

DIHYDROXYVITAMIN D3 PHARMACEUTICAL SYSTEM

Vitamin D₃ is capable of generating a host of biological responses in higher animals via its participation in the vitamin D endocrine system, where it is metabolized to yield daughter metabolites that function as steroid hormones. The principal metabolite is 1-alpha, 25 dihydroxyvitamin D₃ [1,25(OH)₂ D₃, or hormone D], which is generally thought to be the hormonally-active form of vitamin D. Hormone D regulates the maintenance of calcium homeostasis, promoting bone calcium mobilization (BCM) and intestinal calcium absorption (ICA, also known as transcalcachia). In addition, hormone D is a potent immunosuppressant, stimulator of selective cell differentiation, and stimulator of apoptosis.

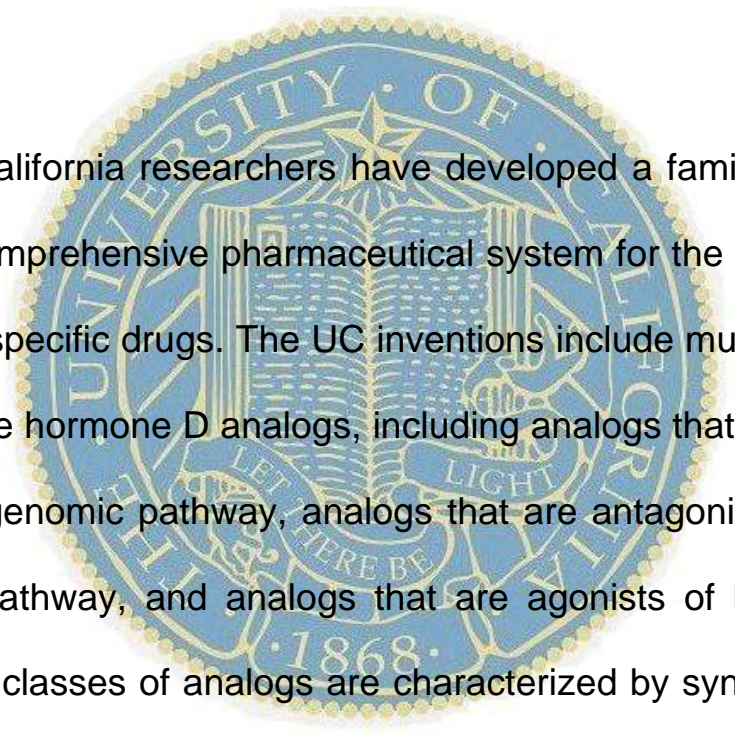
Analogs of hormone D that mimic these metabolites have been employed in numerous pharmacological applications, as such compounds have the potential to treat a large variety of disorders, notably osteoporosis, renal osteodystrophy, Alzheimer's disease, hypoparathyroidism, and psoriasis. There are also potential benefits in using these compounds for immunosuppression during organ transplantation or for treating cancers such as leukemia, breast cancer, colon cancer, and prostate cancer.

Unfortunately, commonly-used hormone D analogs also display undesirable side effects due to the numerous physiological responses that these compounds produce.

Specifically, the metabolism of vitamin D₃ in the liver and kidney gives rise to the hormone D metabolite, which is then transported via the circulatory system to all parts of the body. Vitamin D₃ metabolite circulation requires the binding of the metabolite to the vitamin D binding protein (DBP). Once the metabolite/DBP complex arrives at a target cell and delivers hormone D, this molecule then binds to either a well-characterized nuclear receptor (VDR_{nuc}) or to a newly discovered cell membrane receptor. Thus, hormone D can trigger two distinct signal transduction pathways to generate biological responses.

In one pathway, the cell membrane receptor activity is either directly coupled to the opening of voltage-gated calcium channels, effecting rapid changes in calcium distribution, or to the activation of a MAP kinase within the cell. The activated MAP kinase, in conjunction with hormone D, acts on the VDR_{nuc} receptor to slowly change the rate of genomic mRNA synthesis. VDR_{nuc} regulates gene transcription in over 30 different target organs.

To prevent undesirable side effects, agonists and antagonists specific to each signal transduction pathway would be highly desirable as candidate drugs for achieving more specific pharmacological responses. For example, a compound that stimulated the slow genomic response without simultaneously inducing hypercalcemia via the rapid non-genomic response may be valuable for suppressing cell proliferation (e.g. for treating cancer).

The seal of the University of California is visible as a large, semi-transparent watermark in the background of the text. It features a central sunburst, a book, and the motto "LET THERE BE LIGHT". The text "UNIVERSITY OF CALIFORNIA" and "1868" are also present within the seal's border.

University of California researchers have developed a family of inventions that offers a comprehensive pharmaceutical system for the development of such pathway-specific drugs. The UC inventions include multiple classes of DBP-compatible hormone D analogs, including analogs that are agonists of the rapid non-genomic pathway, analogs that are antagonists of the rapid non-genomic pathway, and analogs that are agonists of both pathways. Some of these classes of analogs are characterized by syntheses that are far simpler than is the case for many of the non-specific and/or DBP-incompatible vitamin D₃ analogs that are currently available. Preliminary analyses have also shown that they are as potent as the naturally-occurring metabolites.

In addition, these UC researchers have also described the three-dimensional structure of the ligand-binding domain of the hormone D nuclear receptor. With this information, it should be possible to design, generate, and select nuclear receptor-specific agonists and antagonists for controlling the slow genomic pathway. Thus, there is a potential for further extending the range of available hormone D analogs with important therapeutic applications.

The ability to produce potent, DBP-compatible hormone D analogs with receptor-specific effects represents a significant improvement over existing vitamin D₃-based pharmaceuticals. Ultimately, these inventions will probably give rise to several new compounds for use in therapeutic formulations with application in a wide variety of clinical circumstances.

PATENT STATUS: US Patent No. [6,103,709](#) issued August 15, 2000; US Patent No. [6,121,469](#) issued September 19, 2000; US Patent No. [6,307,075](#) issued October 23, 2001; US Patent No. [6,329,357](#) issued December 11, 2001