Pancreatic ductal adenocarcinoma is characterized by extensive local tumor invasion, metastasis and early systemic dissemination. The vast majority of pancreatic cancer (PaCa) patients already have metastatic complications at the time of diagnosis, and the death rate of this lethal type of cancer has increased over the past decades. Thus, efforts at identifying novel molecularly targeted therapies are priorities. Recent studies have suggested that serotonin (5-HT) contributes to the tumor growth in a variety of cancers including prostate, colon, bladder and liver cancer. However, there is lack of evidence about the impact of 5-HT receptors on promoting pancreatic cancer. Having considered the role of 5-HT-1 receptors, especially 5-HT$_{1B}$ and 5-HT$_{1D}$ subtypes in different types of malignancies, the aim of this study was to investigate the role of 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors in PaCa growth and progression and analyze their potential as cytotoxic targets. We found that knockdown of 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors expression, using specific small interfering RNA (siRNA), induced significant inhibition of proliferation and clonogenicity of PaCa cells. Also, it significantly suppressed PaCa cells invasion and reduced activity of Integrin/Src/Fak-mediated signaling, as one of the integral part of tumor cell pathways associated with invasion, migration, adhesion, and proliferation. Moreover, targeting 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors down-regulates zinc finger ZEB1 and Snail proteins, the hallmarks transcription factors regulating epithelial-mesenchymal transition (EMT), concomitantly with up-regulating of claudin-1. In conclusion, our data suggests that 5-HT$_{1B}$– and 5-HT$_{1D}$–mediated signaling play an important role in the regulation of the proliferative and invasive phenotype of PaCa. It also highlights the therapeutic potential of targeting of 5-HT-1 receptors in the treatment of PaCa, and opens a new avenue for biomarkers identification, and valuable new therapeutic targets for managing pancreatic cancer.