In vitro ADME & PK

Carboxylesterase (CE) Inhibition

Background Information

- Human carboxylesterases (CE) are Phase I drug metabolising enzymes of the serine hydrolase superfamily. They hydrolyse a variety of ester containing drugs and prodrugs.

- hCE1 and hCE2 are the most extensively studied of the human CEs. They differ in their substrate specificity and tissue distribution. hCE1 is expressed in many organs especially in the liver, with low expression in the gastrointestinal tract. CE2 protein is also expressed in many extrahepatic tissues, especially in the gastrointestinal tract and at lower levels in the liver.

- Carboxylesterase inhibitors may play a role in improved efficacy of compounds inactivated by this class of enzymes and/or reduce the toxicity of agents that are activated by these enzymes.

- Cyprotex’s carboxylesterase inhibition assay identifies if your compound is an inhibitor of the carboxylesterase (CE) isoforms, hCE1 or hCE2.

Protocol

Test System
hCE1-b, hCE1-c, hCE2 expressed enzymes

Substrates
Trandolapril (hCE1)
Irinotecan (hCE2)

Metabolites
Trandolaprilat (hCE1)
7-Ethyl-10-hydroxycamptothecin (hCE2)

Test Article Concentrations
0, 0.4, 1, 4, 10, 40 and 100 µM (different concentrations available)

Positive Control Inhibitors
Benzil (hCE1)
Loperamide (hCE2)

Test Article Requirements
100 µL of a 40 mM DMSO solution (or equivalent amount in solid)

Analysis Method
LC-MS/MS

Data Delivery
IC_{50} Standard error of IC_{50} % Control at each concentration

CE inhibitors potentially have dual roles in modulating drug action, by both reducing induced toxicity and/or increasing molecule half-life.’


To find out more contact enquiries@cyprotex.com
‘modulation of CE activity may present an opportunty to alter drug metabolism and pharmacokinetics, with the ultimate goal of improving therapy.’

Figure 1
Inhibition of trandolapril (hCE1 substrate) and irinotecan (hCE2 substrate) metabolism in recombinant hCE isoforms by rivastigmine.

The experimental design in Figure 1 can be used to identify specificity of hCE inhibitors. For example, it can be shown that rivastigmine demonstrates greater potency (>500 times) for hCE2 than hCE1 isoform.

References
1 Hatfield M.J. and Potter P.M. (2011) Expert Opin Ther Patents 21(8):1159-1171