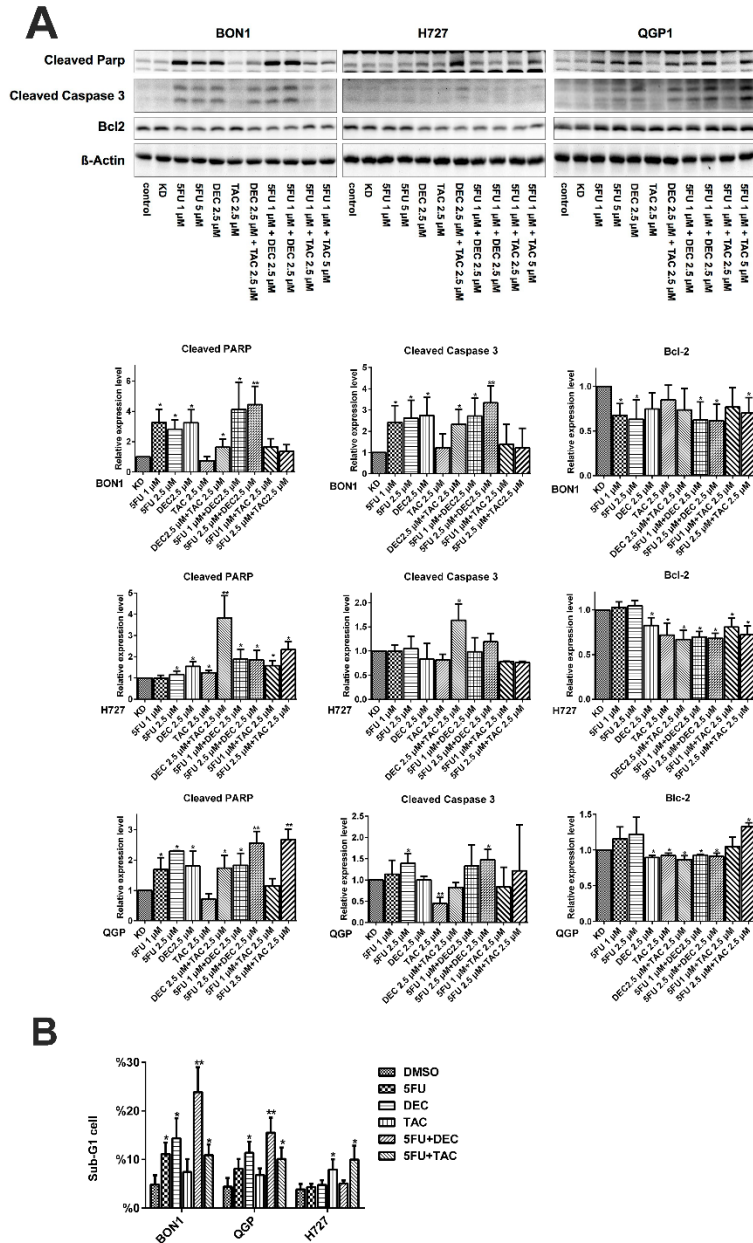


SUPPLEMENTAL FIGURE 1. Effects of decitabine (DEC) or tacedinaline (TAC) on regulation of Bon1, QGP, and H727 NET cell viability. NET cells were grown and treated with different doses of decitabine (DEC) (A) and tacedinaline (TAC) (B) for 144 h and then subjected to the cell viability assay. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared with controls.



SUPPLEMENTAL FIGURE 2. Western blot analysis of apoptosis related proteins (A) and flow cytometry of subG1 events (B) in NET cells treated with 5-fluorouracil (5-FU) in combination with decitabine (DEC) or tacedinaline (TAC). A) A representative western blot and quantified data of several representative western blots are shown. β -actin was a normalized control. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared with controls. B) NET cells were grown and treated simultaneously with 5-FU in combination with decitabine (DEC) or tacedinaline (TAC) for 72 h and then subjected to flow cytometry subG1 event analysis.

SUPPLEMENTAL Table 1. Combination index values for 5-fluorouracil (5-FU) in combination with decitabine (DEC) or tacedinaline (TAC) in different NET cell lines. Combined treatment with 5-fluorouracil (5-FU) plus decitabine (DEC) or with 5-fluorouracil (5-FU) plus tacedinaline (TAC) caused synergistic anti-proliferative effects in Bon1, QGP1 and H727 cells, respectively (Fig. 1). The combination index (CI), calculated as the fractional cell growth inhibition (FA) as a function of the CI, was less than 1 for 5-fluorouracil (5-FU) in combination with decitabine (DEC) and 5-fluorouracil (5-FU) in combination with tacedinaline (TAC), indicating that treatment with two different drugs indeed showed synergistic effects on NET cells.

Cell line	Treatment	CI values at experimental dose	ED50	ED75	ED90
Bon1	5FU+DEC	0.2692	0.3239	0.2018	0.1584
	5Fu+TAC	0.513	0.5563	0.5295	0.6234
QGP	5FU+DEC	0.780	0.800	0.8394	0.8849
	5FU+TAC	0.789	0.7819	0.9146	1.03
H727	5FU+DEC	0.187	0.8590	0.7042	0.5824
	5FU +TAC	0.885	0.7003	0.5540	0.4830

Combination index (CI): a quantitative measure of the degree of drug interaction.; CI > 1 indicates antagonism; CI = 1 indicates additive effect, CI < 1 indicates synergism.