

Supplemental Table 1. Bosentan metabolism by human liver microsomes (HLM) and recombinant P450 enzymes

	m/z	HLM	CYP3A4	CYP2C9	CYP2C8	CYP2C19	CYP1A2	CYP2B6	CYP2D6	Metabolite
		(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	
Bosentan	552	83	39	89	100	100	100	100	100	Parent
Ro 64-1056	554	1	12	ND	ND	ND	ND	ND	ND	Oxidation
Ro 48-5033	568	6	27	11	ND	ND	ND	ND	ND	Oxidation
Ro 47-8634	538	4	4	ND	ND	ND	ND	ND	ND	O-demethylation
Others		6	18	0	0	0	0	0	0	

Final protein concentration was 0.5 mg/ mL in HLM incubations, and the enzyme concentration was 40 pmol/mL in the incubations with recombinant CYP enzymes. Samples were incubated for 0 and 60 minutes. Data is presented as percent of bosentan remaining or percent of bosentan converted to a specific metabolite.