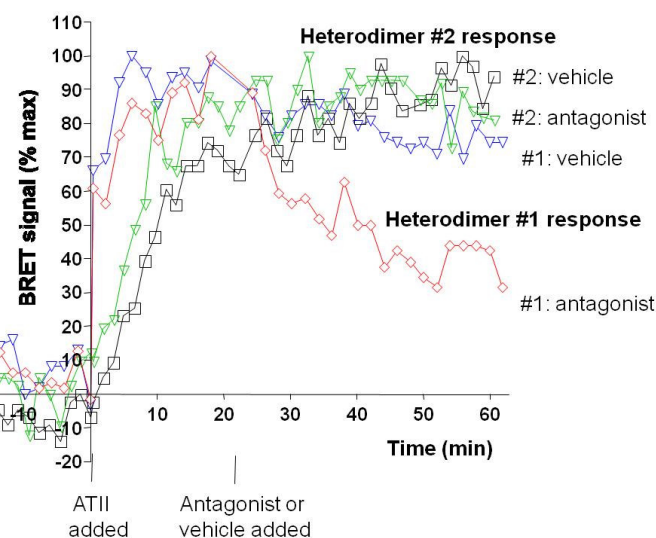
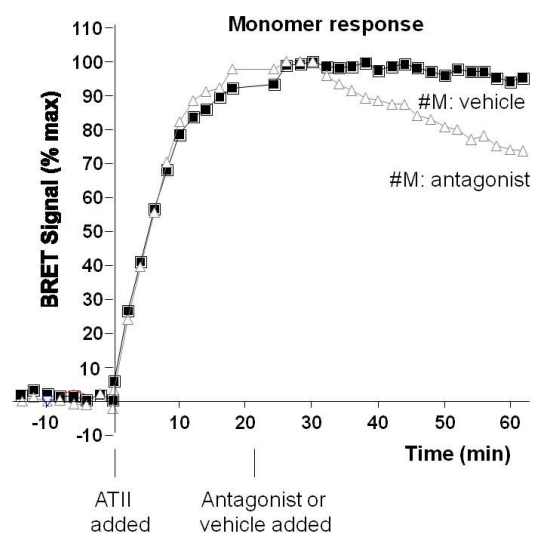


Profiling Drugs for GPCR heterodimer effects:

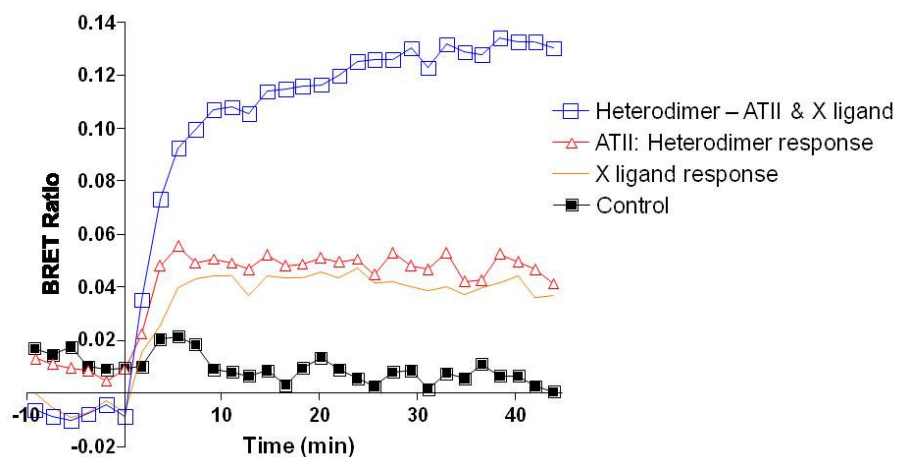
Assessing effect of Angiotensin Receptor Blockers (ARBs) on Angiotensin II AT1R Heterodimers

Dimerix's GPCR-HIT Technology tested the blocking effect of some marketed ARBs¹ against the angiotensin monomer (or homodimer) and two different angiotensin heterodimers demonstrating (a) different blocking responses for monomer versus one of the heterodimers tested; and (b) failure of ARBs to attenuate certain angiotensin heterodimer responses (see Heterodimer #2).

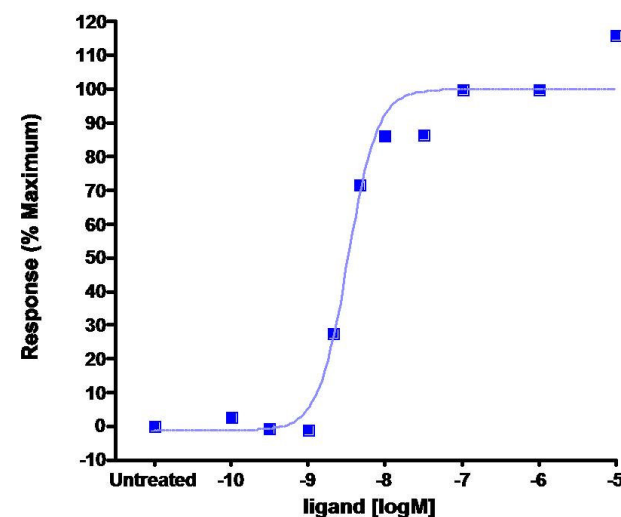


¹ Marketed angiotensin antagonists include: valsartan – Diovan (Novartis); losartan – Cozaar (Merck); irbesartan – Avapro (Bristol-Myers-Squibb); candesartan – Atacand (Astra Zeneca); olmesartan medoxomil – Benicar (Sankyo Pharma); telmisartan – Micardis (Boehringer Ingelheim), Pritor/Kinzal (Bayer Schering Pharma), Telma (Glenmark Pharma), Teleact D (Ranbaxy).

Formation of heterodimers leading to hypersensitization has been shown with heterodimer combinations, including angiotensin heterodimers.² Dimerix GPCR-HIT has been used to show hypersensitization for an angiotensin heterodimer with dual treatment having a substantially greater than additive effect. Moreover, the EC₅₀ (3nM) for ATII activation of the AT1R heterodimer response is suitable for compound screening.



The blue/open box line is the heterodimer response to a combination of the angiotensin II and receptor X ligands – consistent with hypersensitization, the dual response is significantly more than additive.



ATII agonist activation of the heterodimer has an EC₅₀ of 3nM and is not identified through a traditional receptor monomer profiling screen.

² Hilaret et al. (2003) Hypersensitization of the orexin 1 receptor by the CB1 receptor, *Journal of Biological Chemistry* 278:23731-23737.