TP53, one of the most important oncosuppressors, is frequently mutated in cancer. Several p53 mutant proteins escape proteolytic degradation and are highly expressed in an aberrant conformation often acquiring pro-oncogenic activities that promote tumor progression and resistance to therapy. Therefore, it has been vastly proposed that reactivation of wild-type (wt) function(s) from mutant p53 (mutp53) may have therapeutic significance. We have previously reported that Zn(II) restores a folded conformation from mutp53 misfolding, rescuing wild-type (wt) p53/DNA-binding and transcription activities. However, whether Zn(II) affects mutp53 stability has never been investigated. Here we show that a novel Zn(II) compound induced mutp53 (R175H) protein degradation through autophagy, the proteolytic machinery specifically devoted to clearing misfolded proteins. Accordingly, pharmacological or genetic inhibition of autophagy prevented Zn(II)-mediated mutp53H175 degradation as well as the ability of the Zn(II) compound to restore wtp53 DNA-binding and transcription activity from this mutant. By contrast, inhibition of the proteasome failed to do so, suggesting that autophagy is the main route for p53H175 degradation. Mechanistically, Zn(II) restored the wtp53 ability to induce the expression of the p53 target gene DRAM (damage-regulated autophagy modulator), a key regulator of autophagy, leading to autophagic induction. Accordingly, inhibition of wtp53 transactivation by pifithrin-α (PFT-α) impaired both autophagy and mutp53H175 degradation induced by curcumin-based zinc compound (Zn(II)-curc). Viewed together, our results uncover a novel mechanism employed by Zn(II)-curc to reactivate mutp53H175, which involves, at least in part, induction of mutp53 degradation via wtp53-mediated autophagy.