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Design and Synthesis of Deuterated Analogs of Ivacaftor With Enhanced Pharmacokinetic Properties

www.concertpharma.com
Lexington, MA 02421

Adam J. Morgan; Sophia Nguyen; Changfu Cheng; Gary Bridson; Vinita Uttamsingh; Lijun Wu; Philip B. Graham; Scott Harbeson

DCE Platform®

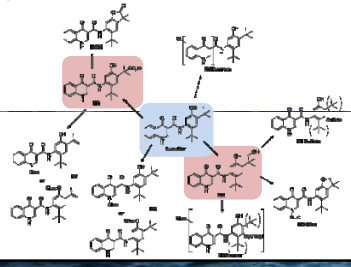
Abstract

As part of an ongoing effort to apply the Deuterated Chemical Entity Platform (DCE Platform®) to clinically validated drugs, several deuterated analogs of the CFTR potentiator ivacaftor (Kalydeco®) have been prepared. The devised synthetic routes allowed for site selective deuterium incorporation with high levels of isotopic purity. Due to the fact that ivacaftor was poorly metabolized in standard liver microsome assays under the conditions tested, human CYP3A4 Supersomes™ were used to assess and compare the *in vitro* metabolic stability of ivacaftor and the DCEs. In this manner, multiple deuterated analogs displaying marked levels of *in vitro* metabolic stabilization have been identified. One such analog, compound **110**, exhibited a 55% increase in half life vs. ivacaftor. Synthetic routes to the individual isotopologs along with metabolic stabilization data using human CYP3A4 Supersomes™ will be presented.

Introduction

Ivacaftor undergoes extensive metabolism in humans as shown in Figure 1 (only 2.52% excreted as unchanged parent).[1,2] The two major circulating metabolites, M1 and M6, exhibit significantly greater plasma exposure than ivacaftor: the ratios of AUCs for M1 and M6 to ivacaftor are 6 and 2, respectively. While M1 represents a pharmacologically active metabolite with 1/6th the potency of ivacaftor; M6 exhibits less than 1/50th the potency and is considered not active. *In vitro* studies have established that ivacaftor and M1 are both substrates for CYP3A4 in humans. The importance of metabolism by CYP3A4 metabolism in humans is shown by the marked drug-drug interaction observed with ketoconazole, a strong CYP3A4 inhibitor.[1] The approved standard dosing regimen for ivacaftor is 150 mg q12h. However, when taken concomitantly with a strong CYP3A4 inhibitor, a significant dose reduction to 150 mg twice-a-week is recommended. These metabolic properties made ivacaftor a promising candidate for optimization via our deuterium technology.

Figure 1: ^{14}C-Ivacaftor metabolism[2]



Results

Schemes 1-4: Synthesis of deuterated analogs of ivacaftor[3]

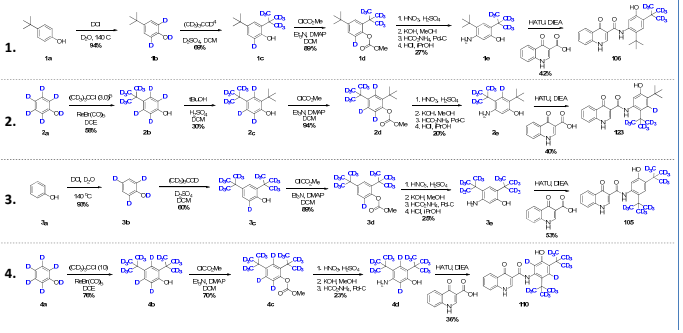


Figure 2: Crude product profile for 3b to 3c[5]

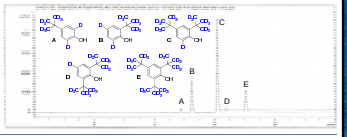


Figure 3: Attempted synthesis of 2e[5]

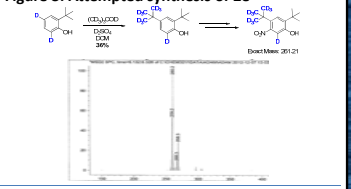
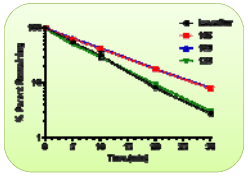
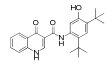
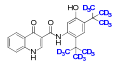
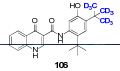


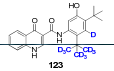
Figure 4: Metabolic stability in CYP3A4 supersomes





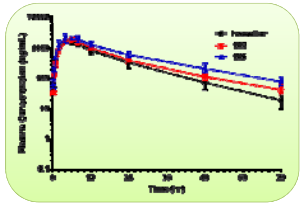




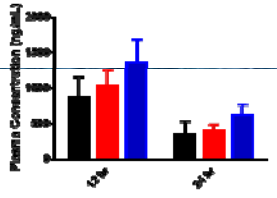


Compounds (1 μM) incubated with CYP3A4 supersomes (50 pmol/mL) for 30 minutes. Analytical measurements of parent remaining were carried out using LC/MS- MS methods.

Figure 5: Oral PK in rats

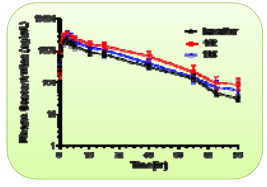


Parameter	Ivacaftor	106	105
$t_{1/2}$ (hr)	10.49 ± 1.75	13.24 ± 1.20 (26% increase)	14.84 ± 1.32 (41% increase)
C_{max} (ng/mL)	1913 ± 126	1970 ± 304 ---	2460 ± 685 (28% increase)
AUC_{last} (ng*hr/mL)	28378 ± 8944	32557 ± 6139 (15% increase)	45220 ± 10002 (59% increase)

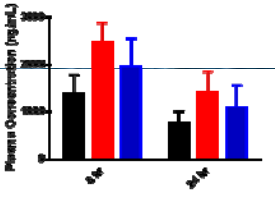


Rats (3/group) were dosed (PO; 10 mg/kg) with ivacaftor, 106, and 105 as solutions in PEG400 (2 mg/mL). Plasma samples were analyzed using LC/MS- MS methods (LOQ=1 ng/mL). PK parameters were calculated using WinNonlin®.

Figure 6: Oral PK in dogs



Parameter	Ivacaftor	106	105
$t_{1/2}$ (hr)	14.7 ± 4.8	15.9 ± 2.6	15.7 ± 6.0
C_{max} (ng/mL)	2255 ± 748	3643 ± 339 (62% increase)	3030 ± 1144 (34% increase)
AUC_{last} (ng*hr/mL)	49396 ± 12553	88685 ± 20163 (80% increase)	66663 ± 20779 (35% increase)



Dogs (4/group) were dosed (PO; 3 mg/kg) with ivacaftor, 106, and 105 as solutions in PEG400 (1.5 mg/mL). Plasma samples were analyzed using LC/MS- MS methods (LOQ=1 ng/mL). PK parameters were calculated using WinNonlin®.

Conclusions

- Several deuterated analogs of the CFTR potentiator ivacaftor have been prepared via synthetic routes that allow for highly site-selective deuterium incorporation.
- The *in vitro* metabolic stability of ivacaftor and the DCEs was assayed in the presence of human CYP3A4 supersomes. Compounds **105**, **106** and **110** exhibit significant stabilization to CYP3A4 metabolism (~50% increase in $t_{1/2}$) whereas stabilization was not observed with compound **123**.
- Ivacaftor, **105** and **106** were then dosed orally to both rats and dogs and plasma levels were measured out to 72 and 96 hours respectively. In rats and dogs, both DCEs were metabolically stabilized and achieved greater exposure levels than ivacaftor. In rats, compound **105** was stabilized to a greater extent and exhibited a 59% increase in AUC. Interestingly, compound **106** was stabilized to a greater extent in dogs and exhibited an 80% increase in AUC.
- Studies in rat, dog, and human hepatocytes are in progress to determine which *in vivo* result may be predictive of the human PK.
- Compounds **105**, **106** and ivacaftor were compared in a potentiation assay using bronchial airway epithelial cells from patients with the ΔF508 CFTR mutation. All three compounds were indistinguishable in potency and efficacy confirming the *in vitro* pharmacology of the DCEs.[6]

Literature cited

1. Chen, Y.. et al., *J. Clin. Pharmacol.* **2011**, *51*, 1358-1359.
2. Fda.gov/drugsatfda_docs/nda/2012/203188Orig1s000ClinPharmR pp. 18-50.
3. (a) Hadida Ruah, S. et al., WO2006002421A2 (b) Morgan, A. WO2012158885A1.
4. Kurahashi, T. et al., *J. Am. Chem. Soc.* **2009**, *131*, 12394-12405.
5. Low-resolution mass spectra (LRMS) were collected on an Agilent 1100 Series LC/MSD (Column: 20mm C18-RP 5-95% ACN+0.1% HCO_2H/H_2O+0.1% HCO_2H in 5 min with a 5 minute hold at 95% ACN+0.1% HCO_2H /H_2O+0.1% HCO_2H, MSD: single quadrupole LC/MS (Agilent 6120) mass spectrometer using electrospray ionization (ESI) in positive or negative mode).
6. Ussing Chamber Assay performed at ChanTest

For further information

Please contact: *amorgan@concertpharma.com*