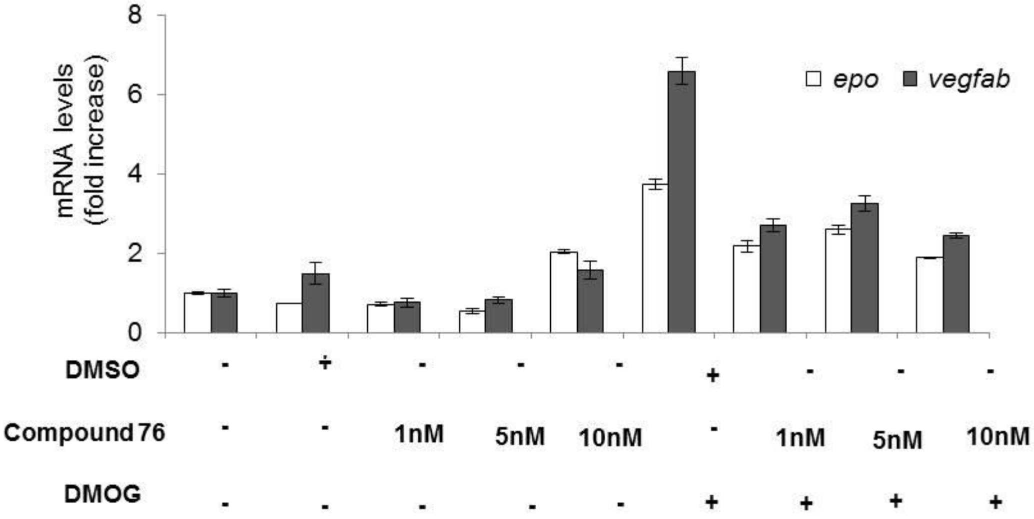

Figure S1: Small molecule compound 76 suppresses DMOG-induced expression of HIF2a-target genes in wild type zebrafish embryos. mRNA expression of the HIF-target genes *epo* and *vegfab* in wild type embryos challenged with 100µM of DMOG and treated with compound 76 (as indicated) or vehicle only control. Gene expression levels were normalized by *18S* gene expression. All experiments were performed in biological triplicates. Data represents mean ± SEM.

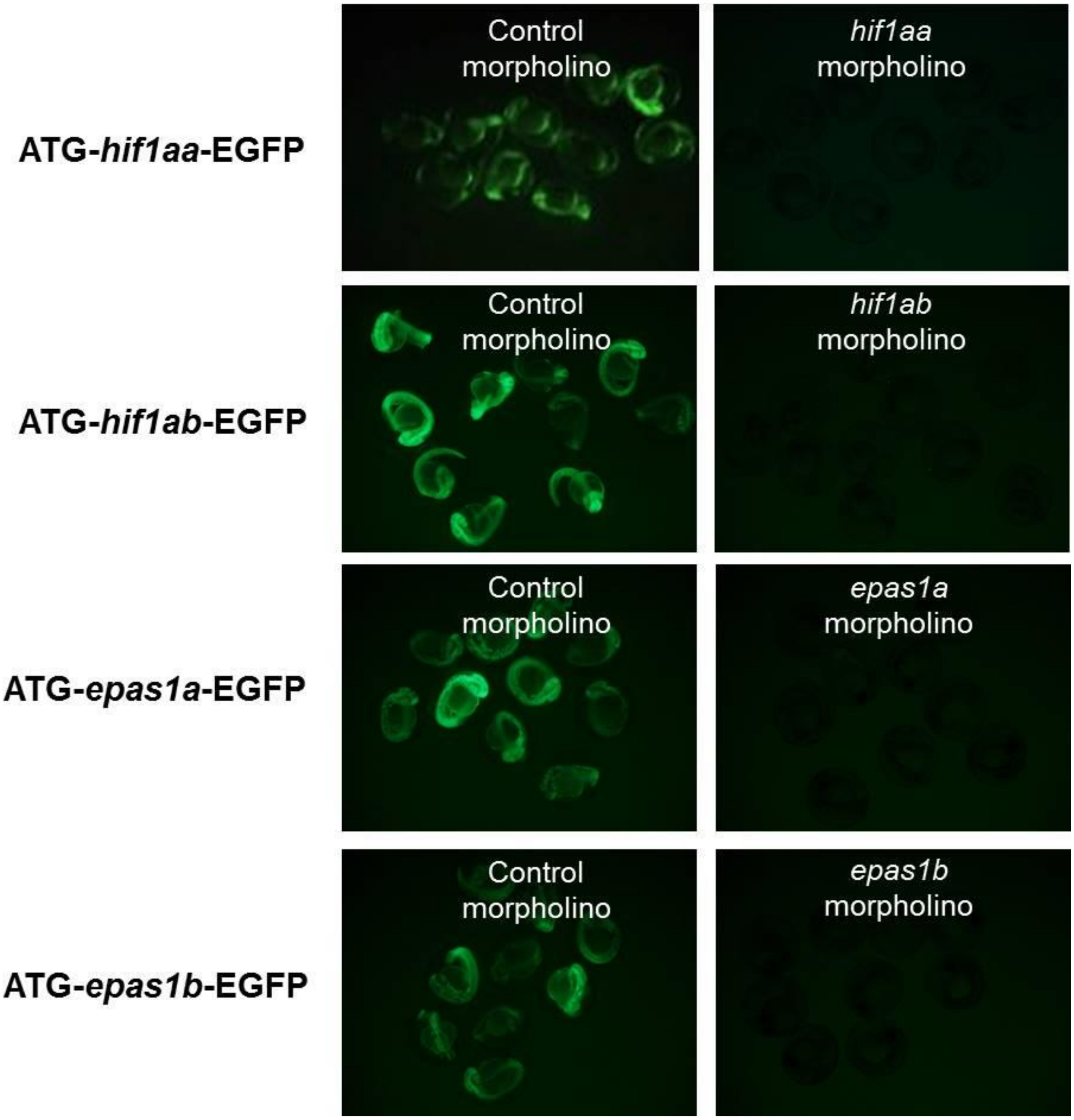

Figure S2: Inhibition of *hif1aa, hif1ab, epas1a* and *epas1b* translation by morpholinos is specific for the cognate paralog. Single-cell embryos were injected with the indicated morpholino combined with the morpholino target sequence upstream of EGFP mRNA (indicated on the left side of each figure). A scrambled morpholino was used as control. Each morpholino inhibited the translation of the cognate only paralog but not the translation of the non-targeting paralogs.

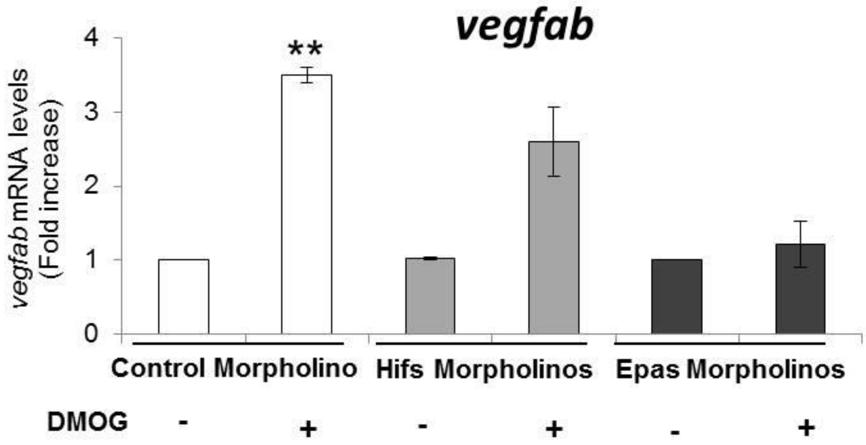

Figure S3: *Epas1a* and *epas1b* are the main paralogs transactivating Vascular Endothelial Growth Factor ab (*vegfab*). Changes in DMOG-induced expression of *vegfab* in *wt* embryos injected with control morpholino, *hif1aa* and *hif1ab* combined morpholinos (hifs morpholinos) or *epas1a* and *epas1b* combined morpholinos (epas morpholinos) and treated with DMOG from 3dpf to 4dpf. Gene expression levels were obtained by qRT-PCR and normalized to the expression of *18S*. All experiments were performed in biological triplicates. Data represents mean ± SEM. Paired, two-tailed *t* test was used for statistical analysis. ** $p<0.01$

Figure S4: The sequences of the *hif1ab* and *epas1b* knock-out mutations. Exon sequences are in upper case letters, whereas intron sequences are in lower case letters. The dashes indicate the deletions in the mutant allele. *wt*, wild-type; mt, mutant. The numbers on top of the sequences indicate the number of the nucleotide in its coding sequence.