cyprotex AN EVOTEC COMPANY

In vitro **ADME & PK**

Carboxylesterase (CE) Inhibition

Background Information

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

[1]Hatfield M.J. and Potter P.M. (2011) *Expert Opin Ther Pat* **21(8)**; 1159-1171

- Human carboxylesterases (CE) are Phase I drug metabolising enzymes of the serine hydrolase superfamily. They hydrolyse a variety of ester containing drugs and prodrugs.
- 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, using hCE1-b and hCE1-c recombinant enzymes.

Protocol

Test System
hCE1-b and/or hCE1-c expressed enzymes

Substrates
Trandolapril (hCE1)

Metabolites
Trandolaprilat (hCE1)

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

Positive Control Inhibitors
Benzil (hCE1)

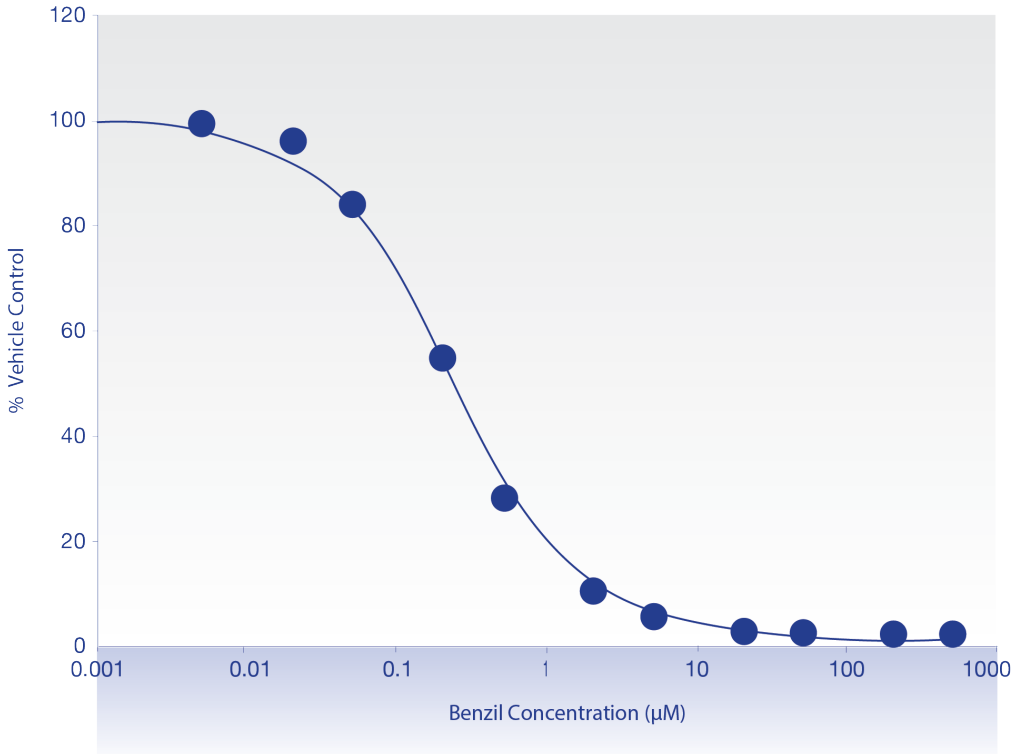
Test Article Requirements
100 µL of a 40 mM DMSO solution (or equivalent amount in solid)

Analysis Method
LC-MS/MS

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

‘modulation of CE activity may present an opportunty to alter drug metabolism and pharmacokinetics, with the ultimate goal of improving therapy.’[1]

Figure 1
Inhibition of trandolapril (hCE1 substrate) metabolism in recombinant hCE1-b by benzil.



References

[1] Hatfield M.J. and Potter P.M. (2011) *Expert Opin Ther Pat* **21(8)**;1159-1171