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(54) **HIGHLY PURIFIED EPA FOR TREATMENT OF SCHIZOPHRENIA AND RELATED DISORDERS**

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(52) **U.S. Cl.** **514/560**
(58) **Field of Search** 514/560

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(57) **ABSTRACT**

A pharmaceutical preparation comprising EPA in an appropriately assimilable form where of all the fatty acids present in the preparation at least 90%, and preferably at least 95%, is in the form of EPA and where less than 5%, and preferably less than 3%, is in the form of DHA is provided for the treatment of a psychiatric or central nervous disorder. The preparation may be administered with conventional drugs to treat psychiatric or central nervous disorders to improve their efficacy or reduce their side effects.

21 Claims, 3 Drawing Sheets

Figure 1. The synthesis of eicosapentaenoic acid from alpha-linolenic acid

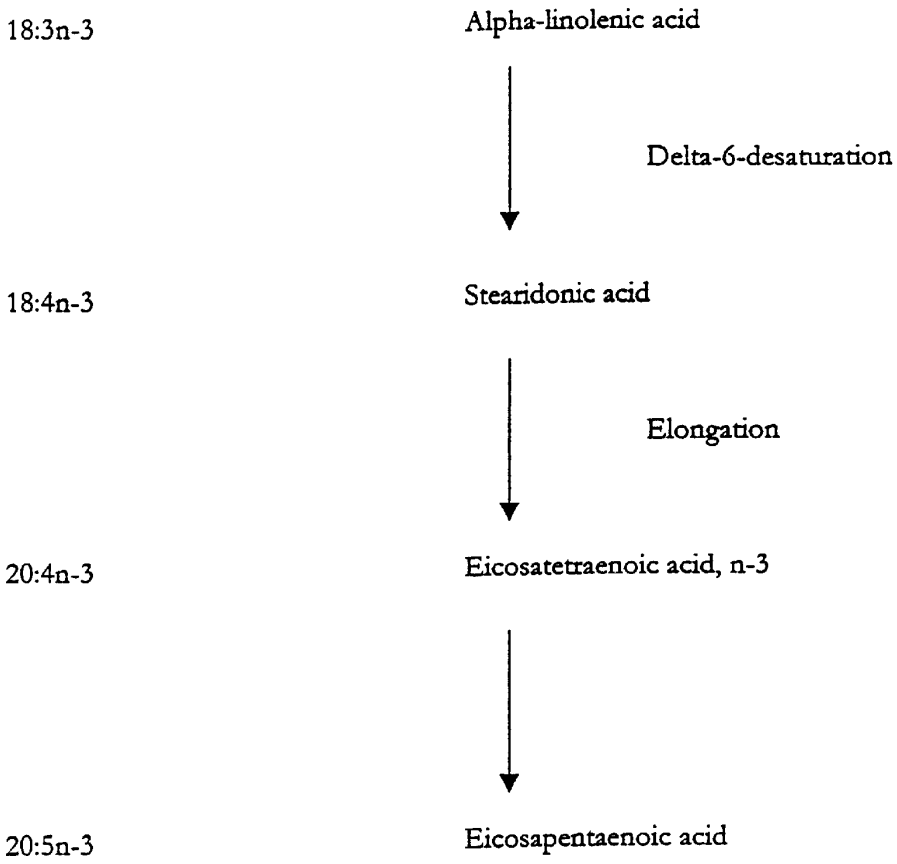


Figure 2

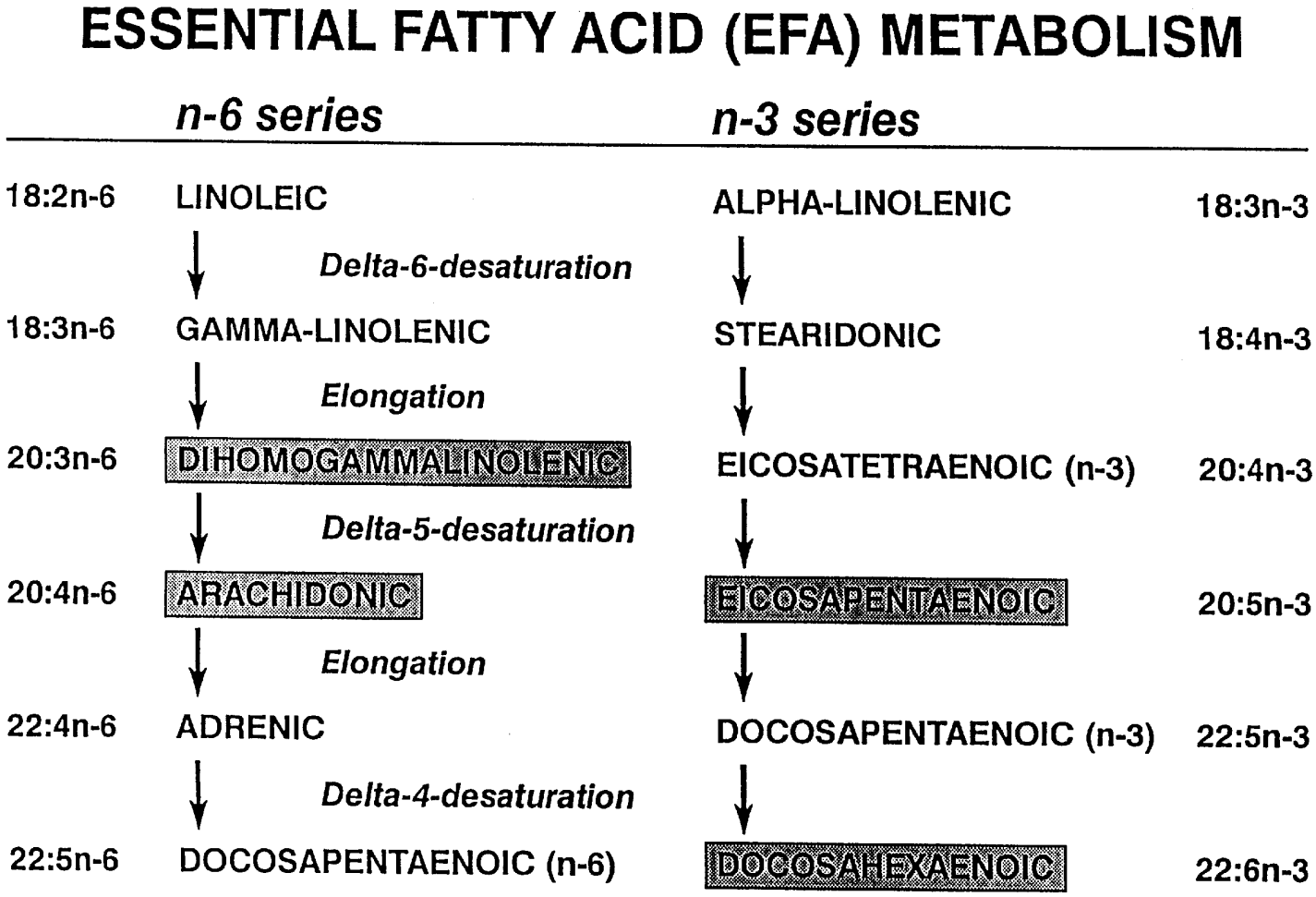
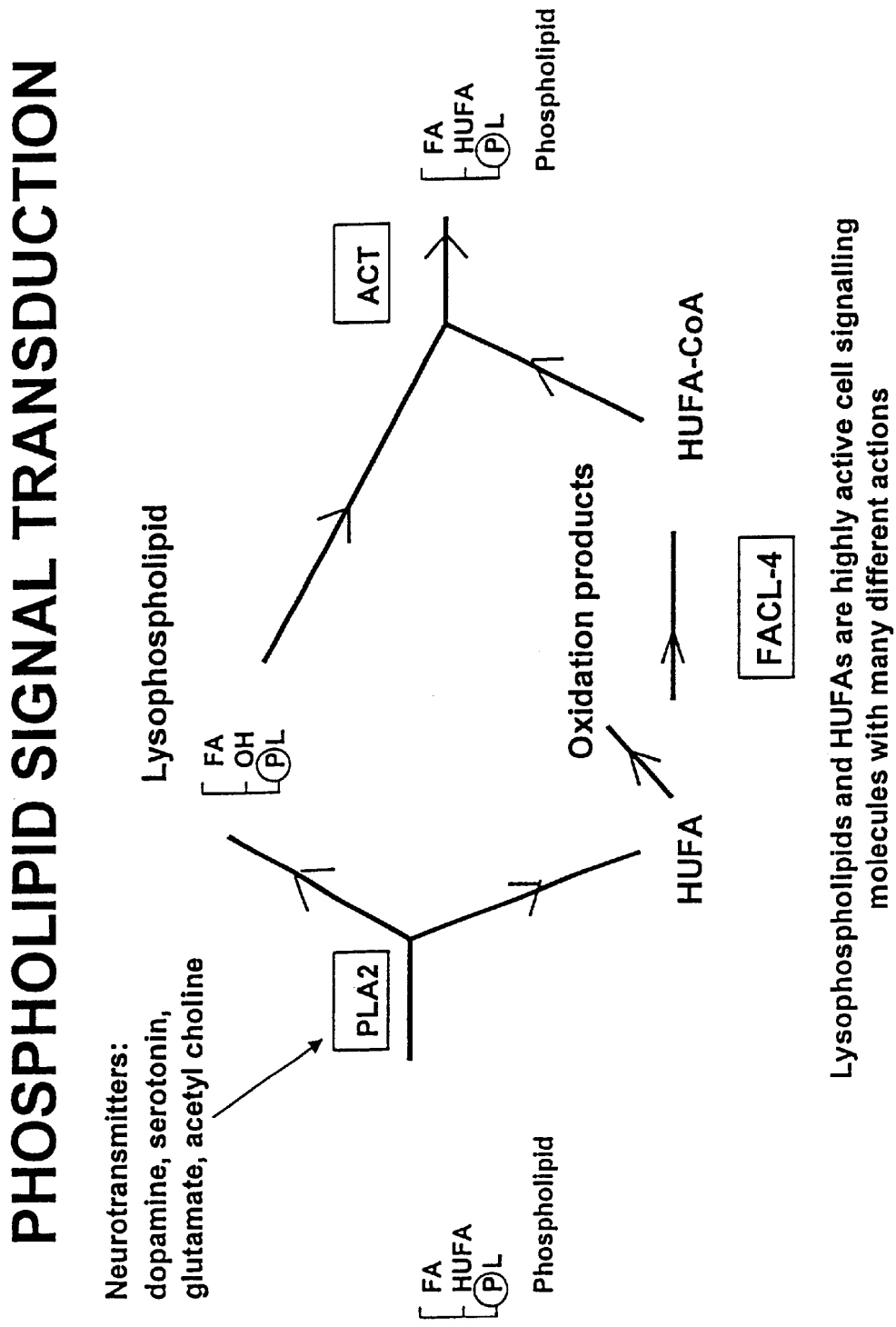


Figure 3



HIGHLY PURIFIED EPA FOR TREATMENT OF SCHIZOPHRENIA AND RELATED DISORDERS

BACKGROUND OF THE INVENTION

Even though many new drugs have been discovered over the past twenty years, psychiatric disorders are still relatively poorly treated. With most psychiatric illnesses, drug treatments do not treat all patients successfully. This is true of schizophrenia, schizoaffective and schizotypal disorders, bipolar disorder (manic-depression), unipolar depression, dementias, panic attacks, anxiety, sleep disorders, attention, hyperactivity and conduct disorders, autism, personality disorders, and all other psychiatric conditions. For example, in depression, standard drugs achieve a 50% reduction in standard depression scores in about two thirds of patients: the others do not respond. In schizophrenia, the average improvements are only of the order of 20–30% (S Leucht et al, Schizophrenia Research 1999;35:51–68) although individual patients may do much better than this.

The same is true of neurological disorders like Alzheimer's disease and other dementias, Parkinson's disease, multiple sclerosis, stroke, epilepsy and Huntington's disease. Again, many patients fail to respond to existing treatments, or respond only to a limited degree. In none of these conditions do existing drugs reliably produce a complete remission of symptoms. There is therefore a great need for new treatments, particularly ones which have novel mechanisms of action.

In PCT filing WO98/16216 attention was drawn to the value of a particular fatty acid, eicosapentaenoic acid (EPA), and its derivatives, in the treatment of schizophrenia, depression and dementias. EPA is a highly unsaturated fatty acid which can be derived from the dietary essential fatty acid, α-linolenic acid by a series of three reactions (FIG. **1**). EPA is a fatty acid containing 20 carbon atoms and 5 double bonds, all in the cis-configuration. The double bonds are located at the 5, 8, 11, 14 and 17 positions and the full chemical name is therefore all cis (or all z) 5, 8, 11, 14, 17-eicosapentaenoic acid (or sometimes icosapentaenoic acid). The abbreviation which is always used is EPA. EPA is one of the highly unsaturated fatty acids, the main types of which are shown in FIG. **2**. The reactions which convert alpha-linolenic acid to EPA are slow in humans and only a very small proportion of dietary α-linolenic acid is converted to EPA. EPA is also found in marine micro-organisms and, via the food chain, makes up between 3% and 30% of natural marine oils derived from oily fish and marine mammals. EPA is found linked to many different chemical structures. It can be found in the form of phospholipids, tri, di- and monoglycerides, amides, esters of many different types, salts and other compounds. In each case the EPA moiety can normally be split from the complex molecule to give the free acid form which can then be linked again to other complex molecules.

As described in PCT filing WO 98/16216 it was unexpectedly found that an oil enriched in EPA was of value in treating schizophrenia, while an oil enriched in the closely related fatty acid, docosahexaenoic acid (DHA), was not. This was surprising because DHA is found in large amounts in human brain whereas EPA is found only in trace quantities. It was therefore anticipated that DHA would be effective but EPA would not. In fact the opposite was found. WO 98/16216 disclosed the use of EPA and its derivatives for the treatment of psychiatric disorders.

SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical preparation comprising EPA in an appropriately assimilable form where of all the fatty acids present in the preparation at least 90%, and preferably at least 95%, is in the form of EPA and where less than 5%, and preferably less than 3%, is in the form of docosahexaenoic acid. Such preparations are for the treatment of any disorder except peripheral vascular disease and hyper-triglyceridaemia.

Preferably, among the other fatty acids present there are less than 5%, and preferably less than 3%, of each of AA or DPA-n-3, individually. The same preferably applies for any other fatty acids which might compete with the EPA.

It is preferred that the aggregate DHA, AA and/or DPA-n-3 content is less than 10%, of the total fatty acids present, and preferably less than 5%.

The EPA may be in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action on psychiatric or brain disorders to any substantial degree (N. Willumsen et al., Biochimica Biophysica Acta, 1998, 1369: 193–203).

Such pharmaceutical preparations may be used for the treatment of a psychiatric or central nervous system disorder, including: schizophrenia, schizoaffective disorder or a schizotypal disorder; depression or manic-depression (bipolar disorder); anxiety or panic disorder or social phobia, or a sleep disorder or an attention deficit, conduct, hyperactivity or personality disorder; autism; Alzheimer's disease, vascular dementia or another dementia, including multi-infarct dementia, Lewy body disease and diseases attributable to prion disorders; Parkinson's disease, or other motor system disorder; multiple sclerosis; stroke; epilepsy; and Huntington's disease or any other neuro-degenerative disorder.

The present invention further provides formulations for use in psychiatric and neurological disorders in which a drug which acts primarily on neurotransmitter metabolism or receptors is prepared for co-administration with a pharmaceutical preparation according to the first aspect of the invention, as well as pharmaceutical formulations comprising a preparation according to the first aspect of the invention together with a drug which acts primarily on neurotransmitter metabolism or receptors. The conventional drug may administered in conventional dosage, and the EPA formulations according to the first aspect of the invention administered to the patient separately. The conventional drug may be combined with the EPA preparations of the first aspect of the invention in a combination formulation, or the two may be provided in separate individual formulations but in a combination pack.

The EPA-containing preparations of the present invention may be administered with any drug known to have an effect on the treatment of psychiatric or central nervous system disorders to improve the efficacy of the drug or reduce its side effects.

Suitable drugs for co-administration with the EPA preparations of the first aspect of the invention are clozapine; and any one of the class of typical or atypical neuroleptics, including chlorpromazine, haloperidol, risperidone, olanzapine, sertindole, ziprasidone, zotepine or amisulpiride. Others are mentioned below.

The present invention still further provides a method of treating or preventing the side effects of a drug used in treating psychiatric or neurological disorders by administration of the drug and a pharmaceutical preparation according to the first aspect of the present invention.

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