



Concert Pharmaceuticals, Inc.

Precision Deuterium Chemistry Backgrounder

Non-Confidential

OVERVIEW: CONCERT PRODUCT PLATFORM

Concert Pharmaceuticals is the first company dedicated to creating safer, more effective medicines using Precision Deuterium Chemistry.

Concert's proprietary product platform offers:

- Improved, best-in-class compounds derived from existing, validated drugs;
- New Chemical Entities (NCE's) protected by patent applications claiming composition of matter;
- Greatly reduced R&D risk, time and expense; and
- Rapid phase 1 proof-of-concept.

PRECISION DEUTERIUM CHEMISTRY

Subtle changes result in surprising benefits

Isolated from seawater, deuterium is a naturally-occurring relative of hydrogen that has been used extensively in human metabolic and clinical studies. Deuterium-substituted compounds retain their molecular shape and thus have selectivity and potency comparable to their hydrogen analogs. However, since deuterium is heavier than hydrogen, it forms significantly stronger bonds with carbon resulting in differentiated ADME (Absorption, Distribution, Metabolism and Excretion). This offers a number of potential clinical benefits (Figure 1):

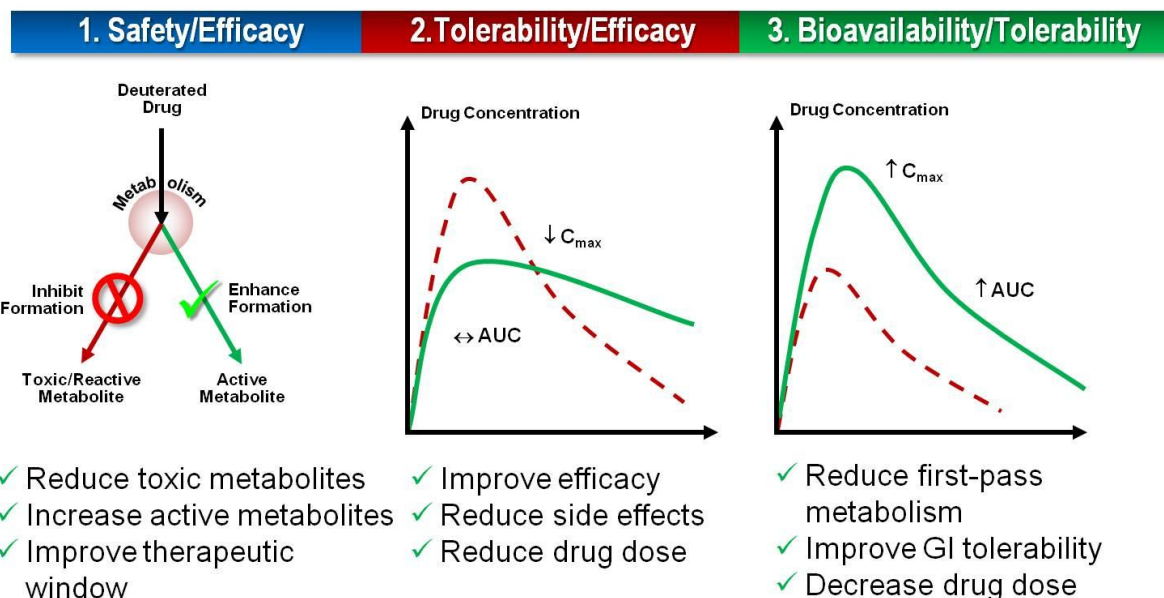


Figure 1. Deuterium substitution has the potential to create NCE's with improved safety, tolerability and efficacy.

Deuteration provides novel agents with the potential for:

- **Improved safety** by inhibiting the formation of toxic metabolites and reducing drug-drug interactions.
- **Better tolerability** through reduction of overall dose and C_{max} .
- **Enhanced efficacy** by increasing bioavailability, AUC and C_{min} with minimal impact on C_{max} . Deuteration may also block elimination pathways enhancing the formation of active metabolites.

Since the magnitude and nature of the deuterium benefit cannot be predicted *a priori*, Concert must test multiple compounds in a range of assays to identify those that are differentiated. For novel compounds with meaningful differentiation, Concert expects to have significant patent term, including claims to composition of matter.

Concert compounds are based on drugs with known efficacy and safety that address clinically validated targets. This allows Concert to rapidly create novel, differentiated compounds with substantially reduced R&D risk, time and expense.

Concert has created a deep pipeline with lead programs in HIV and Chronic Kidney Disease (Figure 2). In addition, Concert has over 20 on-going discovery-stage programs selected due to their significant clinical differentiation and potential for strong intellectual property protection.

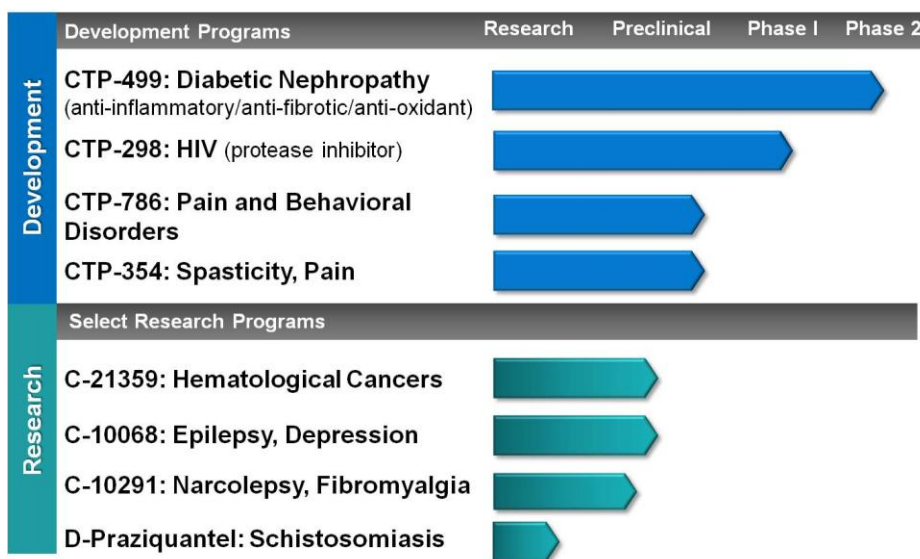


Figure 2. Concert's product pipeline.

D-TORCETRAPIB ILLUSTRATES BENEFITS OF PRECISION DEUTERIUM CHEMISTRY

Concert selected torcetrapib while it was still in development as an exciting new opportunity that had the potential to benefit from Precision Deuterium Chemistry. Oxidative metabolism had been reported for the portions of the molecule highlighted in Figure 3a. This information was used to design a lead series to assess the deuterium structure-activity relationships (SAR). See below figure 3b, analogs A-L.

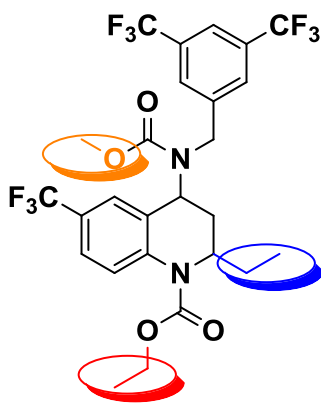


Figure 3a. Metabolic “hotspots” were identified from literature reports of *in vivo* metabolism

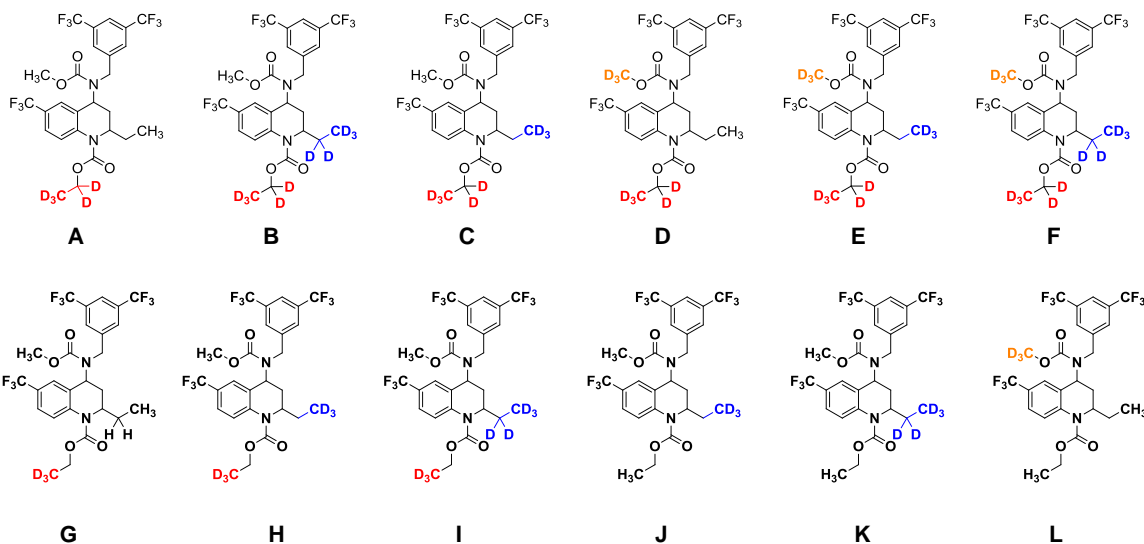


Figure 3b. A lead series of analogs was developed to assess the deuterium SAR

Human liver microsomes (HLMs) were used to measure the metabolic stability of compounds A-L. Analogs A-F were dramatically stabilized in HLM's while analogs G-L exhibited metabolic rates of degradation similar to that of torcetrapib (Figure 3c & 3d). This surprising metabolic stabilization offers the potential to create D-torcetrapib NCE's with more favorable pharmacokinetics for once-a-day dosing. Based on improved metabolic stability, a decrease in C_{max} and an increase in C_{min} could lead to an improved efficacy and side-effect profile respectively.

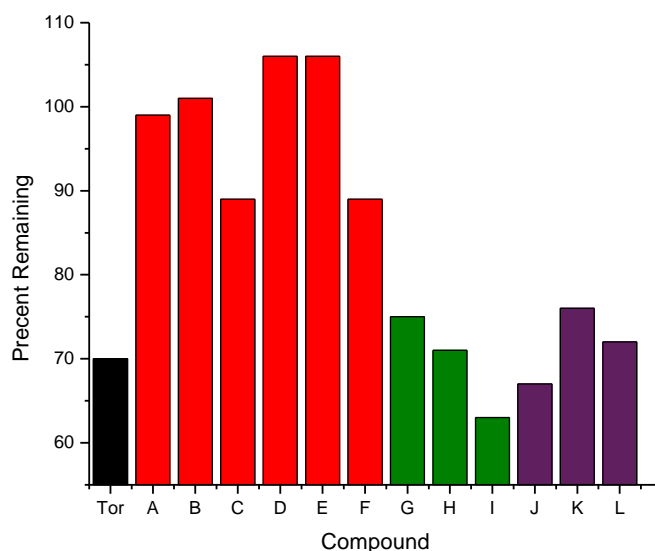


Figure 3c. Metabolism of torcetrapib (Tor) and deuterated compound series A-F, G-I and J-L in human liver microsomes (HLM's) showing compound stability within each series.

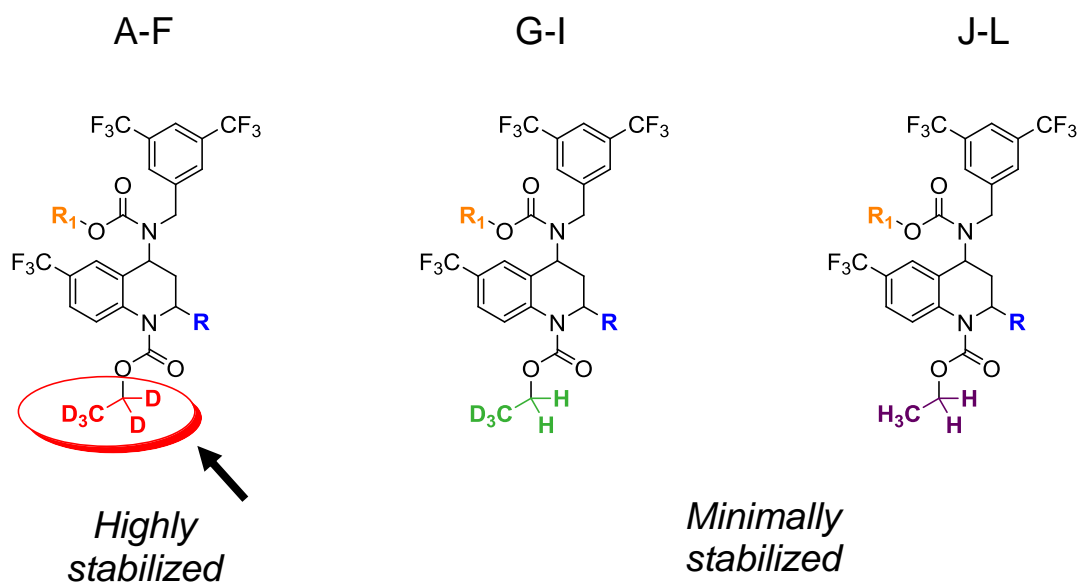


Figure 3d. SAR of deuterated torcetrapib. Only analogs that contain a fully deuterated ethoxy side chain are stabilized markedly in human liver microsomes

INTELLECTUAL PROPERTY

Deuterium substitution results in patentable New Chemical Entities (NCE's). Concert holds >90 issued or pending U.S. and European patents on deuterated drug families, addressing a broad range of therapeutic areas of commercial importance to the pharmaceutical industry. (Figure 4).

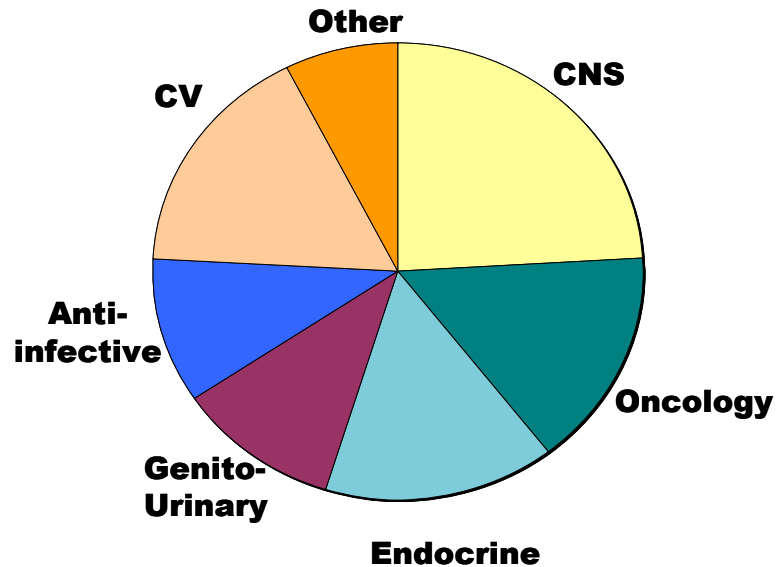


Figure 4. Concert patent portfolio by therapeutic class.

CONCERT STRATEGY

Industrialized deuteration platform

Concert is deploying its product technology platform to rapidly assemble a pipeline of valuable new deuterated drugs. Concert's platform supports advancing multiple NCE drug candidates into clinical development each year with an objective of demonstrating clinical proof-of-concept for each program. In this manner, Concert expects that it will provide an unprecedented opportunity for pharmaceutical value creation across multiple important product categories. To fully exploit the commercial opportunity, Concert is interested in identifying partners who are motivated to build substantial value by using Concert NCEs to create or grow key commercial franchises.

CONTACT INFORMATION

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