Hepatic, intestinal, renal and plasma hydrolysis of prodrugs in human, cynomolgus monkey, dog and rat - implications for in vitro-in vivo extrapolation of clearance of prodrugs

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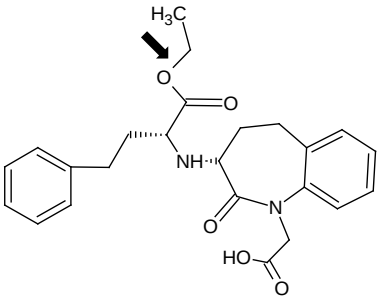
Supplemental Figure Legend

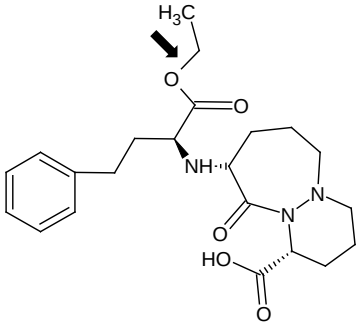
Supplemental Figure 1. Structures of compounds used in the current study.

Arrows are sites of ester hydrolysis.

Supplemental Figure 1



1. Benazepril



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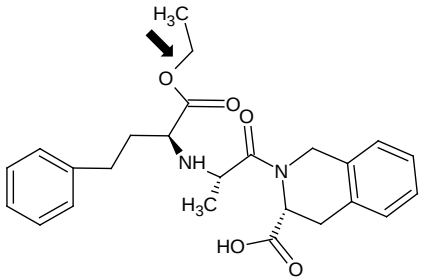
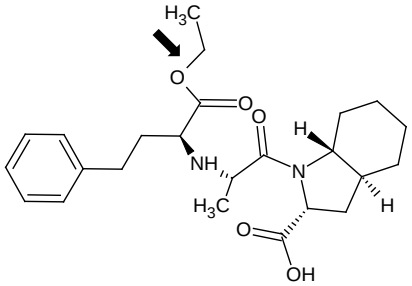
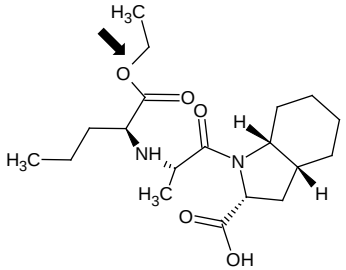


3. Quinapril



4. Trandolapril



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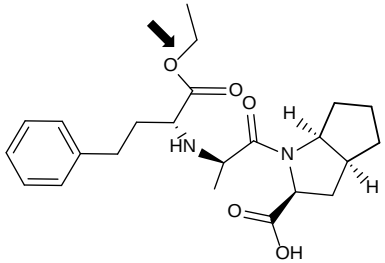

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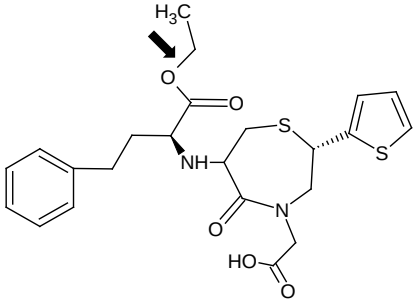
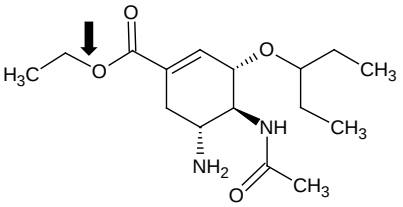
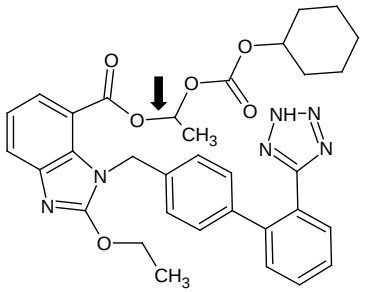


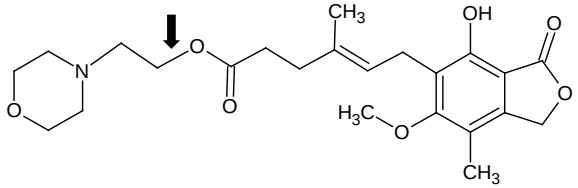
7. Temocapril



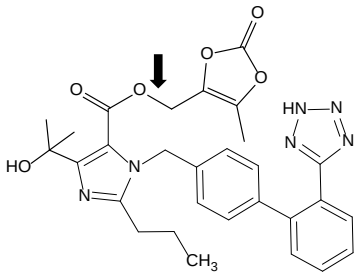
8. Oseltamivir



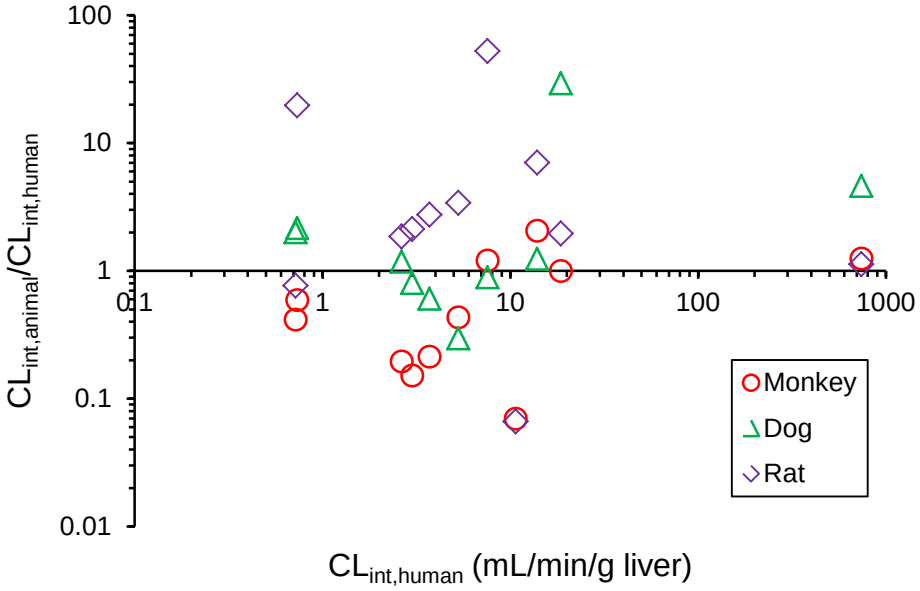
9. Candesartan cilexetil



10. Mycophenolate mofetil



11. Olmesartan medoxomil



Supplemental Figure 2. Comparison of scaled $CL_{int,animal}$ relative to $CL_{int,human}$ values obtained in hepatocytes. Scaling to CL_{int} (mL/min/g liver) was done using Equation 3. In the case where >90% of the compound still remained after 120 min, the CL_{int} values could not be obtained and were not considered in this Figure.

Supplemental Table 1. Tissue-specific expression profile of CES1 and CES2 isozymes in mammals and humans

Species	Isozyme	Liver	Small intestine	Kidney
Rat	CES1	+++	–	+++
	CES2	–	+++	–
Dog	CES1	+++	–	NT
	CES2	++	–	NT
Monkey	CES1	+++	++	–
	CES2	+	+++	+
Human	CES1	+++	–	+
	CES2	+	+++	+++

-, undetectable; +, weakly expressed; ++, moderately expressed; +++, strongly expressed; NT, not tested. Data obtained from a report by Hosokawa et al (2008).

Supplemental Table 2. Half-life ($t_{1/2}$) values obtained in plasma of human, monkey, dog and rat

No.	Compounds	$t_{1/2}$ (min)			
		human	monkey	dog	rat
1	Benazepril	–[a]	–[a]	–[a]	4.5
2	Cilazapril	–[a]	–[a]	–[a]	3.1
3	Quinapril	–[a]	–[a]	–[a]	1.4
4	Trandolapril	–[a]	–[a]	–[a]	0.11
5	Perindopril	–[a]	–[a]	–[a]	0.96
6	Ramipril	–[a]	–[a]	–[a]	2.2
7	Temocapril	–[a]	–[a]	–[a]	0.16
8	Oseltamivir	–[a]	–[a]	–[a]	5.2
9	Candesartan cilexetil	–[a]	–[a]	–[a]	1.4
10	Mycophenolate mofetil	–[a]	–[a]	–[a]	1.9
11	Olmesartan medoxomil	0.087	0.084	0.074	2.3

[a] The remaining ratio of the compounds incubated for 60 min was >90%.

Supplemental Table 3. CL_{int} values in kidney S9 of human, monkey, dog and rat scaled by two kinds of scaling factors

		$CL_{int,KS9}$ (mL/min/g kidney)		
		Candesartan cilexetil	Mycophenolate mofetil	Olmesartan medoxomil
scaled up by scaling factor A	human	74	15	25
	monkey	278	641	104
	dog	859	678	16
	rat	218	121	46
scaled up by scaling factor B	human	57	11	20
	monkey	215	496	80
	dog	664	524	12
	rat	168	94	36

Scaling factor A was assumed to be same as for liver S9 (121 mg S9 protein/g); Scaling factor B based on liver cytosolic and kidney microsomal scaling factors, as defined in Methods (93.5 mg S9 protein/g)

Supplemental Table 4. Blood to plasma ratios, plasma protein binding and observed and predicted hepatic intrinsic clearances for 8 CES1 substrates

		Rb	fu_p	$CL_{int,h,observed}$	$CL_{int,h,predicted}$		References for oral clearance data
					Hepatocytes	Liver S9	
				mL/min/kg	mL/min/kg		
1	Benazepril	0.55[a]	0.028	553	80	285	Kaiser et al., 1989
2	Cilazapril	0.55[a]	0.032	66	113	440	Williams et al., 1989
3	Quinapril	0.55[a]	0.025	651	16	73	Olson et al., 1989
4	Trandolapril	0.55[a]	0.103	1250	56	54	Lenfant et al., 1994
5	Perindopril	0.55[a]	0.243	19	15	10	Devissaguet et al., 1990
6	Ramipril	0.55[a]	0.065	135	64	158	Debusmann et al., 1987; Verho et al., 1995
7	Temocapril	0.55[a]	0.020	1392	162	570	Püchler et al., 1998; Suzuki et al., 1993
8	Oseltamivir	1.42[b]	0.683	168	229	173	Morimoto et al., 2011

[a] Rb for acidic drugs were assumed 0.55.

[b] Instiaty et al., 2013

References for clinical data:

1.Kaiser G, Ackermann R, Brechbühler S, Dieterle W (1989) Pharmacokinetics of the angiotensin converting enzyme inhibitor benazepril.HCl (CGS 14 824 A) in healthy volunteers after single and repeated administration. *Biopharm Drug Dispos* **10(4):**365-76.

2. Williams PE, Brown AN, Rajaguru S, Francis RJ, Walters GE, McEwen J, Durnin C. (1989) The pharmacokinetics and bioavailability of cilazapril in normal man. *Br J Clin Pharmacol* **27 Suppl 2**:181S-188S.

3. Olson SC, Horvath AM, Michniewicz BM, Sedman AJ, Colburn WA, Welling PG (1989) The clinical pharmacokinetics of quinapril. Angiology **40(4 Pt 2):**351-9.

4. Lenfant B, Mouren M, Bryce T, De Lauture D, Strauch G (1994) Trandolapril: pharmacokinetics of single oral doses in healthy male volunteers. *J Cardiovasc Pharmacol* **23 Suppl 4**:S38-43.

5. Devissaguet JP, Ammoury N, Devissaguet M, Perret L (1990) Pharmacokinetics of perindopril and its metabolites in healthy volunteers. *Fundam Clin Pharmacol* **4(2)**:175-89.

6. Debusmann ER, Pujadas JO, Lahn W, Irmisch R, Jané F, Kuan TS, Mora J, Walter U, Eckert HG, Hajdú P, et al.(1987) Influence of renal function on the pharmacokinetics of ramipril (HOE 498). *Am J Cardiol* **59(10):**70D-78D.

7. Verho M, Luck C, Stelter WJ, Rangoonwala B, Bender N (1995) Pharmacokinetics, metabolism and biliary and urinary excretion of oral ramipril in man. *Curr Med Res Opin* **13(5):**264-73.

8. Püchler K, Sierakowski B, Roots I (1998) Single dose and steady state pharmacokinetics of temocapril and temocaprilat in young and elderly hypertensive patients. *Br J Clin Pharmacol* **46(4):**363-7.

9. Suzuki H, Kawaratani T, Shioya H, Uji Y, Saruta T (1993) Study on pharmacokinetics of a new biliary excreted oral angiotensin converting enzyme inhibitor, temocapril (CS-622) in humans. *Biopharm Drug Dispos* **14(1):**41-50.

10. Morimoto K, Kishimura K, Nagami T, Kodama N, Ogama Y, Yokoyama M, Toda S, Chiyoda T, Shimada R, Inano A, Kano T, Tamai I, Ogihara T (2011) Effect of milk on the pharmacokinetics of oseltamivir in healthy volunteers. *J Pharm Sci* **100(9):**3854-61.

11. Instiaty I, Lindegardh N, Jittmala P, Hanpithakpong W, Blessborn D, Pukrittayakamee S, White NJ, Tarning J (2013) b Comparison of oseltamivir and oseltamivir carboxylate concentrations in venous plasma, venous blood, and capillary blood in healthy volunteers. *Antimicrob Agents Chemother* **57(6)** :2858-62.