Abstract

Crystallographic analysis of ligands bound to HDM2 suggested that 7-substituted 1,4-diazepine-2,5-diones could mimic the α-helix of p53 peptide and may represent a promising scaffold to develop HDM2–p53 antagonists. To verify this hypothesis, we synthesized and biologically evaluated 5-[(3S)-3-(4-chlorophenyl)-4-[(R)-1-(4-chlorophenyl)ethyl]-2,5-dioxo-7-phenyl-1,4-diazepin-1-yl]valeric acid (10) and 5-[(3S)-7-(2-bromophenyl)-3-(4-chlorophenyl)-4-[(R)-1-(4-chlorophenyl)ethyl]-2,5-dioxo-1,4-diazepin-1-yl]valeric acid (11). Preliminary in vitro testing shows that 10 and 11 substantially antagonize the binding between HDM2 and p53 with an IC₅₀ of 13 and 3.6 ÂµM, respectively, validating the modeling predictions. Taken together with the high cell permeability of diazepine 11 determined in CACO-2 cells, these results suggest that 1,4-diazepine-2,5-diones may be useful in the treatment of certain cancers.
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Graphical abstract

Novel 1,4-diazepine-2,5-diones that act as antagonists of the HDM2–p53 interaction are reported.

Keywords

HDM2–p53; Diazepine; Selenium; Cancer

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