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# Structure-based design, synthesis, and biological evaluation of novel 1,4-diazepines as HDM2 antagonists

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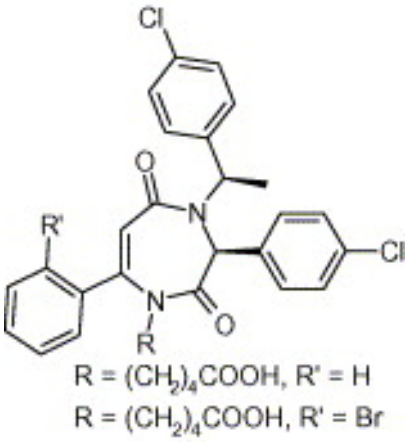
## Abstract

Crystallographic analysis of ligands bound to HDM2 suggested that 7-substituted 1,4-diazepine-2,5-diones could mimic the Î±-helix of p53 peptide and may represent a promising scaffold to develop HDM2â€“p53 antagonists. To verify this hypothesis, we synthesized and biologically evaluated 5-[(3*S*)-3-(4-chlorophenyl)-4-[(*R*)-1-(4-chlorophenyl)ethyl]-2,5-dioxo-7-phenyl-1,4-diazepin-1-yl]valeric acid (**10**) and 5-[(3*S*)-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 $IC_{50}$ of 13 and 3.6Â Î¼M, 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.

## Graphical abstract

Novel 1,4-diazepine-2,5-diones that act as antagonists of the HDM2â€“p53 interaction are reported.

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## Keywords

HDM2â€“p53; Diazepine; Selenium; Cancer

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