the distal end of the tube so that spray exiting it can be directed upwards. There is a marker on the container that indicates when the exit hole is oriented upwards towards the cribriform plate.

Therefore, in accordance with the present invention, there is provided an intranasal spray device comprising:

a) a hollow container having a first opening,

b) a flexible tube having a throughbore, a distal end portion having a second opening, a proximal end having a third opening,

c) a formulation comprising an effective amount of curcumin contained within the container,

wherein the third opening of the proximal end of the tube is in fluid connection with the first opening of the hollow container.

In other embodiments, the intranasal spray device comprises:

a) a hollow container having a first opening,

b) a flexible tube having a throughbore, a side surface having a second opening, a proximal end having a third opening, and a distal end having an end surface,

c) a formulation comprising an effective amount of curcumin contained within the container,

wherein the third opening of the proximal end of the tube is in fluid connection with the first opening of the hollow container.

The user directs the tube towards the medial wall of the nostril and points upwards so as to direct it medially to and over the middle nasal concha. The length of the tube is predetermined so that when the user has the shoulder of the container flush against the nostril, the hole is adjacent the cribriform plate.

If there is concern about the safety of inserting a tube through a nasal passage, then the tube can also be balloon-like, so that it expands to full length upon being pressurized.

Delivery through anterior nares

It has been reported that less than about 10% of inspired air travels through the olfactory slit. Accordingly, a great deal of the curcumin delivered to the nasal cavity does not region the olfactory mucosa. Therefore, it is an object of the present invention to increase the amount of curcumin delivered to the olfactory mucosa.

It has been reported in the literature that when the airflow in the nasal cavity can be characterized as laminar, streamlines from the anterior 10% of the nares reach the olfactory slit.

Accordingly, in some embodiments of the present invention, at least 25% of the formulation comprising curcumin is delivered into the anterior 10% of the nares. Preferably, at least 50% of the formulation comprising curcumin is delivered into the anterior 10% of the nares. More preferably, at least 75% of the formulation comprising curcumin is delivered into the anterior 10% of the nares.

In some embodiments, focused delivery of the formulation into the anterior portion of the nares is assisted by providing a guidance tube located substantially in the anterior 10% of the nares.

In some embodiments, there is provided a device for assisting delivery of a formulation to the anterior portion of the nares, comprising:

a) an annulus adapted to fit in the opening of the nares and

b) a guidance tube extending from the annulus and connected to the annulus in the region of the anterior 10% of the nares.

As the streamlines just inside the opening of the nares travel at an angle of about 90 degrees, the guidance tube is preferably situated at that angle in order to deliver the formulation into those streamlines. Preferably, the annulus is oval-shaped to correspond to the shape of the nares.

In use, the user simultaneously slowly inhales while actuating the spray container containing the formulation. The formulation is delivered to the anterior portion of the guidance tube as an aerosol in a laminar flow. The formulation travels through the guidance tube and exits is posterior end as an aerosol in a laminar flow. Thus, the formulation should enter the nasal cavity in conformance with the laminar streamlines of the inspired air produced by the inhalation. Once in these streamlines, the formulation travels preferentially to the olfactory slit and thus to the olfactory mucosa.

Helium

In some embodiments, the curcumin is delivered to the olfactory mucosa through helium-laden microbubbles that can rise in the air. This takes advantage of the fact that the olfactory mucosa is located in the highest portion of the nasal cavity. Theoretically, helium-filled microbubble of proper dimensions that are conventionally delivered into the nasal cavity should travel upwards to the highest spot in the nasal cavity – the olfactory mucosa.. Once they are in place, the microbubbles can be exploded with a simple hand held, non-invasive ultrasound device, thereby releasing their contents. This invention would greatly increase the amount of curcumin that ends up in the olfactory mucosa.

Therefore, in accordance with the present invention, there is provided a method for transporting a neurotherapeutic drug to a brain of a mammal, comprising:

a) applying a plurality of microbubbles comprising the neurotherapeutic drug (preferably, curcumin), wherein the microbubbles are lighter than air (and preferably contain helium gas), to a nasal cavity of the mammal, whereby the microbubbles rise to an upper third of a nasal cavity of the mammal, whereupon the neurotherapeutic drug is absorbed through an olfactory mucosa and transported to the brain of the mammal.

In other embodiments, the curcumin is delivered to the olfactory mucosa as an aerosol in a bolus of helium gas that can rise in the air. This also takes advantage of the fact that the olfactory mucosa is located in the highest portion of the nasal cavity. Theoretically, a helium bolus and the aerosols therein that are conventionally delivered into the nasal cavity should travel en masse to the highest spot in the nasal cavity – the olfactory mucosa. Once they are in place, the aerosols can deposit upon the nasal walls containing the olfactory mucosa. This invention would greatly increase the amount of curcumin that ends up in the olfactory mucosa.

Therefore, in accordance with the present invention, there is provided a method for transporting a neurotherapeutic drug to a brain of a mammal, comprising:

a) providing a formulation comprising aerosol droplets of a neurotherapeutic drug (preferably, curcumin) in a bolus of helium gas, and

b) applying the formulation to a nasal cavity of the mammal, whereby the formulation rises to an upper third of a nasal cavity of the mammal, whereupon the neurotherapeutic drug is absorbed through a nasal mucosa and transported to the brain of the mammal.

US Patent Publication No. 2003/0199594 ("Shah") discloses a propellant composition for use with an aerosol wherein the composition comprises between 70% and 100% helium, wherein the composition may be used in intranasal spray devices such as metered dose inhalers. Shah discloses that the composition may further include a solvent (such as an alcohol such as ethanol) and a dispersing agent (such as oleic acid).

Therefore, in accordance with the present invention, there is provided an intranasal spray device having a formulation comprising:

a) an effective amount of curcumin, and

b) a propellant comprising helium (preferably, at least about 70% helium by weight), and

c) (optionally) a solvent (such as water or an alcohol such as ethanol), and

d) (optionally) a dispersing agent (such as oleic acid)

Curcumin prodrugs

Although high lipophilicity in a therapeutic compound enables it to easily cross the blood brain barrier and penetrate brain tissue, that high lipophilicity also usually means that the compound is not very soluble in water. For example, US 2003/0153512 reports that lipophilic curcumin has a solubility in water of only about 0.004 mg/ml. Because intranasal formulations are generally provided in small doses of between 50 µl and 200 µl (typically, 100 µl), there may be an issue in providing a sufficient amount of the lipophilic compound in a single dose in order to generate a therapeutic response.

Therefore, one aspect of the present invention involves providing the therapeutic compound in the form of a water-soluble prodrug. The high water solubility of the prodrug allows large amounts of it to be provided in a single dose, enter the nasal mucosa and passively diffuse across the nasal mucosa. Once the prodrug has reached the boundary of brain tissue, the prodrug is metabolized (typically through a chemical or enzymatic hydrolysis reaction with brain esterases) to the parent lipophilic molecule, whereby it can diffuse into the brain tissue bulk and provide a therapeutic benefit.

Therefore, in accordance with the present invention, there is provided a method for administering curcumin to a brain of a mammal, comprising:

a) applying a pharmaceutical composition comprising a water soluble curcumin prodrug to an upper third of a nasal cavity of the mammal, wherein the curcumin prodrug is absorbed through a nasal mucosa and transported to the brain of the mammal.

In some embodiments, the parent lipophilic compound is a phenol that is rendered water-soluble by creating an ester having an added polar moiety or a permanent charge. Preferably, the ester has a polar moiety. Preferably, the polar moiety contains a tertiary or quaternary nitrogen.

Therefore, in some embodiments, the ester contains an aminoalkanecarboxylic acid as the polar moeity. These compounds are characterized by an ester moiety having an alkane group between the nitrogen compound and the carboxyl group. Preferably, the moiety has terminal alkyl groups. More preferably, the aminoalkanecarboxylic acid contains a glycinate moiety, more preferably a methylated glycinate moiety, such as N, N, dimethylglycinate.

Therefore, in accordance with the present invention, there is provided a curcumin ester prodrug comprising an aminoalkylcarboxylic acid moeity. Preferably, the aminoalkylcarboxylic acid moiety comprises an aminoalkanecarboxylic acid moiety. In some embodiments, the aminoalkanecarboxylic acid contains a glycinate moiety. Methods of making such compounds are found in Pop, Pharm. Res., Vol. 13(1) 1996, 62-69.

Now referring to FIGS. 1a –1c, there are provided novel curcumin prodrugs of the present invention, labeled **(1)** to **(30)**.

Therefore, in some embodiments, the aminoalkanecarboxylic acid moiety comprises a single terminal methyl group **(1)**, two terminal methyl groups **(2), (17),(20)**, or three terminal methyl groups **(3)(19)**.

In some embodiments, the aminoalkanecarboxylic acid moiety comprises a single terminal ethyl group **(5)**, two terminal ethyl groups **(6)(18)**, or three terminal ethyl groups**(8)**.

In some embodiments, the aminoalkanecarboxylic acid moiety comprises a terminal ethyl group and a terminal methyl group; a terminal ethyl group and two terminal methyl groups **(10)**; or two terminal ethyl groups and a terminal methyl group **(9)**.

In some embodiments, the aminoalkanecarboxylic acid moiety comprises a terminal propyl group.

In some embodiments, the prodrug is in the form of a salt, as in compounds **(3), (8)-(14), (17)-(20)**. Preferably, the salt comprises an anion selected from the group consisting of chloride **(14)(17)(18)(20)**, iodide **(19)** and bromide.

In some embodiments, the prodrug is characterized by an ester moiety in which an ethane **(17-18)** or propane **(19-20)** group lies between the carboxyl group and the nitrogen group, and preferably has a terminal alkyl group.

In some embodiments, the prodrug is characterized by an ester moiety in which the alkane that lies between the carboxyl group and the nitrogen group is substituted. In some embodiments, this is a terminal ethyl group **(7)** lying between the carboxyl group and the nitrogen group. Preferably, the moiety has a second terminal alkyl group.

In some embodiments, the curcumin prodrug comprises a carbamoyl moiety, preferably a (carboxymethyl)carbamoyl moiety **(16).** The (carboxymethyl)carbamoyl moiety of **(16)** can be made in substantial accordance with Mulholland, Annals Oncology, 12, 245-8(2001).

In some embodiments, the aminoalkanecarboxylic acid moiety comprises a nitrogen heterocycle **(21,23)**. In some embodiments, the heterocycle contain oxygen **(23)**. Moeity **(23)** may be may in accordance with the procedure disclosed in Pop, Pharm. Res., 13,3, 469-475 (1996) and Trapani, Intl. J. Pharm., 175(1998) 195-204. Moeity **(21)** may be may in accordance with the procedure disclosed in Trapani, Intl. J. Pharm., 175(1998) 195-204. Pop, Pharm. Res., 13,3, 469-475 (1996) discloses that dexanabinol having a nitrogen heterocycle moiety like **(21,23)** has a solubility of about 5-7 mg/ml.

In some embodiments, the aminoalkanecarboxylic acid moiety comprises a L-proline group**(15)**. Moeity **(15)** may be may in accordance with the procedure disclosed in Altomare, Eur. J. Pharm. Sci., 20, 2003, 17-26 and Trapani, Intl. J. Pharm., 175(1998)

195-204. Altomare reports that the L-proline ester of propofol provides the prodrug with a solubility of about 1.1 mmol/ml.

In some embodiments, the aminoalkanecarboxylic acid moiety comprises a benzoate group**(22)**. Moeity **(22)** may be made in accordance with the procedure disclosed in Bundgaard, Pharm. Res., 8,9,1087-1093, (1991). Bungaard discloses that providing a benzoate moeity **(22)** between the carboxyl and amino groups of a glycinate moiety raises the solubility of Acyclovir from 1.4 mg/ml to 3 mg/ml at a pH of about 7, and to about 300 mg/ml at a pH of about 5.

Other curcumin glycine esters are disclosed in Mishra, Bioorganic & Medicinal Chemistry, 13 (2005) 1477-86; Kumar, Nucleic Acids Symposium Series No. 44, 2000, pp. 75-76; Kapoor, Cancer Lett., 2007, Apr. 18, 248(2) 245-50; Tong, Anti-Cancer Drugs 17(3) 279-187 March 2006; and Mishra, Free Rad. Biology & Medicine, 38, (2005) 1353-1360

Desirable Prodrug Qualities

The curcumin prodrugs of the present invention should have three qualities: high solubility in water, high stability in water and rapid conversion to curcumin in the brain.

solubility

The literature has demonstrated that glycinate-containing moieties provide much greater water solubility to phenolic compounds, typically increasing the solubility of the parent compound to the 25-50 mg/ml range. Examples of the solubility increase provided to low solubility phenolics by their esterification by glycinates are as follows:

Table I

Parent Phenol	**Parent Solubility**	**Ester solubility**	**Reference**

	(mg/ml)	(mg/ml)	
dexanabinol	2-7	~50	(a)
d-χ-tocopherol	--	~25	(b)
17β-estradiol	0.008	0.8-20	(c)
testosterone	0.01	>100	(d)
menahydroquinone	---	~25	(e)
phenol (+L-dopa)	---	5	(f)

(a) Pop, J. Pharm Sci, 88,11,1999, 1156
(b) Takata, J. Lipid Res., 2002,43,2196
(c) Al-Ghananeem, AAPS PharmSciTech, 2002,3,1,article 5
(d) Hussain, J. Pharm Sci., 91:785-789,2002.
(e) Takata, Pharm. Res., 21,1,1995,18-23(solubility reported as 50 mM)
(f) Kao, Pharm. Res., 17,8,2000,978-984

It further appears that pH has a great influence upon the solubility of nitrogen – containing esters of phenols. The influence of pH upon the solubility of nitrogen–containing esters of phenols as reported in the literature is presented below:

Table II

Parent	**ester solubility at neutral pH (mg/ml)**	**ester solubility at acidic pH (mg/ml)**	**Reference**
Propofol	0.064	4.67	(a)
	0.735	6.920	(a)

	0.213	0.35	(a)
Acyclovir	3	300	(b)

(a) Trapani, Intl. J. Pharm., 175(1998) 195-204.

(b) Bundgaard, Pharm. Res., 8,9,1087-1093, (1991).

The literature shows that, in most cases, providing the ester in an acidic pH (about 4-5) increases its solubility in water by about 10 fold.

There also appears to be a special class of glycinate-like moieties that increase the water solubility of the phenolic compound even further. In particular, there are a number of glycinate-like moieties possessing additional oxygens that increase the water solubility of the phenolic compound to concentrations in the 100-1000 mg/ml range. Examples of such compounds are provided below:

Examination of these compounds reveals that each is characterized by terminal substitution of the amine by oxygen-containing moeities. They are particularly characterized by:

a) a (carboxymethyl) carbamoyl moiety (Mullholland, Ann. Oncology, 12,245-248 (2001)),
b) an N-acyloxymethyl moiety (Neilsen, Eur.J.Pharm.Sci., 2005, April ,24,5,433-40), or
c) a (oxyalkyl) acetamide moiety (USP 5073641),
d) glycine benzoates (WO90/08128)

Without wishing to be tied to a theory, it is believed that that these moieties may act as surfactants which, in the appropriate concentration, produce micelles. Indeed, it has been reported that a (dihydroxyethyl) glycinate moiety acts as a surfactant (USP

6831108), and that the (carboxymethyl) carbamoyl moiety can produce micelles (Shamsi, Electrophoresis, 2005, 26, 4138-52).

Therefore, in accordance with the present invention, there is provided a formulation comprising a micellar curcumin prodrug.

The (carboxymethyl) carbamoyl moiety (Mullholland) is of particular interest because is has a high solubility (>20 mg/ml). Its rapid hydrolysis in blood ($t_{1/2}$ = 0.39 hr) may indicate that it is also rapidly hydrolyzed by brain esterases as well. Lastly, it appeats to be relatively stable in water ($t_{1/2}$ = 16.9 hr) and so likely is very stable in acidic aqueous solutions.

It has been reported that converting the prodrug into a salt likewise increases its solubility in water. For example, WO90/08128, which relates to glycine-like ester prodrugs, reports that conversion of such prodrugs into salts produce water solubilities of up to 15 w/v%. Jensen, Acta Pharm. Nord., 3,(1) 31-40 (1991) reports that a dichloride salt of one aminoalkylbenzoate ester was found to have a water solubility of greater than 40% v/v at 20°C. Lastly, US Patent No. 4,482,722 reports an addition salt of metrazole glycinate to have a water solubility of about 30%.

Stability

Because the formulations of the present invention are desirably used in the form of aqueous-based nasal sprays, the ester prodrugs of the present invention should remain stable in water for an appreciable time. It appears that glycinate esters are much more stable in acidic aqueous solutions than in neutral aqueous solutions. Al-Ghananeem, AAPS PharmSciTech, 2002, 3,1, article 5, reports that the stability of phenol esters is influenced by pH, that at slightly acidic pHs (pH 3-5), one phenol ester (17-DMABE$_2$HCl) would have sufficient shelf life to be formulated in a solution dosage form, and that a pharmaceutical nasal spray solution of the prodrug at pH 4 would have a shelf life of approximately 19 months at 25°C. Similarly, Kao, Pharm. Res., 17,8,2000,978-984 reports a maximum stability for the L-dopa butyl ester at a pH of 4.4, that the estimated time for 10% decomposition at pH 4.4, (0.05M phosphate buffer) and

10 °C is calculated to be 2.7 years, and that at slightly acidic pHs (pH 3-5), the ester would have sufficient shelf-life stability to be formulated in a solution dosage form. Lastly, PCT Published Patent Application WO90/08128, which relates to benzoate-containing glycine-like ester prodrugs, reports that one hydrocortisone-based prodrug possessed a shelf-life in aqueous solutions of pH 4.0 of 6.0 and 10.2 years at 25 °C and 20 °C, respectively.

Therefore, in some embodiments of the present invention, the curcumin formulation contains a buffer setting a pH of between about 3.0 and 5.5, preferably a pH of between about 3.5 and 5, preferably a pH of between about 4 and 5. In some embodiments of the present invention, the curcumin formulation contains a buffer setting a pH of between about 3 and 4. It is believed that setting the pH of the formulation in these ranges would allow the formulations to have a commercially satisfactory shelf life.

Also in some embodiments of the present invention, there is provided an intranasal spray device comprising a formulation comprising:

a) an effective amount of curcumin, and

b) a buffering agent setting a pH of between 3 and 5.5.

Conversion rate

Once the prodrug has reached the brain, it is desirable for the esterified prodrug to be converted to its parent compound in a very rapid fashion. Simply, the prodrug should be converted to the parent compound by brain esterases before it is drained from the brain. In order to understand whether a prodrug converts sufficiently rapidly to the parent compound, it is important to know the residence time of the prodrug in the brain or CSF.

Review of concentration versus time profiles of intranasally instilled compounds reveals behavious characterized by a two phase model. In the first phase, the drug rapidly attains a peak concentration and then rapidly decreases to about 10-25% of the peak concentration within about 1-2 hours. The second phase is characterized by a very slow decrease in the concentration of the drug over the next 24 hours.

Therefore, if the concentration of the drug is approximated as that which is present in the 1-2 hour range (i.e., about 10-25% of the peak concentration), it can be assumed that the drug is present in the brain for about 24 hours. Accordingly, in order to be useful, the conversion rate of the prodrug to the parent compound in the brain should be characterized by a half-life $t_{1/2}$ of no more than about 12 hours.

In at least three instances, the literature has reported conversion rates of a glycinate-containing phenolic ester to the parent compound by brain homogenate. Two of these papers report very rapid conversion. Al-Ghananeem, AAPS PharmSciTech, 2002, 3,1, article 5, reports that the rapid conversion of estradiol glycinate esters to the parent estradiol in about 1-2 minutes. Kao, Pharm. Res., 17,8,2000,978-984 reports the rapid conversion of a benzyl L-dopa ester (wherein the L-dopa parent contains the glycinate moiety) in about 1 minute.

Since it is desirable to have a prodrug-to-parent conversion rate characterized by a half life $t_{½}$ of no more than about 12 hours, and the literature reports half-lives the rapid conversion of glycinate esters to the parent phenolic compound in about 1-2 minutes, it is clear that glycinate prodrugs should be assumed to be fully converted in the brain to the parent prodrug. It should be noted that one investigator (Trapani, Intl. J. Pharm., 175(1998) 195-204) reports a much slower conversion of propofol glycinate ester to the parent propofol. However, review of the pertinent structure-activity relationships indicates that the hydroxyl moiety of the propofol is severely sterically hindered by adjacent isopropyl groups of the propofol. Without wishing to be tied to a theory, it is believed that the severe steric hinderance of the etheric oxygen of these propofol glycinates is the reason for its slow conversion from the glycinate ester to propofol.

In contrast, the etheric oxygen of both benzyl L-dopa ester and the estradiol glycinate ester experiences much less streric hinderence, and so the brain esterase has an opportunity to freely approach the etheric oxygen from at least one side of the molecule. As a result, the hydrolysis reaction by brain esterases can occur much more quickly.

Undertaking a similar analysis with curcumin glycinate esters reveals that, like L-dopa and estradiol, the curcumin glycinate ester experiences much less streric hinderence, and so the brain esterases have the opportunity to freely approach the etheric oxygen of the curcumin glycinate ester from at least one side of the molecule.

Moreover, it appears that another research group reports a much faster conversion of the propofol dimethyl glycinate ester to the parent and that the Trapani group has acknowledged this difference. See Altomare, Eur.J.Pharm.Sci., 20,2003 17-26.

Lastly, the Kao paper is noteworthy in that it reports highly similar half-lives for the conversion of L-dopa esters to L-dopa in brain homogenate and plasma. A high coincidence of half-lives for the conversion of propofol glycinate esters to propofol in brain homogenate and plasma is also reported in Trapani. If conversion in plasma is used to reasonably estimate the conversion of glycinate esters in brain homogenate, then the literature may be further consulted for the conversion of glycinate-containing phenolic esters to the parent phenolic compound in plasma. The literature, reported below in Table III, reports the following:

Table III

Parent Compound	**Half-life Of glycinate ester In plasma (min)**	**Reference**
Dexanabinol	0-26	(a)
Phenol (+L-dopa)	0.36	(b)
Acyclovir	0.8	(c)
Estradiol	1-2	(d)
Propofol	24 hrs	(e)

Menahydroquinone 13 (f)

(a) Pop,J. Pharm.Sci., 88,11,1999, 1156

(b) Kao, Pharm. Res., 17,8,2000,978-984

(c) Bundgaard, Pharm. Res., 8,9,(1991) 1087-1093

(d) Al-Ghananeem, AAPS PharmSciTech, 2002,3,1,article 5

(e) Trapani, Intl. J. Pharm., 175(1998) 195-204

(f) Takata,_ Pharm. Res., 21,1,1995,18-23

Thus, using literature reports of conversion in plasma to reasonably estimate the likely conversion window of glycinate esters in brain homogenate, it appears that the conversion of glycinate-containing phenolic esters to the parent phenolic compound in brain is again quite rapid.

Therefore, because unhindered phenolic glycinate esters rapidly convert to the parent phenol in brain homogenate, and because dimethylglycinate phenolic esters convert rapidly in plasma, it is believed that the conversion rates of glycinate-containing curcumin esters to the parent curcumin compound will be rapid in a brain environment.

How to make prodrugs

Al-Ghananeem, AAPS PharmSciTech, 2002, 3,1, article 5, teaches how to make an ester comprising the following amino-alkane-carboxylic acid moieties: 3-N,N dimethylamino butyl ester HCl (3-DMABE$_2$HCl); 3-N,N-diethylamino propionyl ester hydrochloride (DEAPE$_2$HCl); 3-N,N,N-trimethylamino butyl ester iodide (3-TMABE$_2$ iodide) and 17-N,N dimethylamino butyl ester HCl (17-DMABE$_2$HCl);

In some embodiments, the water-soluble ester prodrug is created by reacting the phenolic parent compound with dimethylglycine. The literature reports rendering lipophilic phenolic compounds water soluble by reacting the phenolic parent compound with dimethylglycine. For example, Al-Ghananeem, AAPS PharmSciTech, 2002, 3,1, article 5, reports increasing the water solubility of 17B-estradiol from 0.008 mg/ml to 0.8

mg/ml (a 100-fold increase) by creating a dimethylglycine ester of the parent compound. Al-Ghananeem further found that this ester was readily hydrolyzed by rat brain homogenate to provide the parent compound, and that intranasal administration of the prodrug provided a 5-8 fold higher CSF concentration of 17B-estradiol when compared with a comparable intravenous dose of the prodrug. Al-Ghananeem concluded that the prodrug provides for targeted intranasal delivery of 17B-estradiol to the brain.

In some embodiments, creation of the water soluble ester prodrug from the parent phenolic compound is carried in substantial accordance with the method described in Hussain, J. Pharm. Sci., 91,3,March 2002, 785-789. In particular, dimethylglycine HCl and oxalyl chloride are gently warmed at 40 °C until evolution of HCl gas ceases. Nitrogen gas is then bubbled through the solution to remove unreacted oxalyl chloride. The resulting acid chloride is dissolved in dimethylformamide and added dropwise with stirring to a solution of the parent phenolic compound in methylene chloride. The reaction mixture is refluxed for 3 hours. The ester is then isolated, and converted to an HCl salt.

In some embodiments, creation of the water soluble ester prodrug from the parent compound is carried in substantial accordance with the method described in Al-Ghananeem, AAPS PharmSciTech, 2002, 3,1, article 5. In particular, 4-(dimethylamine) butyric acid hydrochloride (2.0 g, 0.012 mol) or 3-(dimethylamine) proprionic acid hydrochloride (2.2 g, 0.012 mol) is used as a starting material. The amino acid is refluxed gently with oxalyl chloride (1.6 mL, 0.018 mol) for a short period of time until a clear yellow solution is formed. The solution mixture is then flushed very gently with a stream of nitrogen to remove excess oxalyl chloride leaving a solid behind (the acid chloride).

The phenolic esters having 3-N,N-dimethylamino butyl ester hydrochloride (3-DMABE$_2$HCl); 3-N,N-dimethylamino propionyl ester hydrochloride (3-DEAPE$_2$HCl); and 3-N,N,N-trimethylamino butyl ester iodide (3-TMABE$_2$ iodide) as moieties are synthesized after the appropriate acid chloride following the procedure reported in Hussian, Pharm. Res., 1988, 5,1,44-47. The alcoholic ester, 17-N,N-dimethylamino butyl

ester hydrochloride (17-DMABE_2HCl) is prepared by dissolving the acid chloride slowly in 10 mL N,N, dimethylformamide (DMF) while in an ice bath since the reaction is exothermic. The parent phenolic compound is then dissolved in methylene chloride, and the DMF solution of acid chloride was added dropwise to the solution of the parent phenolic compound with stirring; The reaction mixture is refluxed gently for 45 minutes, then filtered. The filtrate is evaporated using a Buchi model rotavaporator (Westbury, New York) then redissolved in a small volume of 80 $CHCl_3$: 20 MeOH. The content of the mixture is separated and purified using a silica gel column. The solvent mixture is evaporated and the product redissolved in a small volume of methylene chloride, then hydrogen chloride gas is carefully bubbles through the solution with stirring. The ester hydrochloride is precipitated by adding enough diethyl ether to make the solution turbid and then the mixture is placed in a refrigerator at 4 °C overnight. The final product is collected by solvent evaporation in a vacuum dessicator using a Precision Scientific model D75 pump (Chicago, IL) at room temperature and stored in a desiccator until used.

In some embodiments, creation of the water soluble ester prodrug from the parent compound is carried in substantial accordance with the method described in Takata, J. Lipid Res., 2002, 43, 2196-2204. In particular, to a dry pyridine solution of the parent phenolic compound (4.8 mmol), 5.7 mol of N,N,-dimethylglycine HCl and 5.7 mmol of dicyclohexylcarbodiimide are added. The reaction mixture is stirred at room temperature for 20 hours and the dicyclohexylurea formed is removed by filtration. After the solvent is evaporated, the residue is treated with 100 ml of water and made alkaline by sodium bicarbonate. The solution is then extracted with ethyl aceate (100 ml x 3). The organic layer is dried over anhydrous sodium sulfate with ethyl acetate and evaporated. The residue is fractionated with a flash column packed Wakogel LP40, 60A using n-hexane ethyl acetate (8:2, v/v) as the eluent. The isolated ester is directly collected in isopropyl ether containing 3% HCl dioxane solution, and the precipitate and recrystallized from acetone to give the HCl salt of the parent phenolic compound.

Brain levels

Evidence that the intranasal installation of a water soluble prodrug of curcumin can deliver high levels of curcumin to the brain is found in the estradiol-based work of Al-Ghananeem, AAPS PharmSciTech, 2002, 3,1, article 5. 17β-Estradiol is a 272 dalton phenol having a octanol/water partition coefficient of about log P = 3.1 - 4.0. Therefore, estradiol is similar to curcumin in that each is a lipophilic, phenolic small molecule. Also, like curcumin, 17β-estradiol also suffers from poor bioavailability. Moreover, Al-Ghananeem reports that estradiol is not very soluble in water, thereby making impractical the nasal administration of an effective dose (0.1 mg in 0.1 ml). Al-Ghananeem reports modifying estradiol with a dimethylglycinate moiety to increase the water solubility of estradiol from 0.008 mg/ml to about 0.8 mg/ml – a 100-fold increase, and modifying estradiol with a 3-DEAPE$_2$HCl moiety to increase the water solubility of estradiol from 0.008 mg/ml to about 20 mg/ml - over a 1000 fold increase. Thus, the solubility of a lipophilic, phenolic small molecule like curcumin, which has a solubility in water of only about 0.004 mg/ml, can be greatly increased.

Because the typical volume of an intranasal dose for a human can be up to 0.2 ml, and Table I above reports increases in solubility in the range of 20 mg/ml, nasal administration can be expected to achieve a payload of up to about 20 mg/ml x 0.2 ml = 4 mg/dose. Because providing two doses per nostril twice a day provides 8 doses per day, it is believed that up to about 32 mg/day of estradiol can be intranasally administered. This amount provides a whole body concentration of nearly about 0.5 mg/kg.

Further, Al-Ghananeem reports that the nasal installation of 0 1 mg/kg of water soluble prodrugs of 17β-Estradiol results in peak cerebrospinal fluid (CSF) concentrations of estrdiol of between about 30 ng/ml (for 17-DMABE$_2$-HCl) to about 66 ng/ml (for 3-DMABE$_2$-HCl), which provides a molar concentration of the compound of between about 0.075 μM and 0.15 μM. The pharmacokinetic results of Al-Ghananeem correspond quite well with those of Kao, who reported that nasal installation of 20 mg/kg of water soluble ester prodrug of L-dopa results in peak cerebrospinal fluid (CSF) concentration of about 10-20 ug/ml. Accordingly, a 0.5 mg/kg nasal instillation of a water soluble prodrug of a lipophilic, small molecule phenolic compound such as

estradiol or curcumin can likely provide CSF concentrations of up to about 0.75 μM. Since it has been reported that 0.1 – 1.0 μM curcumin inhibits the *in vitro* formation of amyloid beta oligomers, and blocks the *in vitro* toxicity of $A\beta_{1-42}$ oligomers in differentiated neuroblastoma cells (Yang, J. Biol. Chem., 280,7, Feb. 18.,2005, 5892-5901), it appears that the intranasal installation of a water soluble prodrug of curcumin will likely allow an attainable dosing schedule to attain a brain concentrations of curcumin that will provide a therapeutic benefit against Alzheimer's Disease.

Dual phase curcumin

In some embodiments, curcumin is present within two separate phases of the formulation. The first phase is preferably a quick release phase that quickly delivers curcumin to the olfactory mucosa. The quick delivery of curcumin will have the effect of transiently disabling enzymes systems such as UGTs and P450s that metabolize curcumin. The second phase is a slow release phase that slowly delivers curcumin to the olfactory mucosa. Once these enzyme systems are transiently disabled, the slow release phase slowly releases curcumin in an environment that is substantially free of enzymatic metabolic interference.

Therefore, in accordance with the present invention, there is provide a formulation comprising:

a) a first, quick release phase comprising an effective amount of curcumin for transiently disabling enzyme systems, and
b) a second slow release phase comprising an effective amount of curcumin for treating a neurodegenerative disease.

In some embodiments, the first quick release phase can be selected from the group consisting of a mucoadhesive and an oil, such as peppermint oil. Peppermint oil has the quality of independently inhibiting UGT and P450 enzymes.

In some embodiments, the second slow release phase can be selected from the group consisting of liposomes and thermoplastic polymers (such as PLGA).

In accordance with the present invention, there is provided a formulation comprising:

a) a polymeric particulate depot comprising curcumin, and
b) a mucoadhesive.

In some embodiments, the mucoadhesive is present as a coating upon the polymeric particulate depot.

In some embodiments, the mucoadhesive is present as a separate particulate.

In some embodiments, the mucoadhesive comprises a compound selected from the group consisting of a chitosan and a cellulose.

In some embodiments, the mucoadhesive further contains curcumin.

In some embodiments, the polymeric particulate depot is a liposome.

In some embodiments, the polymeric particulate depot is a thermoplastic bioresorbable polymer.

In some embodiments, the curcumin is housed in microspheres. Kumar, Indian J. Physiol. Pharmacol., 2002 Apr. 46(2) 209-17 reports that when curcumin was loaded into either albumin or chitosan microspheres, a biphasic release pattern occurred, characterize by a burst effect followed by a slow release. This biphasic effect corresponds well with the stated desire to have a first dose of curcumin released in order to inhibit enzyme activity in the olfactory mucosa followed by a second dose that is slowly released, taken up by the olfactory neurons and transported to the brain. In some embodiments, the curcumin is housed in microspheres that display a biphasic release effect.

Enzyme inhibition by curcumin

Although curcumin is susceptible to metabolism by enzymes, curcumin is also known as an inhibitor of those very enzymes. For example, Hong, Biochem. Biophys. Res. Comm., 2003 Oct.10, 310(1) 222-7, reports that co-treatment by curcumin of EGCG in cells transfected with hPgP, hMRP1 and hMRP2 genes increased the accumulation of EGCG in those cells.

It has been reported that curcumin influence both multidrug resistance protein 1 (MRP1) multidrug resistance protein 2 (MRP2). It appears that curcumin inhibited both MRP-1 and MRP-2-mediated transport with IC_{50} values of 15 uM and 5 uM. Wortelboer, Chem. Res. Toxicol., 2003 Dec. 16:12, 1642-51. Wortelboer also recognized the "complex interplay between MRP inhibition and metabolism of MRP inhibitors. Chearwae, Cancer Chemother. Pharmacol., 2006, Feb. 57(3) 376-88 reports curcumin to inhibit MRP1, with an IC50 of about 14.5 uM.

Of note, Hong, Biochem. Biophys. Res. Comm. 2003 Oct. 10, 310(1) 222-7 reports that the inhibition of MRPs by curcumin led to a significant increase in the amount of green tea catechin EGCG in MDCKII/MRP1 and HT-29 cells. Therefore, there is a special advantage in providing both curcumin and EGCG in the same formulation, as curcumin can provide therapeutic benefits and increase the bioavailability of EGCG.

It appears that curcumin is metabolized mainly through glucuronidation. Pan, Drug Metab. Dispos., 1999, 27,1, 486-494. However, it has been repeatedly demonstrated that curcumin also inhibits glucuronidation. Basu, Drug. Metab. Dispos. , 2004, Jul. 32(7) 768-73 reports that curcumin transiently inhibits MPA glucuronidation in both human LS180 colon cells and mouse duodenum. Basu, PNAS, May 3, 2005, 102(18) 6285-90 reports the inhibition of cellular UGT1a7 and UGT1A10 activites after exposure to curcumin. Basu, J. Biol. Chem., 279, Jan.9, 2004, 1429-1441 reports that curcumin reversible targets UGTs causing inhibition. In general, curcumin appears to provide its maximum inhibition of UGT activity about 1-2 hours after exposure. Basu, Biochem. Biophys. Res. Comm., 303(2003) 98-104 (Fig. 1) reports that the inhibition of

UGT1A1 by curcumin can reach about 95% after about one hour after exposure, returning to about 80% of the control value after about 10 hours. Naganuma, Biol. Pharm. Bull., 2006 Jul. 29(7) 1476-9 reports the moderate inhibition of UGT activity in the conjugation of 1-naphthol in Caco-2 cells by curcumin.

Because of the strong inhibition of UGTs by curcumin, curcumin has been proposed as a pre-treatment for cancer chemotherapy, and it has been reported that transient inhibition of glucuronidation by oral pretreatment with curcumin before MPA administration caused a six-fold increase in immunosuppression of antigen-stimulated spleen cytotoxic T-lymphocyte proliferation in mice. See (http://nichddirsage.nichd.nih.gov:8080/ar2004/pages/hdb/sgddm.htm).

There is, however, one investigator (van der Logt, Carcinogenesis, 24,10, 1651-56, 2003) that reports enhancement of UGT activity by curcumin.

Because the glucuronidation inhibition by curumin is reversible, it appears that curcumin could be used for a pre-treatment of the olfactory mucosa in order to inhibition enzymatic activity upon the later therapeutic dose of curcumin without a concern for drug-drug interactions.

Therefore, in some embodiments, a first dose of curcumin is intransally administered to the patient (to inhibit enzyme activity in the olfactory mucosa) , and then a second dose of curcumin is intranasally administered to the patient at least about 15 minutes after the first dose (to travel to the brain).

It is well known that that the cytochrome p450 enzymes are significant in the olfactory mucosa. Oetari, Biochem. Pharmacol., 1996, Jan. 12, 51(1) 39-45 reports that curcumin strongly inhibits P450s in rat liver. Thapliyal, Food Chem. Toxicol. 2001, June 39(6) 541-7 reported the inhibition of cytochrome P450 isoenzymes by curcumins both in vitro and in vivo.

Zhou, Drug Metab. Rev., 2004 Feb. 36(1) 57-104 reports curcumin to be an inhibitor of Pgp.

In some embodiments, piperine is used as a glucuronidation inhibitor. Reen, Biochem. Pharmacol., 1993, Jul. 20, 46(2) 229-38 reports piperine to be a potent inhibitor of glucuronidation. Shoba, Planta Med., 1998 May 64(4) 353-6 reports that pre-

administration of piperine led to a 2000% increase in the bioavailability of curcumin in humans.

In some embodiments, the glucuronidation inhibitor is an analog of piperine. Preferably, the piperine analog is antiepilepsirine. Administration of antiepilepsirine is also effective in raising serotonin synthesis (Liu, Biochem. Pharmacol., 1984 Dec 1,33(23) 3883-6), and has been studied as an antiepilepsy drug (Wang, Brain Dev. 1999 Jan. 21(1) 36-40). Accordingly, its intranasal administration should not lead to significant problems.

In some embodiments, the glucuronidation inhibitor is a surfactant. Kurkela, J. Biol. Chem., 2003 Feb.7;278(6) 3536-44 reports that several UGT enzymes were nearly fully inhibited by a surfactant, namely Triton X-100. Preferably, the surfactant is a non-ionic surfactant.

In some embodiments, the glucuronidation inhibitor is a mucolytic agent, such as N-acetylcysteine (NAC). Takatsuka, Int. J. Pharm., 2006 Jun 19, 316(1-2) 124-30, reports that co-administration of a mucolytic agent (NAC) and a surfactant (Triton TX-100) led to enhanced intestinal absorption in a synergistic manner. It was further reported that the damage to the mucosa was reversible.

In some embodiments, the glucuronidation inhibitor is an NSAID. In preferred embodiments, the NSAID is niflumic acid. Mano, Biopharm. Drug Dispos., 2006 Jan, 27(1) 1-6 reports the inhibitory effect of NSAIDs, and niflumic acid in particular, on UGT activity.

Enzyme inhibition by buffer

In some embodiments, low pH buffers are used as glucuronidation inhibitors. Basu, PNAS, May 3, 2005, 102,18,6285-90 reports maximum glucuronidation of lipophiles by UGT1A7 in the pH range of 6-9, and nearly zero glucronidation activity by UGT1A7 at pH 5. Similarly, Basu, J. Biol. Chem., 279, Jan.9, 2004, 1429-1441 reports that pH can drastically alter the level of UGT activity, and that a pH of 5 inhibits nearly all glucuronidation activity for each of UGT1A7 and UGT1A10. Therefore, it appears that low pH formulations are effective in completely inhibiting glucuronidation activity.

In some embodiments of the present invention, the curcumin formulation contains a buffer setting a pH of between about 3.0 and 5.5, preferably a pH of between about 3.5 and 5, preferably a pH of between about 4 and 5. In some embodiments of the present invention, the curcumin formulation contains a buffer setting a pH of between about 3 and 4. Below these cited ranges, there is a chance that the acidic nature of the formulation will be irritating to the nasal cavity. Above this range, there may be minimal inhibition of glucronidation. US Patent No. 6,187,332 ("Gern") discloses a buffered flowable nasal spray formulation having a pH of between 4 and 5 which is able to maintain its pH for prolonged periods in the human nose. Gern discloses formulation comprising citrate and phosphate buffering agents.

Therefore, in accordance with the present invention, there is provided an intranasal spray device comprising a formulation comprising:

a) an effective amount of curcumin, and

b) a buffering agent (preferably, a citrate or phosphate) having a pH of between 4 and 5 which is able to maintain the pH of the formulation between 4 and 5 in the human nose for prolonged periods.

Absorption enhancers

In some embodiments, the absorption enhancer is a bile salt. Chavanpatil, Pharmazie, 2005 May, 60(5) 347-9. In preferred embodiments, the bile salt is selected from the group consisting of sodium deoxycholate, sodium caprate, and sodium tauroglycocholate and EDTA.

In some embodiments, magnesium^{+2} is used as a glucuronidation inhibitor. Wong, Biochem. J. , (1968) 110,99 reports that Mg^{+2} concentrations in excess of about 10 mM were effective in inhibiting about 85% of enzymatic glucuronidation activity.

Cooling

It is appreciated by the inventors that the UGT enzyme is likely very sensitive to temperature. Therefore, it is reasonable to expect that a decrease in the temperature of the mucosal lining will result in a decrease in the enzymatic glucuronidation of curcumin by

the UGTs. Indeed, it has been reported by Castuma, Biochem. J., (1989) 258, 723-731 that the enzymatic activity of UDP-glucuronyltransferase in normal liver microsomes of guinea pigs decreased about 3-fold when the temperature of the microsomes was reduced from about 37 °C to about 10 °C.

Therefore, the present inventors have devised inventions based upon the temporary cooling of the nasal mucosa in order to inhibit the glucuronidation of curcumin.

In one embodiment, the formulation of the present invention contains a cooling agent such as menthol.

In one embodiment, the formulation of the present invention contains an endothermic solute. In preferred embodiments, the endothermic solute is a strong salt, acid or base that dissolves in water by an endothermic process. More preferably, the endothermic solute is a salt.

In some embodiments, the endothermic solute may be selected from the group consisting of sodium bicarbonate (ΔH = +19.1 kJ/mol); potassium bicarbonate (ΔH = +5.3 kcal/mol); potassium sulfate (ΔH = +23.7 kJ/mol); potassium chloride (ΔH = +17.2 kJ/mol); sodium chloride (ΔH = +3.9 kJ/mol); and potassium dihydrogenphosphate (ΔH = +19.6 kJ/mol).

In some embodiments, the endothermic solute may be magnesium sulfate, which would both promote cooling and inhibition glucuronidation.

Therefore, in accordance with the present invention, there is provided an intranasal spray device comprising a formulation comprising:

a) an effective amount of curcumin, and

b) an endothermic solute (preferably magnesium sulfate)

It is well known that curcumin is poorly soluble in water. Because the olfactory mucosa is aqueous-based, the transport of curcumin from the formulation across the olfactory mucosa is problematic.

Therefore, in order to increase the transport of curcumin across the olfactory mucosa, in some embodiments, the curcumin is delivered in a formulation comprising an

effective amount of a curcumin-miscible solvent. Preferably, the solvent is selected from the group consisting of DMSO and ethanol. It is well known that curcumin is highly soluble in DMSO and ethanol. When this formulation is applied to the nasal mucosa, the solvent mixes with the water in the olfactory mucosa and renders curcumin soluble in that mixture.

In preferred embodiments, the solvent is DMSO. DMSO is non-toxic and also can temporarily open the blood brain barrier. Kleindienst, Acta Neurochir. Suppl. 2006; 96,258-62, and Scheld, Rev. Infect. Dis., 1989 Nov-Dec.; 11 Suppl 7; S1669-90.

Therefore, in accordance with the present invention, there is provided an intranasal spray device comprising a formulation comprising:

a) an effective amount of curcumin, and

b) a solvent selected from the group consisting of DMSO and ethanol.

Increasing Solubility

Some embodiments increase the solubility of curcumin in water by employing a solid dispersion, such as those made with polyethylene glycol 6000 (PEG 6000) or polyvinylpyrrolidone K-30 (PVP K30). Ruan, J. Pharm Biomed. Anal. 2005 Jul 1;38(3):457-64. Paradkar, Int. J. Pharm. 2004 Mar 1; 271(1-2):281-6

Some embodiments increase the solubility of curcumin in water by employing inclusion complexes, such as those made with beta-cyclodextrin (BCD) and hydroxypropyl-beta-cyclodextrin (HPBCD). Ruan, J. Pharm Biomed. Anal. 2005 Jul 1; 38(3):457-64.

Other Curcumin analogs

Modifications of curcumin and its functional fragments that either enhance or do not greatly affect the ability to treat AD are also included within the term "curcumin." Such modifications include, for example, additions, deletions or replacements of one or more functional groups. These modifications will either enhance or not significantly alter the structure, conformation or functional activity of curcumin or a functional fragment thereof. Additionally, curcumin or its functional fragments can be modified by the

addition of epitope tags or other sequences that aid in its purification and which do not greatly affect its activity. As used herein, the term "functional fragment," in connection with an curcumin, is intended to mean any portion of curcumin that maintains its to inhibit oxidiation, or to prevent beta amyloid oligomer formation. If desired, a functional fragment can include regions of the curcumin with activities that beneficially cooperate with the ability to inhibit oxidation or oligomer formation.

Also in accordance with the present invention, publicly known analogs of curcumin may be used.

In some embodiments, the curcumin analogs are those found in US Published patent application US 2006/0067998.

Curcumin is soluble in ethanol, alkalis, ketones, acetic acid and chloroform. It is insoluble in water. Curcumin is therefore lipophilic, and generally readily associates with lipids, e.g. many of those used in the colloidal drug-delivery systems of the present invention. In certain embodiments, curcumin can also be formulated as a metal chelate.

As used herein, curcumin analogues are those compounds which due to their structural similarity to curcumin, exhibit anti-proliferative or pro-apoptotic effects on cancer cells similar to that of curcumin. Curcumin analogues which may have anti-cancer effects similar to curcumin include Ar-tumerone, methylcurcumin, demethoxy curcumin, bisdemethoxycurcumin, sodium curcuminate, dibenzoylmethane, acetylcurcumin, feruloyl methane, tetrahydrocurcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (curcumin1), 1,7-bis(piperonyl)-1,6-heptadiene-3,5-dione(piperonyl curcumin)1,7-bis(2-hydroxy naphthyl)-1,6-heptadiene-2,5-dione(2-hydroxyl naphthyl curcumin), 1,1-bis(phenyl)-1,3,8,10-undecatetraene-5,7-dione (cinnamyl curcumin) and the like (Araujo and Leon, 2001; Lin et al., 2001; John et al., 2002; see also Ishida et al., 2002). Curcumin analogues may also include isomers of curcumin, such as the (Z,E) and (Z,Z) isomers of curcumin. In a related embodiment, curcumin metabolites which have anti-cancer effects similar to curcumin can also be used in the present invention. Known curcumin metabolites include glucoronides of tetrahydrocurcumin and hexahydrocurcumin, and dihydroferulic acid. In certain embodiments, curcumin

analogues or metabolites can be formulated as metal chelates, especially copper chelates. Other appropriate derivatives of curcumin, curcumin analogues and curcumin metabolites appropriate for use in the present invention will be apparent to one of skill in the art.

In some embodiments, the curcumin analogs are those found in US Published patent application US 2005/0181036.

Commercial curcumin includes three major components: curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%), which are often referred to as "curcuminoids." As used herein, "curcumin" is defined to include any one or more of these three major components of commercial curcumin, and any active derivative of these agents. This includes natural and synthetic derivatives of curcumin and curcuminoids, and includes any combination of more than one curcumenoid or derivative of curcumin. Derivatives of curcumin and curcumenoids include those derivatives disclosed in U.S. Patent Application Publication 20020019382, which is herein specifically incorporated by reference.

In some embodiments, the curcumin analogs are those found in US Published patent application US 2005/0267221:

In certain aspects, 1,7,-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadi- ene-3,5-dione is the curcumin that may be used in the present invention. Other curcumin analogues (curcuminoids) that may be used include, for example, demethoxycurcumin, bisdemethoxycurcumin, dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, dihydroxytetrahydrocurcumin, Yakuchinone A and Yakuchinone B, and their salts, oxidants, reductants, glycosides and esters thereof. Such analogues are described in U.S. Patent Application 20030147979; and U.S. Pat. No. 5,891,924 both of which are incorporated in their entirety herein by reference.

Other curcumin analogues (curcuminoids) that may be used include dihydroxycurcumin and NDGA.

Further examples of curcumin analogues include but are not limited to (a) ferulic acid, (i.e., 4-hydroxy-3-methoxycinnamic acid; 3,4-methylenedioxy cinnamic acid; and 3,4-dimethoxycinnamic acid); (b) aromatic ketones (i.e., 4-(4-hydroxy-3-methoxyphenyl)-3-buten-2-one; zingerone; -4-(3,4-methylenedioxyphenyly-2-butanone; 4-(p-hydroxyphenyl)-3-buten-2-one; 4-hydroxyvalerophenone; 4-hydroxybenzylactone; 4-hydroxybenzophenone; 1,5-bis(4-dimethylaminophen- yl)-1,4-pentadien-3-one); (c) aromatic diketones (i.e., 6-hydroxydibenzoylmethane) (d) caffeic acid compounds (i.e., 3,4-dihydroxycinnamic acid); (e) cinnamic acid; (f) aromatic carboxylic acids (i.e., 3,4-dihydroxyhydrocinnainic acid; 2-hydroxycinnamic acid; 3-hydroxycinnamic acid and 4-hydroxycinnamic acid); (g) aromatic ketocarboxylic acids (i.e., 4-hydroxyphenylpyruvic acid); and (h) aromatic alcohols (i.e., 4-hydroxyphenethyl alcohol). These analogues and other representative analogues that can be used in the present invention are further described in WO9518606 and WO01040188, which are incorporated herein by reference in their entirety.

Curcumin or analogues thereof may be purified from plants or chemically synthesized using methods well known and used by those of skill in the art. Plant-derived curcumin and/or its analogues can be obtained by extraction from plants including Zingiberaceae Curcuma, such as Curcuma longa (turmeric), Curcuma aromatica (wild turmeric), Curcuma zedoaria (zedoary), Curcuma xanthorrhiza, mango ginger, Indonesian arrowroot, yellow zedoary, black zedoary and galangal. Methods for isolating curcuminoids from turmeric are well known in the art (Janaki and Bose, 1967). Still further, curcumin may be obtained from commercial sources, for example, curcumin can be obtained from Sigma Chemicals Co (St. Louis, Mo.).

Any conventional method can be used to prepare curcumin and its analogues to be used in the present invention. For example, turmericoleoresin, a food additive, which essentially contains curcumin, can be produced by extracting from a dry product of rhizome of turmeric with ethanol at an elevated temperature, with hot oil and fat or propylene glycol, or with hexane or acetone at from room temperature to a high temperature. Alternatively, those can be produced by the methods disclosed in Japanese

Patent Applications 2000-236843, H-11-235192 and H-6-9479, and U.S. Patent Application No. 20030147979, which is incorporated by reference herein in its entirety.

In certain embodiments, a purified product of at least one curcumin and/or its analogue may be used. Alternatively, a semi-purified or crude product thereof may be used, provided that it does not contain impurities which may not be acceptable as a pharmaceutical or food product.

Preferred analogues

There has been limited testing of the potency of curcumin analogs against beta amyloid. Park, J. Nat. Prod., 65,9, Sept. 2002, reports testing the following curcumin analogs for the ability to provide in vitro protection for PC12 cells against beta amyloid insult :

4"-(3'"-methoxy-4'"-hydroxyphenyl)-2"-oxo-3"-enebutanyl3-(3'-methoxy-4'hydroxyphenyl) propenoate (**31**);

1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (demethoxycurcumin)(**32**);

1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (bisdemethoxycurcumin), (**33**); and

1,7-bis(4-hydroxyphenyl)-1-heptene-3,5-dione (**34**).

Each of these compounds is shown in FIG. 1d. Park reports the following results, as shown in Table IV :

Table IV

Analog	**anti- βA (25-35)**	**anti- βA (1-42)**
	ED50[a] (μg/ml)	**ED50 (μg/ml)**
curcumin	7.0+/-1.1	10.0+/-0.9

31	1.0+/-0.3	2.0+/-0.4
32	4.0+/-0.5	5.0+/-0.5
33	2.0+/-0.6	3.5+/-0.7
34	0.5+/-0.2	1.0+/-0.3

[a] ED50 represents the sample concentration that is required to achieve 50% cell viability.

Analysis of the Park data reveals that each of compounds **(31)-(34)** is a more potent neuroprotectant against beta amyloid than curcumin, with compounds **(31)** and **(34)** being on the order of 5 and 10 fold more potent. Therefore, in preferred embodiments, each of compounds **(31)-(34)** is used by itself or in combination as the parent compound for the manufacturing and use of a curcumin prodrug. Each of the parent compounds may be obtained by the methods disclosed in Park.

Kim, Neuroscience Lett. 303 (2001) 57-61 similarly reports testing the following curcumin analogs for the ability to provide in vitro protection for PC12 cells against beta amyloid insult as shown in Table V :

Table V

Analog	**anti-BA (25-35)**	**anti-BA (1-42)**
	ED50 (μg/ml)	**ED50 (μg/ml)**
Curcumin	7.1+/- 0.3	6.8+/-0.4
Demethoxycurcumin	4.7+/-0.1	4.2+/-0.3
Bisdemethoxycurcumin	3.5+/-0.2	3.0+/-0.3

Analysis of the Kim data reveals that each of the demethoxycurcumin and bisdemethoxycurcumin compounds is a more potent neuroprotectant against beta amyloid than curcumin, with the demethoxycurcumin and bisdemethoxycurcumin compounds being on the order of 1.5 and 2 fold more potent. This data is in substantial agreement with the relative potencies of demethoxycurcumin and bisdemethoxycurcumin reported by Park above.

Other Diseases

In other embodiments, the present invention relates to the intranasal administration of a formulation comprising an effective amount of curcumin across the cribriform plate and into the brain in order to treat a stroke.

In other embodiments, the present invention relates to the intranasal administration of a formulation comprising an effective amount of curcumin across the cribriform plate and into the brain in order to treat multiple sclerosis.

Other Polyphenolic Prodrugs

In some embodiments, the curcumin is combined with a second lipophilic therapeutic agent, preferably another polyphenol, such as resveratrol. In some embodiments, the curcumin is provided in a formulation with another compound selected from the group consisting of gingko biloba extract, resveratrol, and a green tea catechin, and then is intranasally administered.

Also in accordance with the present invention, there is provided a method for transporting a gingko biloba extract to a brain of a mammal, comprising: a) applying a pharmaceutical composition comprising a gingko biloba extract to an upper third of a nasal cavity of the mammal, wherein the gingko biloba extract is absorbed through an olfactory mucosa and transported to the brain of the mammal.

Also in accordance with the present invention, there is provided a method for transporting resveratrol to a brain of a mammal, comprising:

a) applying a pharmaceutical composition comprising resveratrol to an upper third of a nasal cavity of the mammal, wherein the resveratrol is absorbed through an olfactory mucosa and transported to the brain of the mammal.

Also in accordance with the present invention, there is provided a method for transporting a green tea catechin to a brain of a mammal, comprising:

a) applying a pharmaceutical composition comprising the catechin to an upper third of a nasal cavity of the mammal, wherein the catechin is absorbed through an olfactory mucosa and transported to the brain of the mammal.

The prodrug rationale provided above for curcumin can also be applied to other therapeutic phenolic compounds (preferably, therapeutic polyphenolic compounds), such as those of the flavonoid class. In preferred embodiments, this compound is selected from the group consisting of resveratrol, hispidin, genistein, ellagic acid, 1,25 dihydroxyvitamin D3, the green tea catechin EGCG, and docosahexaenoic acid (DHA). In another embodiment, this compound is docosahexaenoic acid (DHA). Also in accordance with the present invention, there is provided a method for transporting a flavonoid prodrug to a brain of a mammal, comprising:

a) applying a pharmaceutical composition comprising a flavonoid prodrug (such as a resveratrol prodrug) to an upper third of a nasal cavity of the mammal, wherein the flavonoid prodrug is absorbed through an olfactory mucosa and transported to the brain of the mammal.

Resveratrol

In especially preferred embodiments, the flavonoid prodrug is resveratrol.

Resveratrol, a polyphenolic compound commonly found in red wine, has been promoted as a possible treatment for Alzheimer's Disease because it appears to affect multiple mechanisms of AD pathology. Anekonda, Brain Research Reviews,52, 2006,316-26.

First, resveratrol has been shown to reduce the amount of beta amyloid in brain tissue. The mechanism by which resveratrol accomplishes this has been subject to debate. One recent paper concludes that resveratrol is a specific inhibitor of BACE1 enzyme, with an IC_{50} of about 15 uM. Jeon, Phyomedicine, 2006 Nov. 2 (E-pub). Another recent paper reports that resveratrol reduces beta amyloid content by promoting intracellular degradation of beta amyloid via a mechanism that involves the proteosome. Marambaud, J. Biol. Chem., 280(45), 37377-82.

Second, it is believed that resveratrol inhibits the formation of beta amyloid fibrils. Riviere, Bioorg. Med. Chem., 2006 October 1 (E-pub).

Third, 20 μM resveratrol has a neuroprotective effect against beta amyloid-induced neurotoxicity in rat hippocampal neurons, and is believed to provide this neuroprotection through activation of protein kinase C (PKC). Han, Br. J. Pharmacology, 2004,141,997-1005. Han, J. Pharmacol. Exp. Ther., 2006 Jul. 318(1)238-45 (Epub 2006 March 30), reports the existence of specific plasma membrane binding sites for resveratrol in the rat brain (Ki=102 nM), and notes that the potency of resveratrol analogs in protecting rat hippocampal cells against beta amyloid-induced neurotoxicity correlates well with their apparent affinity.

The hypothesis that resveratrol acts through PKC is of special interest because it is believed that nonamyloidogenic processing of amyloid precursor protein (APP) also acts through activation of PKC.

Fourth, some hypotheses of Alzheimer's Disease involve oxidation via enhanced brain concentrations of heavy metals. Respecting resveratrol, it has been reported that

resveratrol is a highly potent chelator of copper. Belguendouz, Biochemical Pharmacology, 53, 1347-1355, 1997.

Fifth, Anekonda, Brain Research Reviews, 52, 2006,316-26 reports that mechanisms of aging and AD are intricately linked and that these mechanisms can be modulated by both calorie restriction regimens and calories restriction mimetics, the prime mediator of which is the SIRT1 protein. Howitz, Nature, 2003, 425,191-196 reports that resveratrol has been found to exhibit the highest level of SIRT1 activation amongst the small molecules tested. Chen, J. Biol. Chem., 280,48, 40364-74 found that resveratrol markedly reduced NF-KB signaling in microglia, and ascribed this benefit to the induction of SIRT1 by resveratrol. Similarly, Kim, Int. J. Mol. Med., 2006 Jun., 17,6,1069-75 reports that modulation of NF-KB activity is involved in the neuroprotective action of resveratrol against beta amyloid induced neurotoxicity.

Sixth, resveratrol is a well known anti-oxidant, and 5-25 uM resveratrol has displayed an ability to protect cultured hippocampal cells against nitric oxide related neurotoxicity. Bastianetto, Br. J. Pharm., 2000, 131, 711-720. Similarly, Savaskan, Gerontology, 2003 Nov-Dec., 49(6) 380-3 reports that resveratrol maintains cell viability against beta amyloid – related oxidative stress, and exerts its antioxidative action by enhancing the intracellular free radical scavenger glutathione.

The bioavailability of resveratrol has been well studied. Since resveratrol appears to be highly susceptible to glucuronidation in the intestine and liver, it has been concluded that the oral bioavailability of resveratrol is "about zero". Wenzel, Mol. Nutr. Food Res., 2005, 49, 472-481. Accordingly, because of the finding that trans-resveratrol in present in human serum in its glucuronide form rather than in its free form, Vitaglione, Mol. Nutr. Food Res., 2005 May 49(5), 495-504, raises some doubts about the heath effect of dietary consumption of resveratrol. Thus, the intranasal rationale for trans-resveratrol appears warranted.

Nonetheless, it appears that when resveratrol reaches the brain , it has a fairly significant residence time. El-Mohsen, British J. Nutrition,2006, 96,62-70, reports that the resveratrol concentration in the brain about 18 hours after gastric administration was still 43% of that measured at 2 hours. Wang, Brain Research, 958 (2002), 439-447, reports that intraperitoneal administration of resveratrol provides a peak concentration in the brain 4 hours after its administration.

Trans-resveratrol has a molecular weight of about 228, and is very lipophilic (having an octanol-water partition coefficient Log P of about 3.14). However, its solubility in water is very low (<0.01 mol/L). Thus, the prodrug rationale for trans-resveratrol appears warranted.

Hybrids

FIGS. 2-16 disclose various curcumin derivatives that are hybrids of curcumin and various other natural polyphenols. Each of these derivatives is a triphenolic compound, wherein the intermediate diketone structure of curcumin is replaced with a phenolic group. The resulting compound retains the spacing between the two phenols of curcumin, and also possesses the biphenolic spacing of the additional polyphenol.

FIG. 2 discloses the structures of curcumin, resveratrol, and two curcumin-resveratrol hybrids. Note how each of the hybrids retains the interphenolic spacing of each of curcumin and reveratrol.

FIG. 3 discloses a method of making the curcumin-resveratrol I hybrid.

FIG. 4 discloses a method of making the curcumin-resveratrol II hybrid.

FIG. 5 discloses a method of making a curcumin-resveratrol hybrid having three hydroxyl groups in each of the central phenolic group and lateral phenolic groups.

FIG. 6 discloses curcumin, resveratrol and a hybrid thereof, wherein all of the phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a dihydroxyl central phenolic group.

FIG. 7 discloses a method of making the curcumin-resveratrol hybrid of FIG. 6.

FIG. 8 is similar to the hybrid of FIG. 6, but wherein the methoxy groups of the base curcumin molecule are retained.

FIG. 9 discloses curcumin, oxyresveratrol and a hybrid thereof, wherein all of the hydroxyls/phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a trihydroxyl central phenolic group.

FIG. 10 discloses curcumin, piceatannol and a hybrid thereof, wherein all of the hydroxyls/phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a trihydroxyl central phenolic group.

FIG. 11 discloses a method of making a curcumin-resveratrol hybrid,wherein all of the hydroxyls/phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a dihydroxyl central phenolic group.

FIG.12 discloses curcumin, BDMC, resveratrol and curcumin hybrids thereof, wherein all of the phenolics of the natural compounds are represented in the hybrid, providing hydroxyl demethoxy lateral phenolic groups and a hydroxy or dihydroxyl central phenolic group.

FIG. 13 provides a method of making the compound of FIG. 12 that has hydroxyl demethoxy lateral phenolic groups and a hydroxy central phenolic group.

FIG. 14 provides a method of making the compound of FIG. 12 that has hydroxyl demethoxy lateral phenolic groups and a dihydroxy central phenolic group.

FIG.15 discloses curcumin, fistein and hybrids thereof, wherein all of the phenolics of the natural compounds are represented in the hybrid, providing dihydroxyl phenolic groups and a hydroxy central phenolic group in the positions common with the two natural compounds.

FIG. 16 provides a method of making the compound of FIG. 15.

Claims

1. A pharmaceutical formulation comprising:
   a) an effective amount of curcumin ester prodrug, and
   b) a buffering agent setting a pH of between 3 and 5.5.

2. The formulation of claim 1 wherein the prodrug comprises an aminoalkylcarboxylic acid moeity.

3. The formulation of claim 2 wherein the aminoalkylcarboxylic acid moeity comprises an aminoalkanecarboxylic acid moeity.

4. The formulation of claim 3 wherein the aminoalkanecarboxylic acid contains a glycinate moiety.

5. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises a terminal methyl group.

6. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises two terminal methyl groups.

7. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises three terminal methyl groups.

8. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises a terminal ethyl group.

9. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises two terminal ethyl groups.

10. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises three terminal ethyl groups.

11. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises a terminal ethyl group and a terminal methyl group.

12. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises a terminal ethyl group and two terminal methyl groups.

13. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises two terminal ethyl groups and a terminal methyl group.

14. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety comprises a terminal propyl group.

15. The formulation of claim 4 wherein the aminoalkanecarboxylic acid moiety is characterized by terminal substitution of the amine by an oxygen-containing moiety.

16. The formulation of claim 4 wherein the prodrug is in the form of a salt.

17. The formulation of claim 16 wherein the salt comprises an anion selected from the group consisting of chloride and bromide.

18. The formulation of claim 1 wherein the buffer sets a pH of between about 3.5 and 5.

19. The formulation of claim 1 wherein the buffer sets a pH of between about 4 and 5.

20. The formulation of claim 1 wherein the buffer sets a pH of between about 3 and 4.

21. The formulation of claim 1 wherein the prodrug comprises an carbamoyl moeity.

22. A method for administering curcumin to a brain of a mammal, comprising:

a) applying a pharmaceutical composition comprising a water soluble curcumin prodrug to an upper third of a nasal cavity of the mammal, wherein the curcumin prodrug is absorbed through a nasal mucosa and transported to the brain of the mammal.

23. The method of claim 22 wherein the prodrug is an ester prodrug.

24. The method of claim 22 wherein the prodrug contains a glycinate moiety.

25. The method of claim 22 wherein the prodrug contains a carbamoyl moiety.

26. An intranasal spray device comprising a formulation comprising:

a) an effective amount of curcumin, and

b) a buffering agent setting a pH of between 3 and 5.5.

27. The device of claim 26 wherein the formulation contains a buffer setting a pH of between about 3.5 and 5.

28. The device of claim 26 wherein the formulation contains a buffer setting a pH of between, preferably a pH of between about 4 and 5.

29. The device of claim 26 wherein the formulation contains a buffer setting a pH of between 3 and 4.

30. A pharmaceutical formulation comprising:

a. an effective amount of a curcumin ester prodrug, wherein the prodrug is in the form of a salt.

31. The formulation of claim 30 wherein the prodrug comprises an aminoalkylcarboxylic acid moeity.

32. The formulation of claim 31 wherein the aminoalkylcarboxylic acid moeity comprises an aminoalkanecarboxylic acid moeity.

33. The formulation of claim 32 wherein the aminoalkanecarboxylic acid contains a glycinate moiety.

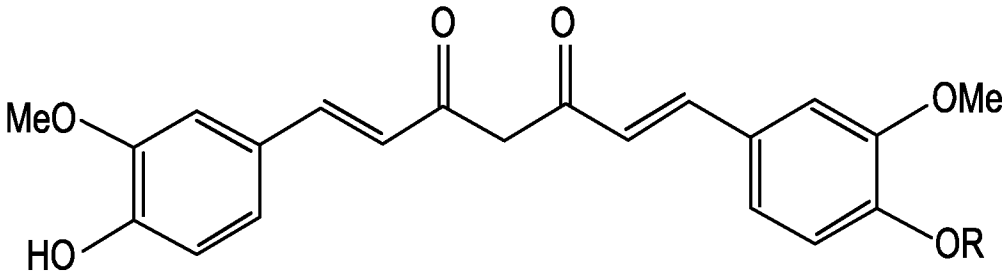
34. The formulation of claim 30 wherein the salt comprises an anion selected from the group consisting of chloride and bromide.

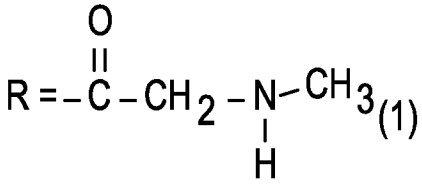
35. A method for transporting a neurotherapeutic drug to a brain of a mammal, comprising:

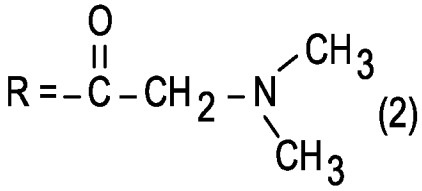
a) providing a formulation comprising aerosol droplets comprising a neurotherapeutic drug in a bolus of helium gas, and

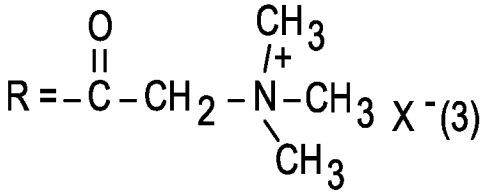
b) applying the formulation to a nasal cavity of the mammal, whereby the formulation rises to an upper third of a nasal cavity of the mammal, whereupon the neurotherapeutic drug is absorbed through a nasal mucosa and transported to the brain of the mammal.

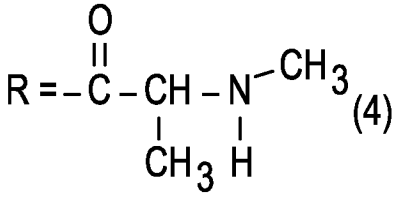
FIG. 1A

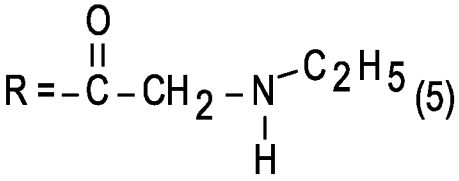

O
O
MeO
OMe
HO
OR

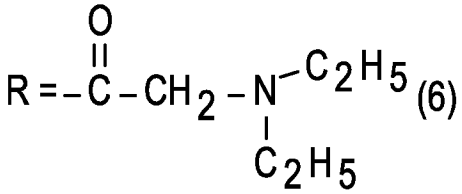

R = –C(=O)–CH2–N(H)–CH3 (1)

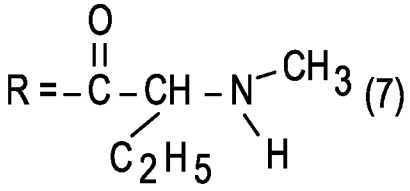

R = –C(=O)–CH2–N(CH3)2 (2)

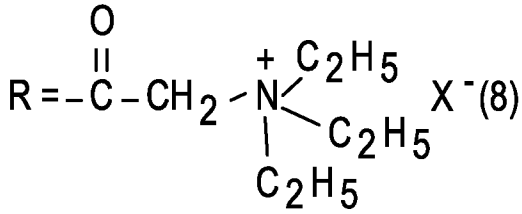

R = –C(=O)–CH2–N+(CH3)3 X- (3)

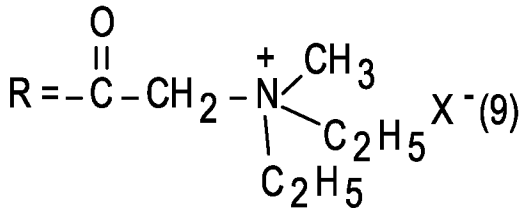

R = –C(=O)–CH(CH3)–N(H)–CH3 (4)

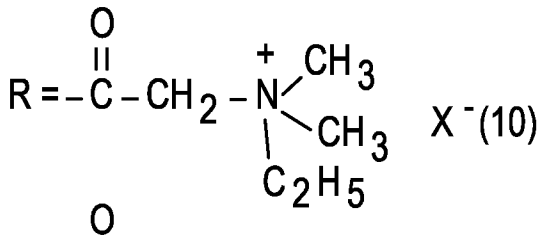

R = –C(=O)–CH2–N(H)–C2H5 (5)

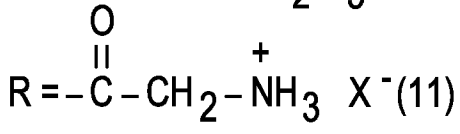

R = –C(=O)–CH2–N(C2H5)2 (6)

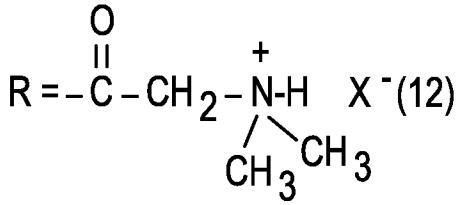

R = –C(=O)–CH(C2H5)–N(H)–CH3 (7)

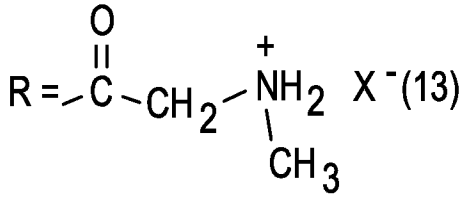

R = –C(=O)–CH2–N+(C2H5)3 X- (8)


R = –C(=O)–CH2–N+(CH3)(C2H5)2 X- (9)


R = –C(=O)–CH2–N+(CH3)2(C2H5) X- (10)


R = –C(=O)–CH2–NH3+ X- (11)


R = –C(=O)–CH2–NH(CH3)2+ X- (12)


R = –C(=O)–CH2–NH2+(CH3) X- (13)

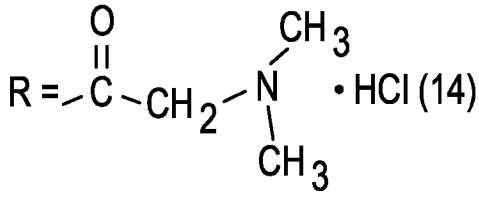
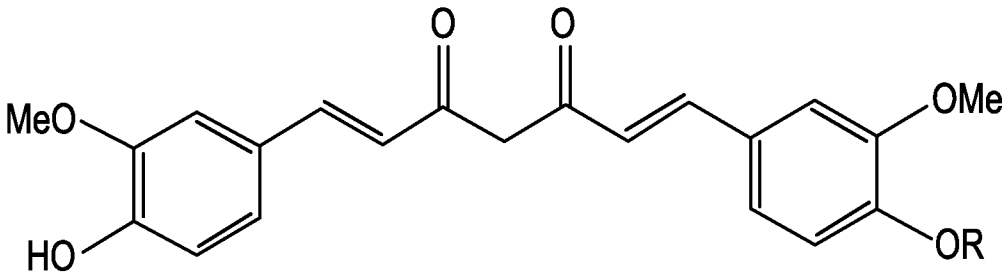
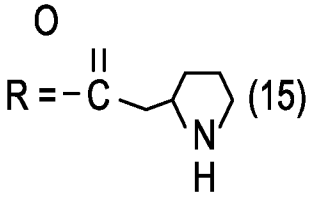
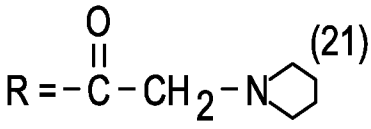
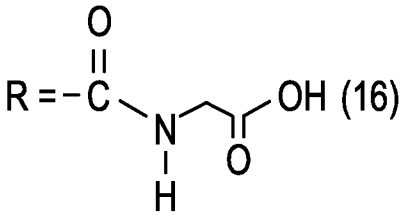

R = –C(=O)–CH2–N(CH3)2 • HCl (14)

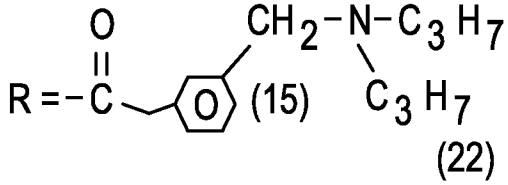
FIG. 1B

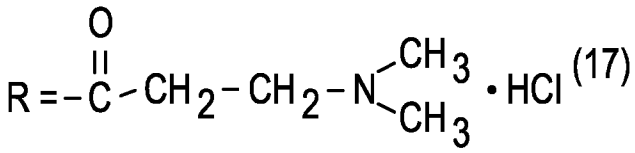

O
O
MeO
OMe
HO
OR

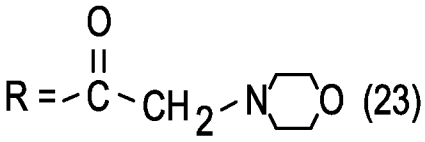

O
R = – C
N
H
(15)

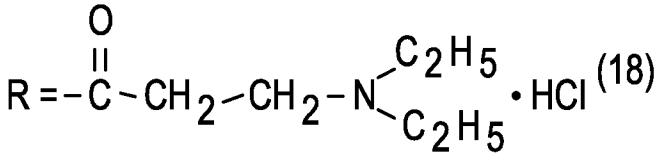

O
R = – C – CH2 – N
(21)

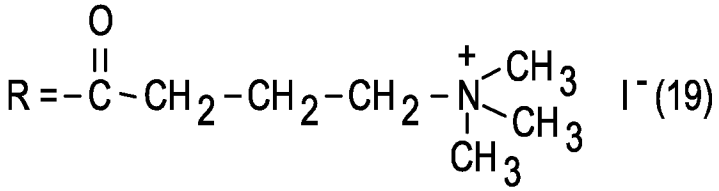

O
R = – C
N
H
OH (16)
O


O
CH2 – N – C3 H7
R = – C
O
(15)
C3 H7
(22)


O
R = – C – CH2 – CH2 – N
CH3
CH3
• HCl
(17)


O
R = – C – CH2 – N
O
(23)


O
R = – C – CH2 – CH2 – N
C2 H5
C2 H5
• HCl
(18)


O
R = – C – CH2 – CH2 – CH2 – N
+
CH3
CH3
CH3
I –
(19)

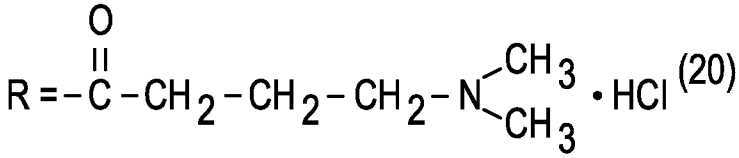
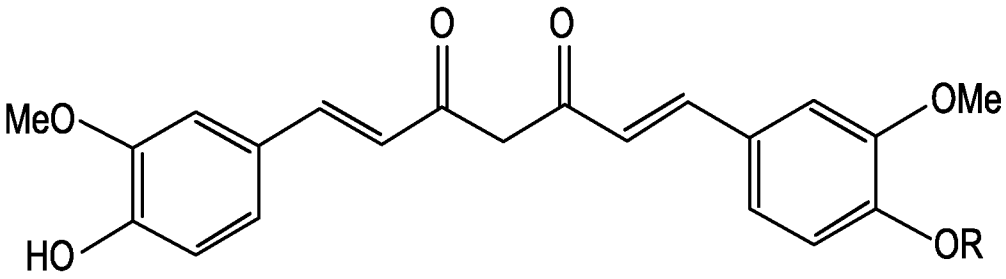
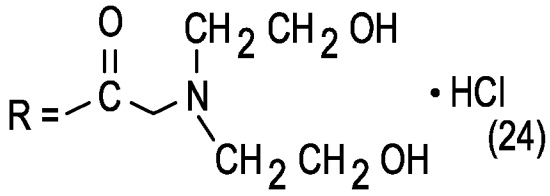

O
R = – C – CH2 – CH2 – CH2 – N
CH3
CH3
• HCl
(20)

FIG. 1C





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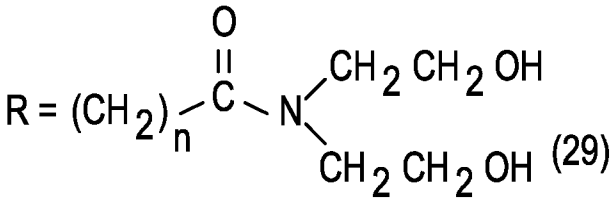

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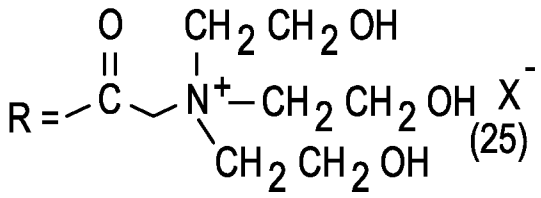

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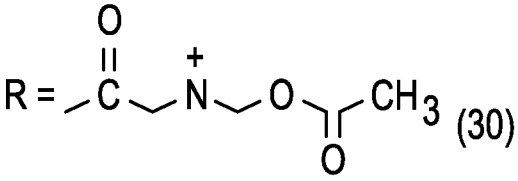

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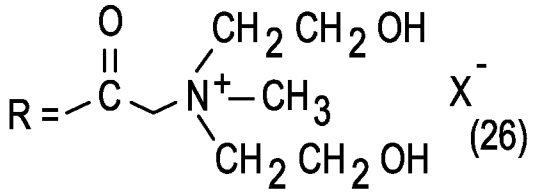

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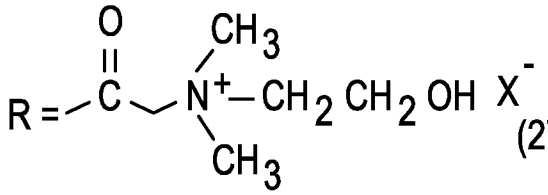
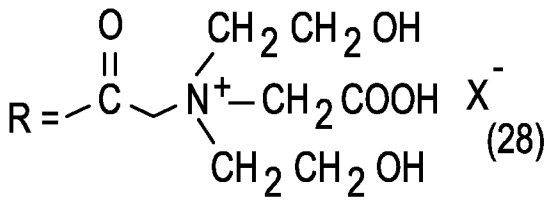


(27)



(28)

FIG. 1D

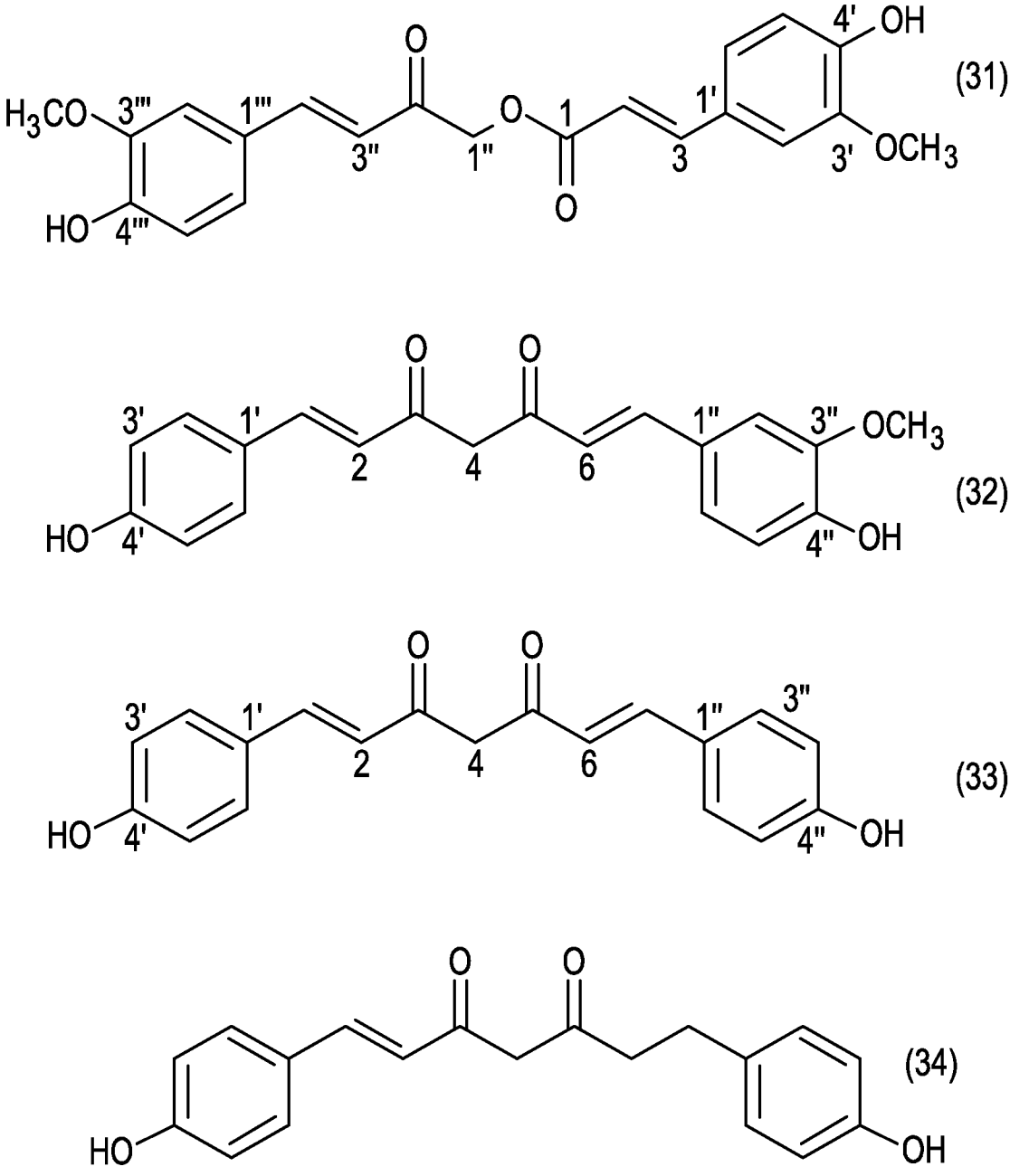
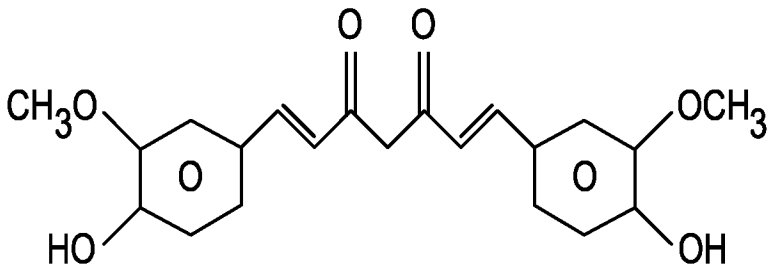
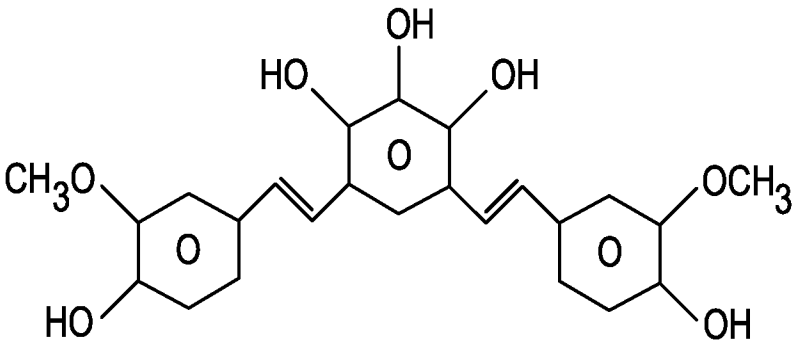

H3CO
3'''
1'''
3''
1''
O
1
1'
4' OH
3' OCH3
3
HO
4'''
(31)
3'
1'
2
4
6
1''
3'' OCH3
4'' OH
HO
4'
(32)
(33)
(34)
OH

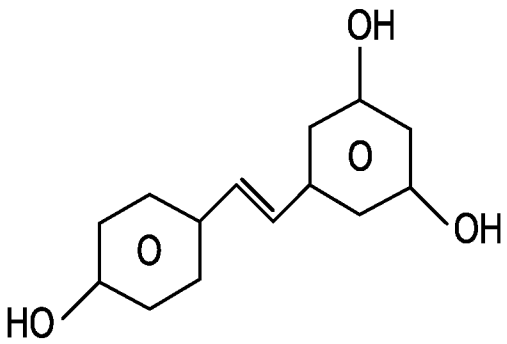
FIG. 2



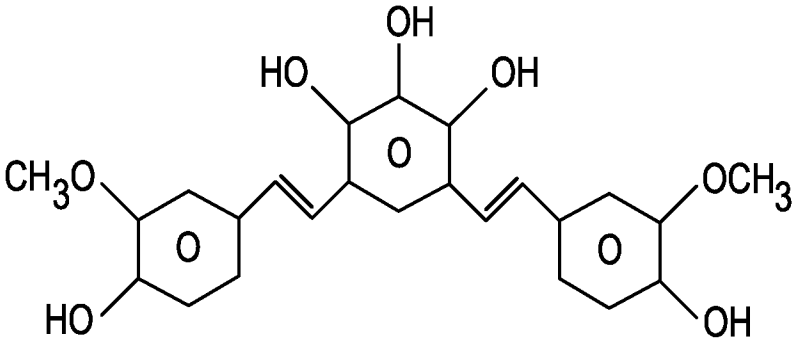
Curcumin



Curcumin-resveratrol I

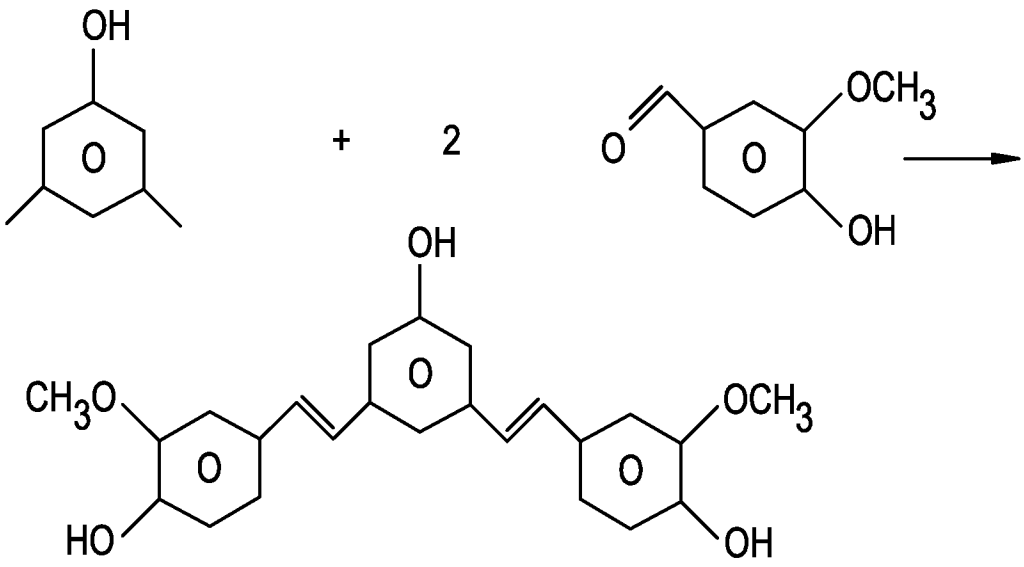


Resveratrol



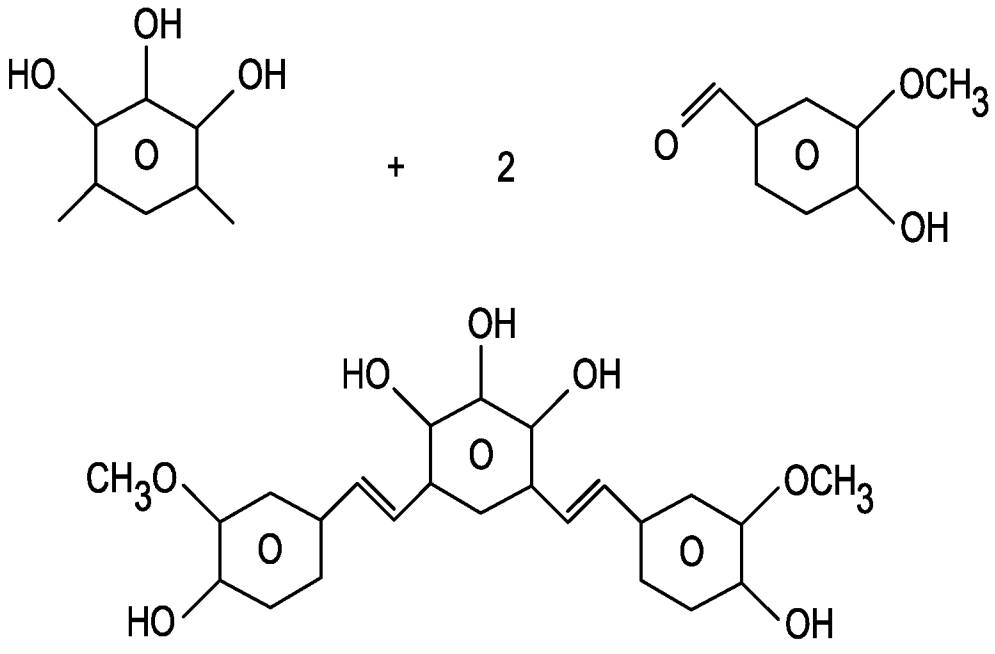
Curcumin-resveratrol II

FIG. 3



Curcumin resveratrol I

FIG. 4



Curcumin-resveratrol II

FIG. 5

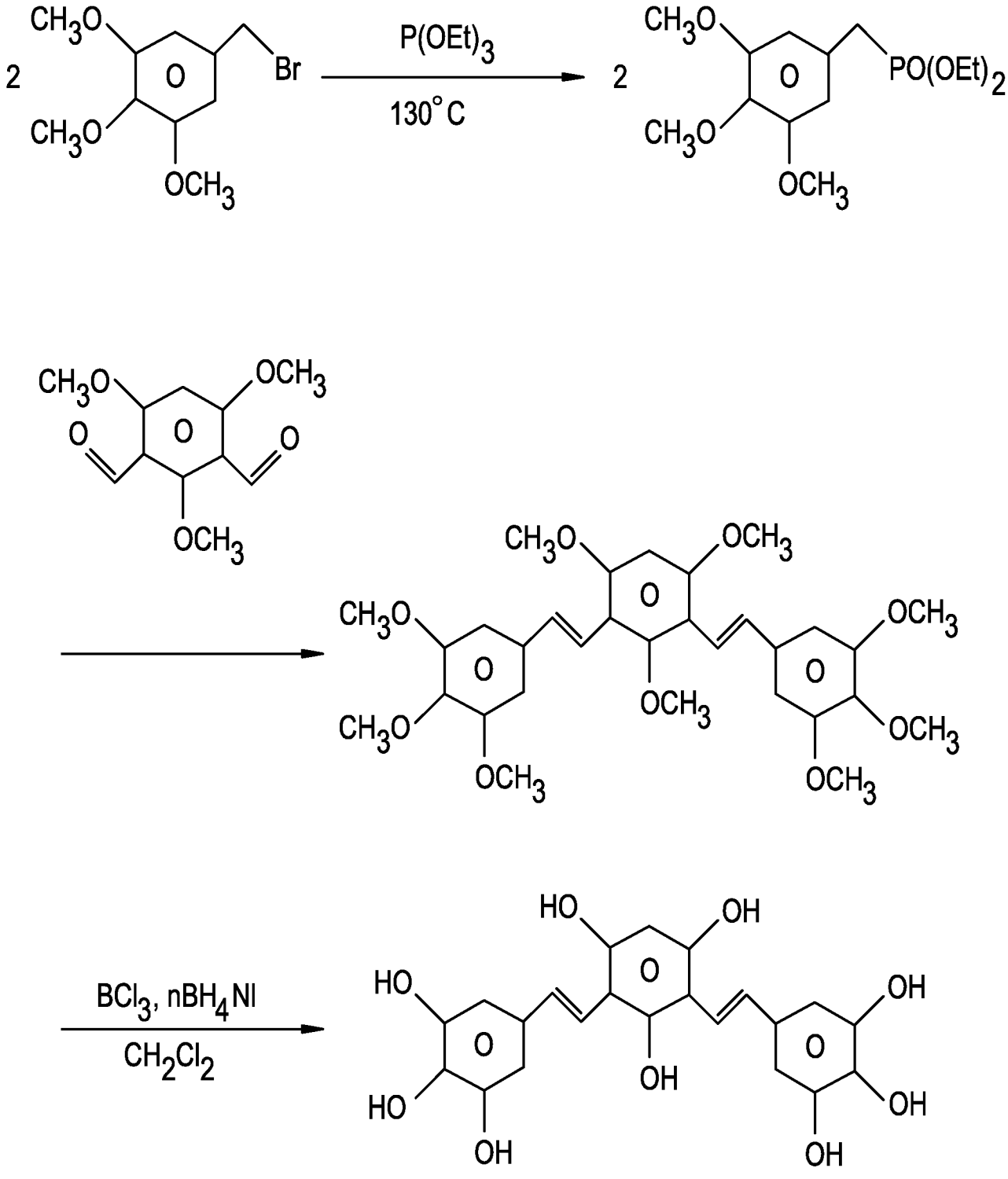
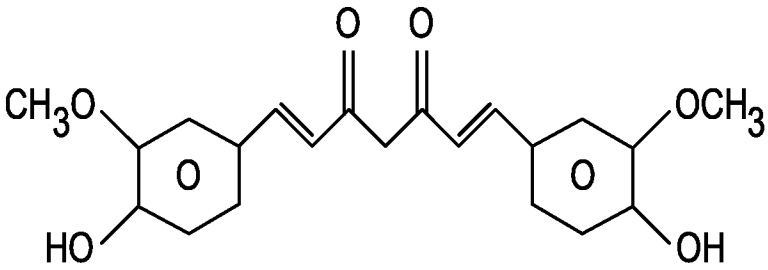
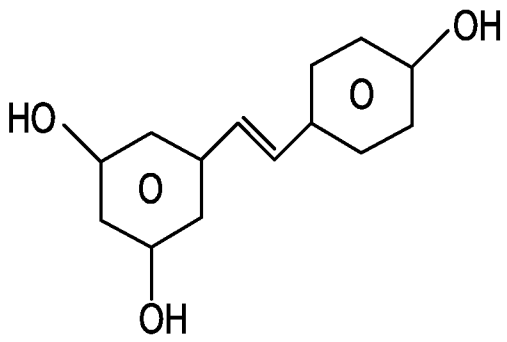

2
CH3O
CH3O
OCH3
O
Br
P(OEt)3
130°C
PO(OEt)2
OCH3
O
BCl3, nBH4NI
CH2Cl2
HO
OH

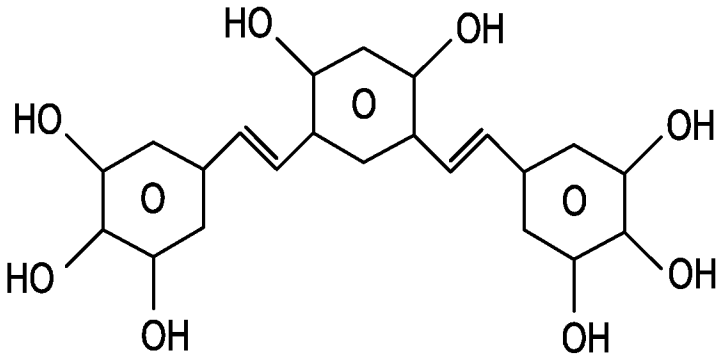
FIG. 6



Curcumin



Resveratrol



Curcumin-resveratrol

FIG. 7

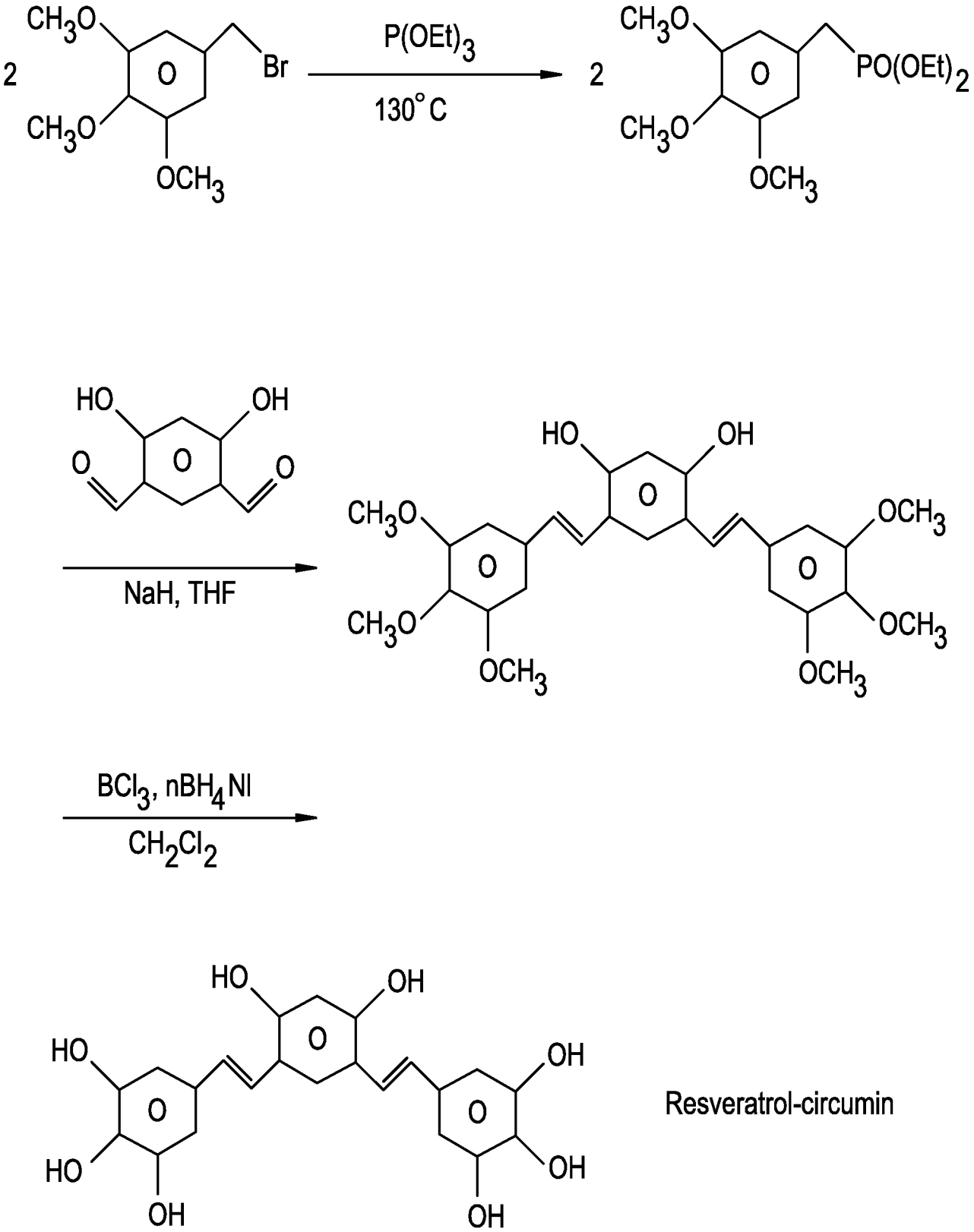
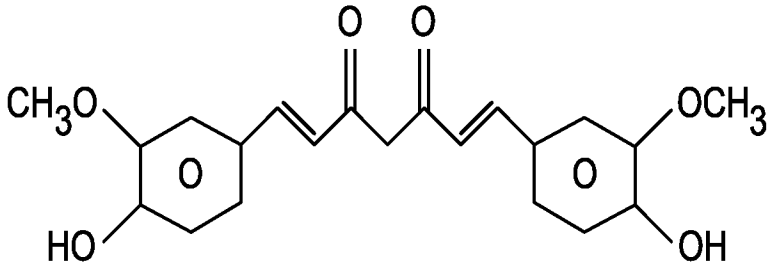
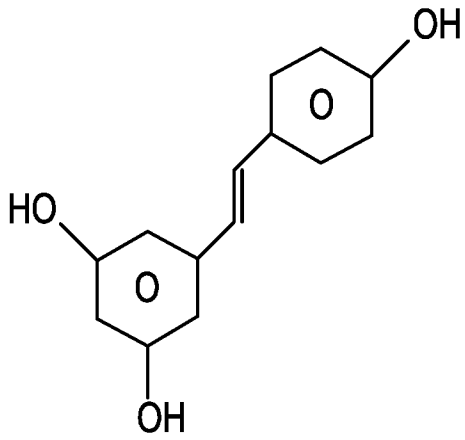

2
CH3O
CH3O
OCH3
O
Br
P(OEt)3
130° C
PO(OEt)2
HO
OH
NaH, THF
BCl3, nBH4NI
CH2Cl2
Resveratrol-circumin

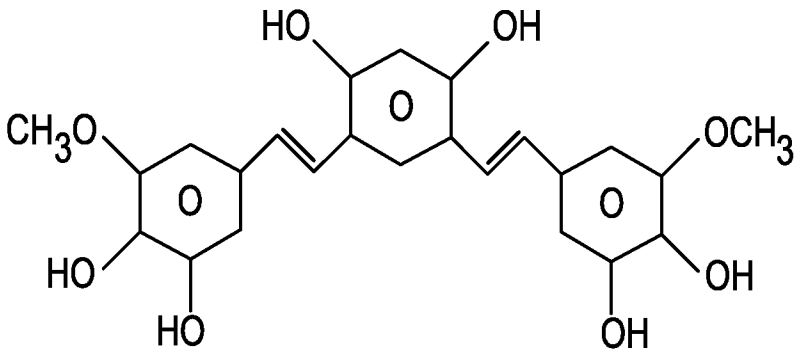
FIG. 8



Curcumin

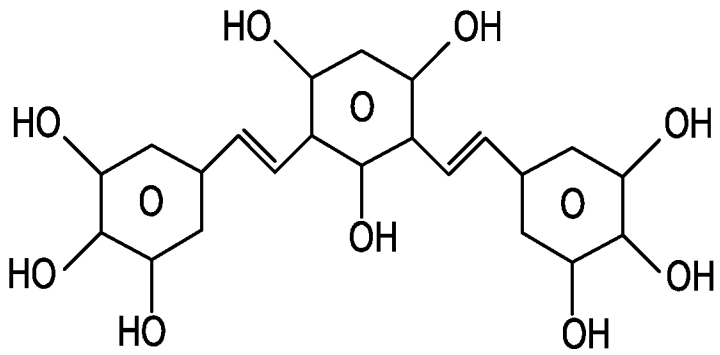


Resveratrol

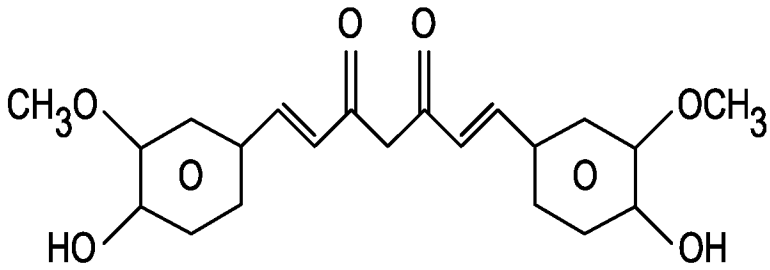


Curcumin-resveratrol III

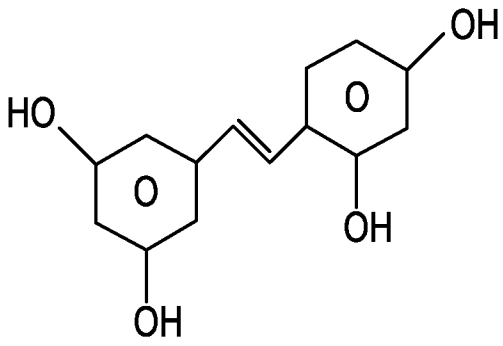
FIG. 9



Curcumin-oxy resveratrol II

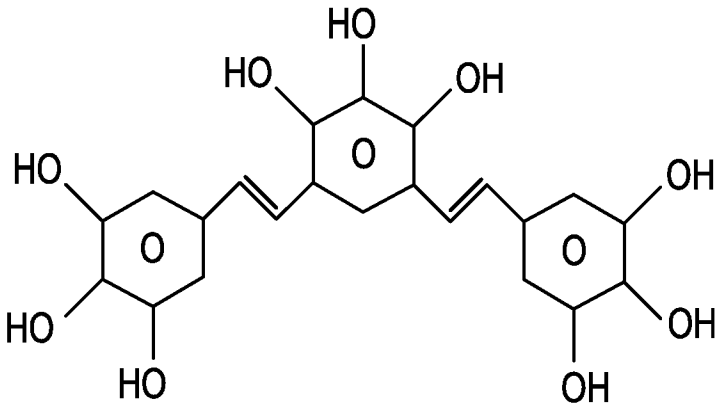


Curcumin



Oxy resveratrol

FIG. 10



Curcumin-piceatannol

FIG. 11

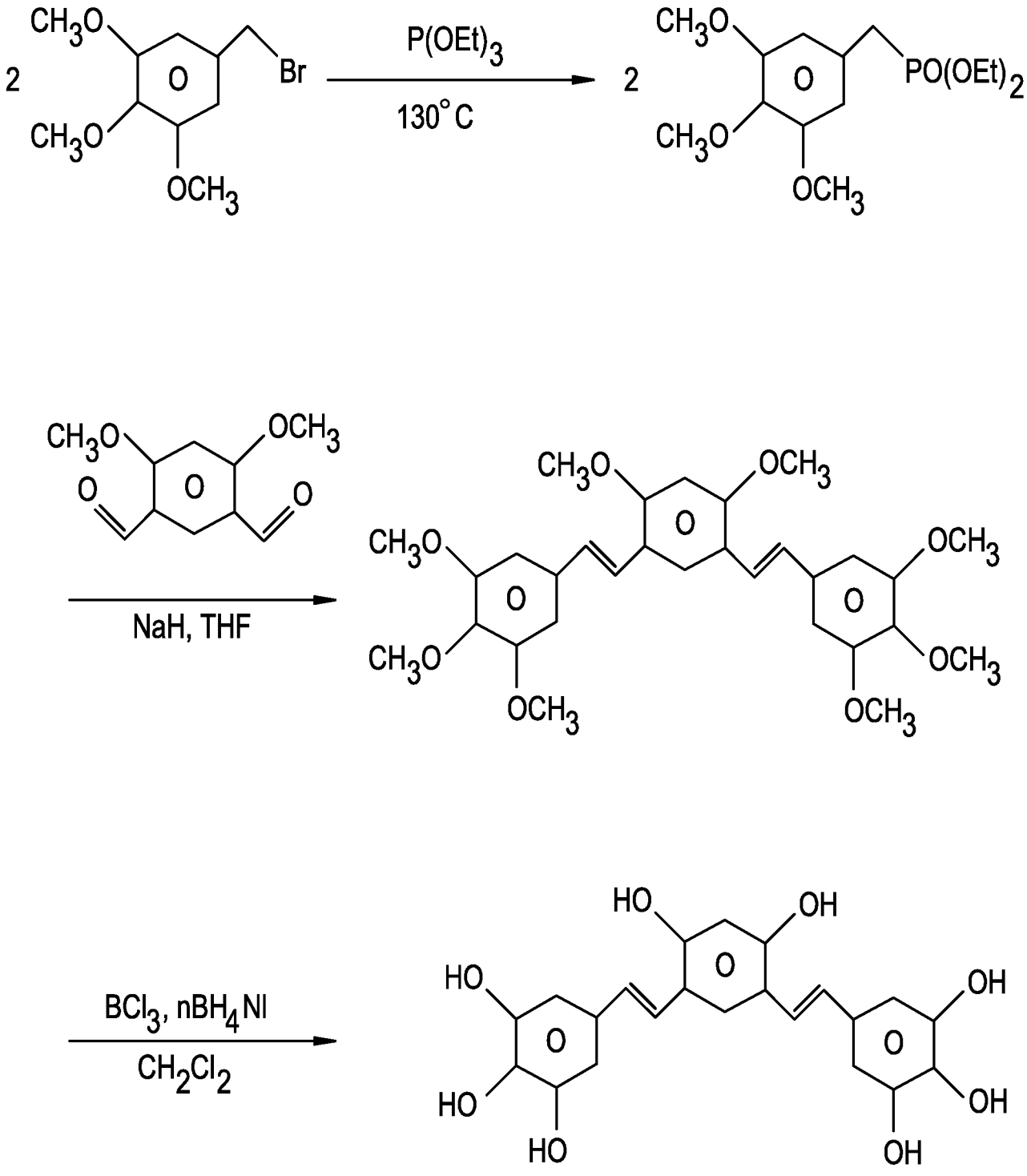

2
CH3O
CH3O
OCH3
O
Br
P(OEt)3
130° C
2
CH3O
CH3O
OCH3
O
PO(OEt)2
CH3O
OCH3
O
O
NaH, THF
CH3O
OCH3
CH3O
OCH3
O
O
CH3O
OCH3
OCH3
OCH3
BCl3, nBH4Nl
CH2Cl2
HO
OH
HO
OH
HO
OH
O
O
O

FIG. 12

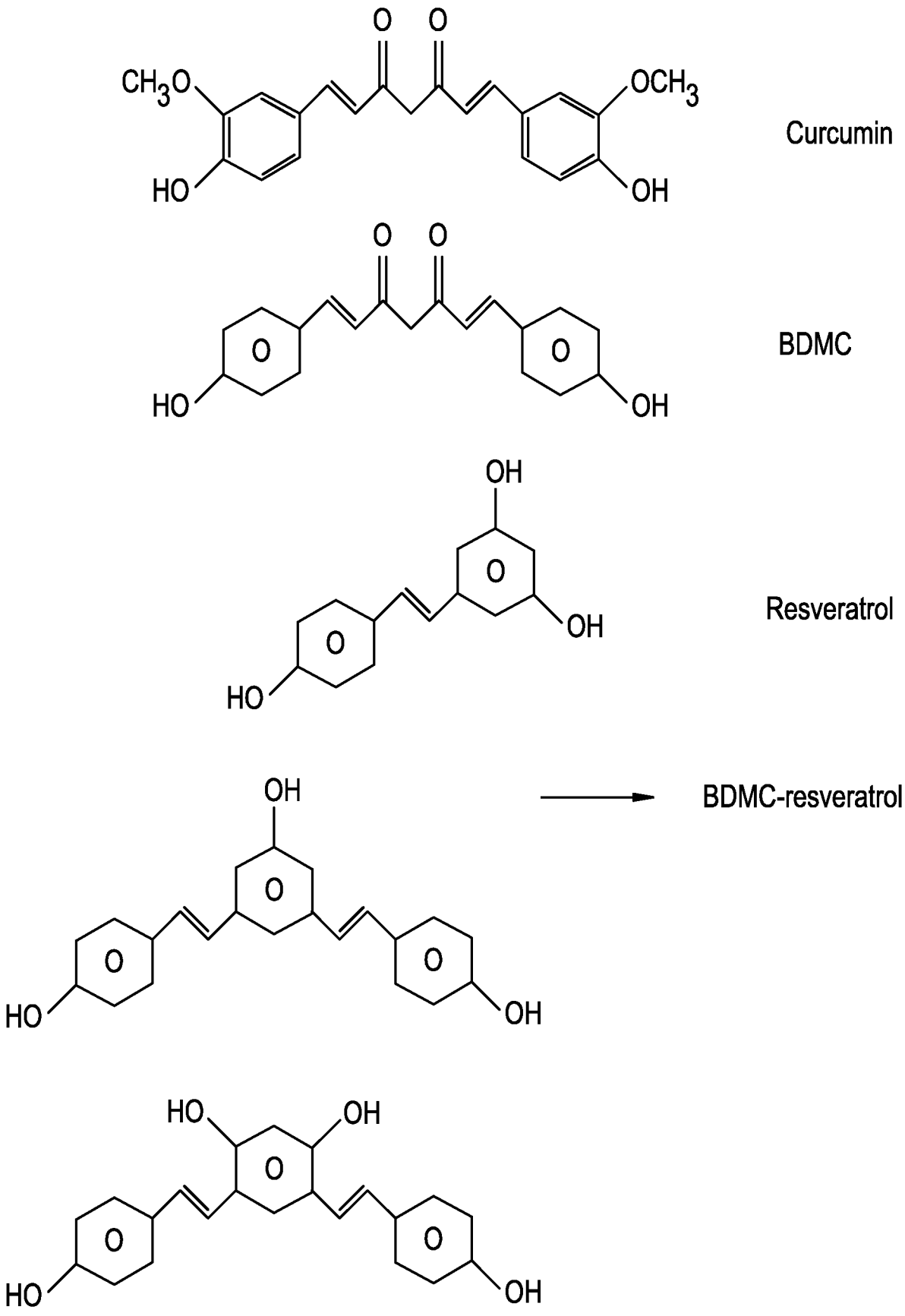

O
O
CH3O
OCH3
HO
OH
Curcumin
O
O
O
O
HO
OH
BDMC
OH
O
O
OH
HO
Resveratrol
OH
O
O
O
HO
OH
BDMC-resveratrol
HO
OH
O
O
O
HO
OH

FIG. 13

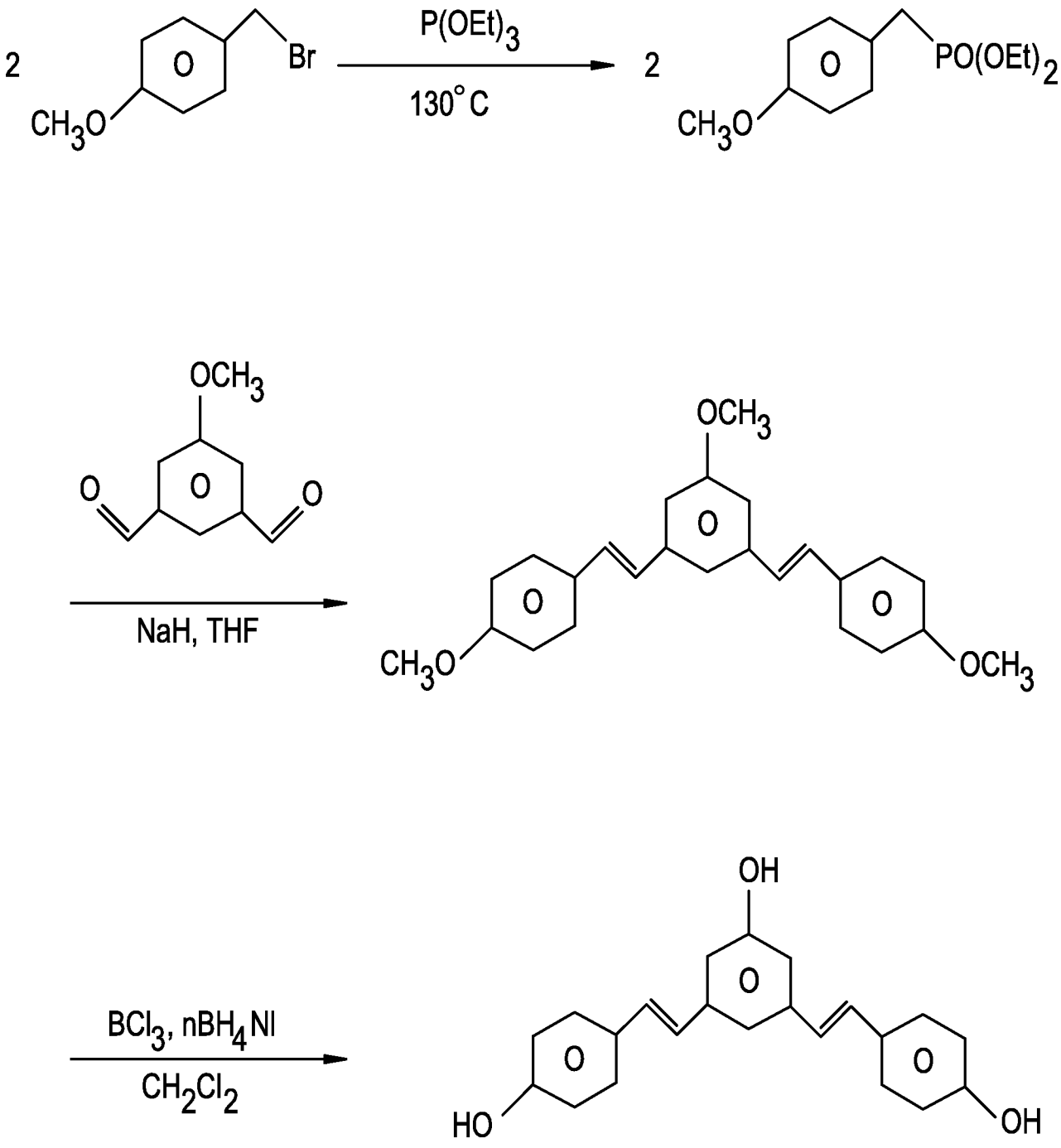
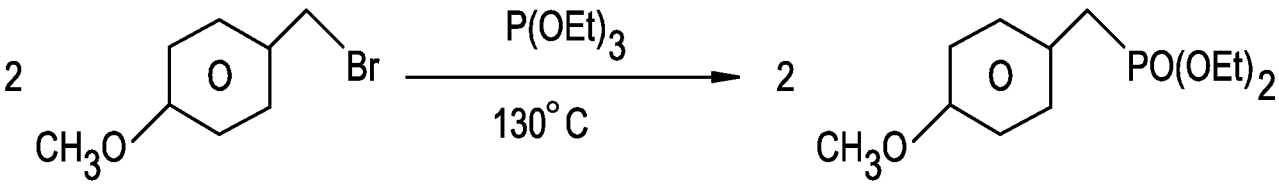
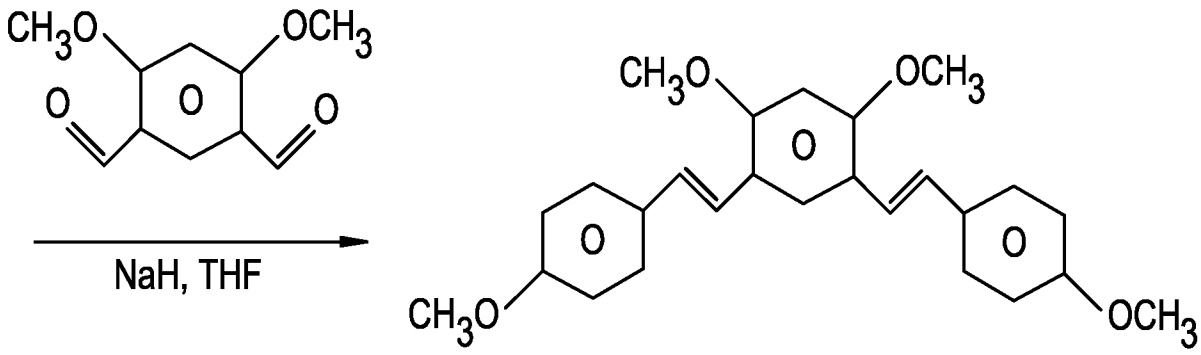

2
O
Br
CH3O
P(OEt)3
130° C
2
O
PO(OEt)2
CH3O
OCH3
O
O
O
NaH, THF
OCH3
O
O
O
CH3O
OCH3
BCl3, nBH4Nl
CH2Cl2
OH
O
O
O
HO
OH

FIG. 14


2
O
Br
CH3O
P(OEt)3
130° C
2
O
PO(OEt)2
CH3O


CH3O
OCH3
O
O
O
NaH, THF
CH3O
OCH3
O
O
O
CH3O
OCH3

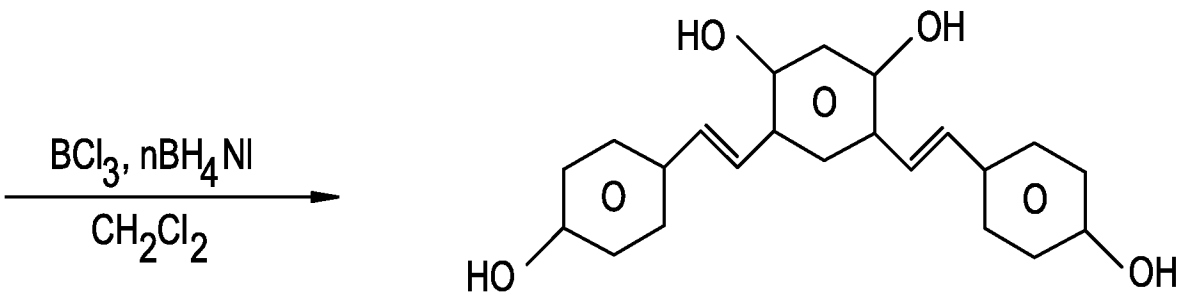
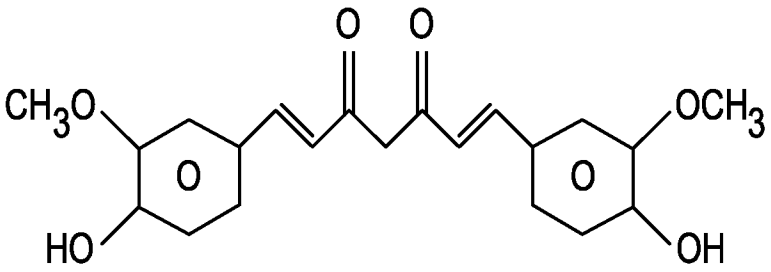
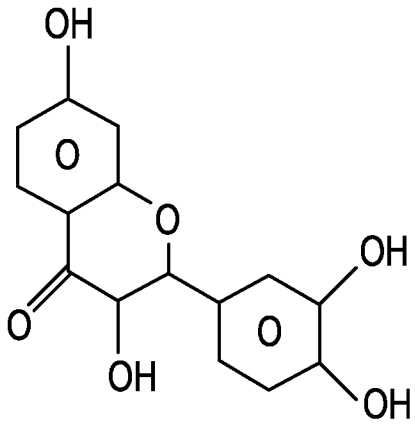

BCl3, nBH4Nl
CH2Cl2
HO
OH
O
O
O
HO
OH

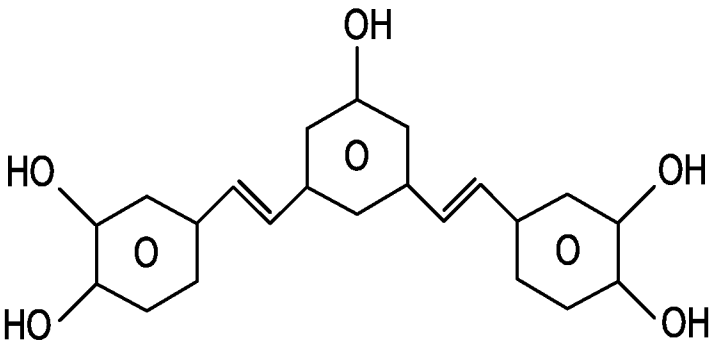
FIG. 15



Curcumin

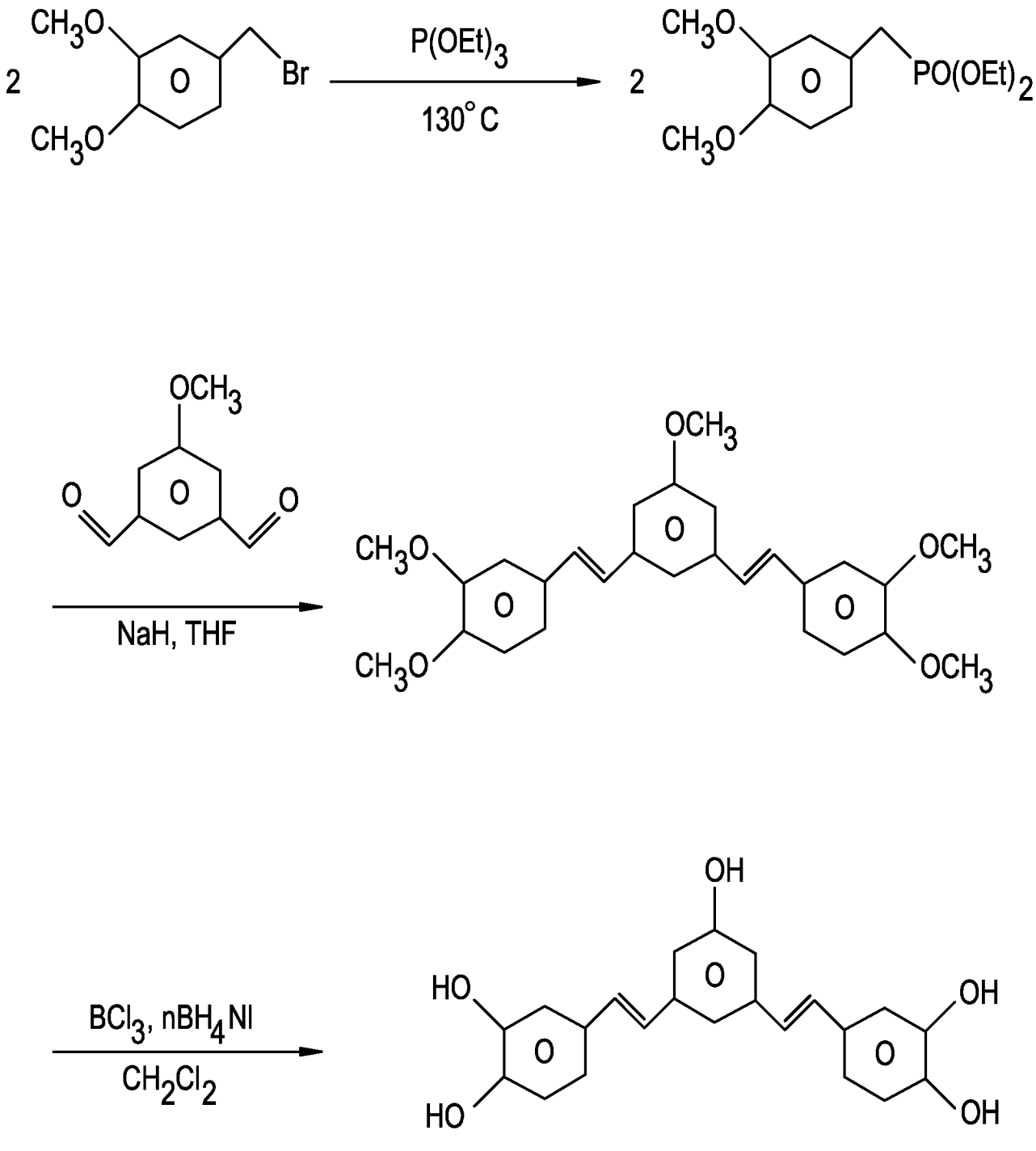


Fisetin



Curcumin-fisetin

FIG. 16


2
CH3O
O
Br
CH3O
P(OEt)3
130° C
2
CH3O
O
PO(OEt)2
CH3O
OCH3
O
O
O
NaH, THF
OCH3
O
CH3O
O
O
OCH3
CH3O
OCH3
BCl3, nBH4Nl
CH2Cl2
OH
O
HO
O
O
OH
HO
OH