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(54) Title: ENHANCEMENT OF THE EFFICACY OF DRUGS BY DEUTERATION

(57) Abstract

A method of enhancing the efficiency and increasing the duration of action of drugs (e.g. dihydropyridines) and particularly of nifedipine wherein one or more hydrogen atoms are deuterated and wherein the deuterated nifedipine has unexpectedly improved hypotensive properties when used in much lower concentrations than nifedipine *per se*. A method for determining the identity and bioequivalency of a new drug is also disclosed wherein the molecular and isotope structure of a new drug is determined by gas chromatography-isotope ratio mass spectrometry and compared with the molecular and isotope structure of a known human drug.

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ENHANCEMENT OF THE EFFICACY OF DRUGS BY DEUTERATION

REFERENCE TO A RELATED APPLICATION

This is a continuation-in-part of our copending U.S. Patent Application Serial No. 08/217,897 filed March 25, 1994 which is relied on and incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

The present invention relates to a process for enhancing the efficacy of known pharmaceuticals or drugs, and to the enhanced drugs so produced, by changing the isotopic form of the molecular structure of the known drug. More particularly, the present invention relates to the modification of the molecular structure of known drugs containing one or more hydrogen atoms by deuterating one or more of the hydrogen atoms to deuterium atoms. The resulting drug is significantly altered and has greatly improved activity over the known drug. Most particularly this invention relates to a method of deuterating a dihydropyridine (e.g., nifedipine) whereby the deuterated nifedipine has an increased hypotensive effect and an increased duration of action on mammals at lower concentration than does nifedipine.

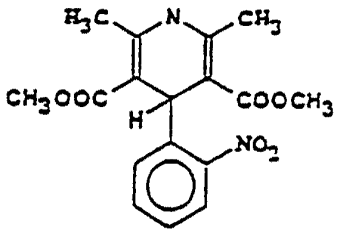
When pharmaceuticals are synthesized, a carbon back-bone is assembled having various substituents including carbon, hydrogen, oxygen, nitrogen, etc. Pharmaceuticals have been designed and synthesized by a number of modes including, for example, serendipity and molecular modification. These and other methods have generated a vast number of drugs over the course of time. As such modifications have allowed individual companies to keep a competitive edge in the marketplace, a

significant part of the industry's time and resources is spent searching for novel agents within certain pharmacologic classifications, e.g., antihypertensives. Such novel agents often have different activities from the prototype compounds, thus justifying the monies spent for their development.

SUMMARY OF THE INVENTION

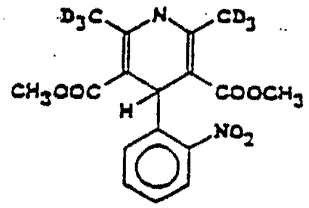
It is known that virtually all drugs now marketed include a number of hydrogen atoms, each of which has a molecular mass of one. It has now been found that when one or more of the hydrogen atoms on a drug are modified so that their molecular mass becomes two, the activity of the drug is significantly altered and is even greatly improved. Thus, for example, isotopic modification of a dihydropyridine, e.g., such as nifedipine, has resulted in an unexpected change in the hypotensive (blood pressure lowering) effect in mammals compared to nifedipine *per se*, and such effects should also be achieved with humans.

Nifedipine is marketed worldwide as an important drug used in the treatment of angina and hypertension. Its structure is as follows:



By modifying nifedipine by replacing one or more hydrogens of the methyl groups with deuterium or by replacing one or more of the methyl groups with CD_3, the therapeutic properties of nifedipine can be altered and can even be significantly improved. For example, by modifying the nifedipine by replacing the two methyl groups at the 2 and 6 positions on the ring with two deuterated groups (CD_3), i.e.,

replacing 6 hydrogen atoms with six deuterium atoms, the structure of the deuterated nifedipine is as follows:



Both of the above molecules are nifedipine and the latter structure is an isotopic form of the former.

BRIEF DESCRIPTION OF THE DRAWING

The present invention will be further understood with reference to the drawings, wherein:

Figure 1 shows the hypotensive effect of the various concentrations of the deuterated nifedipines on the treated rats as compared with nifedipine *per se*;

Figures 2 and 3 show use dependent inhibition of control nifedipine (Nifedipine B) and deuterated nifedipine (Nifedipine D) on T type calcium channels;

Figure 4 shows the effect of control nifedipine and deuterated nifedipine on calcium current inhibition as a function of pulse frequency;

Figure 5 shows the effect of control nifedipine and deuterated nifedipine on use dependency;

Figures 6(a) and (b) show the effect of control and deuterated nifedipine on mean arterial pressure;

Figures 7(a) and (b) show concentration-effect relationships for control (Figure 7(a)) and deuterated (Figure 7(b)) nifedipine fitted using an asymmetric sigmoidal model;

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