The GHS-R1a is activated by ghrelin to induce growth hormone secretion and food intake as well as to control energy homeostasis and reward seeking behaviors. GHS-R1a induces signaling pathways through both Gq/Gi activation and arrestin recruitment. To further explore the emerging concept of ligand-directed functional selectivity, we analyzed in detail the efficacy of synthetic ligands at activating the different signaling pathways associated to GHS-R1a expressed in HEK293T cells. To this aim we used classical BRET1 to monitor arrestin recruitment and a recently developed BRET2-based assay to monitor the activation of the different G protein isoforms using new G protein activation biosensors. We show that ghrelin is likely to induce GHS-R1a-mediated activation of Gq,Gi1,Gi2,Gi3,GoA and GoB but not of G11,G12,G13. Unexpectedly, by measuring inositol phosphate production we demonstrate that the high level of constitutive activity of GHS-R1a may conceal the partial agonist properties of ligands that were so far classified as antagonists based on calcium flux assay. Moreover, unlike full agonists, these partial agonists are unable to trigger recruitment of b-arrestin 2, so they fall in a Gq biased category. Even more interestingly, we identified some biased GHS-R1a ligands that selectively activate Gq but antagonize ghrelin-mediated Gi /Go activation. These results provide new insights into the ligand-directed selectivity of the ghrelin receptor and this may have implications for designing new drugs with higher selectivity and, thherfore, limited side effects.