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Substituted piperidines as HDM2 inhibitors

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ABSTRACT

Novel small molecule HDM2 inhibitor, substituted piperidine, was identified. Initial SAR study indicated potential for several position optimizations. Additional potency enhancement was achieved by introducing a sidechain off the aromatic ring. DMPK study of one of the active compounds has shown a moderate oral PK and reasonable bioavailability.

The tumor suppressor protein p53 plays a central role in maintaining the integrity of the genome in a cell. It regulates the expression of a diverse array of genes responsible for DNA repair, cell cycle and growth arrest, and apoptosis.[1–3] As with murine MDM2, the human homologue HDM2 acts to down-regulate p53 activity in an autoregulatory manner in which the cellular level of each protein is controlled by the other.[4–6] Attenuating this negative feedback loop could have a critical effect on cell homeostasis. It was found that in many types of human tumors, HDM2 was overexpressed and p53 function was decreased.[7,8] To restore the function of wt-p53 in tumor cells by inhibition of HDM2 should result in decreased proliferation and apoptosis thus inhibiting tumor growth, which offers great therapeutic potential for the treatment of a variety of cancers.[9,10]

The co-crystal structure of the HDM2 N-terminal domain bound to a p53-derived peptide revealed a major pocket of interaction driven by three nearby amino acid residues on one face of a helix, corresponding to p53 residues Phe19, Leu26, and Trp23.[11] It was anticipated that a small molecule could mimic this interaction and antagonize the HDM2 protein, freeing p53 to perform its downstream oncogenic functions. Despite the large surface area of protein–protein interaction (PPI) interfaces and relative complexity, several potent low molecular weight p53/HDM2 inhibitors have been discovered to date and were recently reviewed.[12,13] Herein, we report a series of novel HDM2 small molecule antagonists that selectively inhibit proliferation of several wild-type p53 human cancer cells. SAR trends identified within this chemotype for substituents correlating to the three aforementioned residues on p53 guided the optimization of this series.

From our in-house high-throughput screening (HTS) platform, several hits (**1**–**3**) were identified which inhibit the p53/HDM2 protein–protein interaction with IC_{50} values in the low single digit micromolar range (Fig. 1). These geminally disubstituted piperidines (**4**) were shown to bind to HDM2's p53 binding pocket based on a fluorescence polarization (FP) peptide displacement assay.[14]

Synthesis of this class of compounds was straightforward (Scheme 1) and has been detailed in previously published patent applications.[15,16] Key intermediates **6** were readily prepared in racemic form through the Bargellini reaction of ketone **5** with the corresponding phenol in the presence of chloroform under basic conditions.[15–17] Extensive optimization of the reaction conditions identified the order of addition of the reagents as a key factor in producing intermediates **6** in the best yields. Depending on the stability of the phenol to the basic reaction conditions, adding it after all the other reagents could considerably improve the yield of desired products **6**. Intermediates **6** were subsequently subjected to amidation, deprotection, and acylation to produce fully substituted final compounds **4**.

Compound **1**, chosen as the starting point for optimization based on the frequency with which its substituents appeared in hits within the initial HTS results, was resynthesized from the corresponding common intermediate carboxylic acid **6**. Palladium-catalyzed hydrogenolysis of **6** in the presence of di-tertbutyl dicarbonate and Hunig's base gave **7** as the diisopropylethylamine salt, which was used directly in an amidation with 1-(2-pyridin-2-

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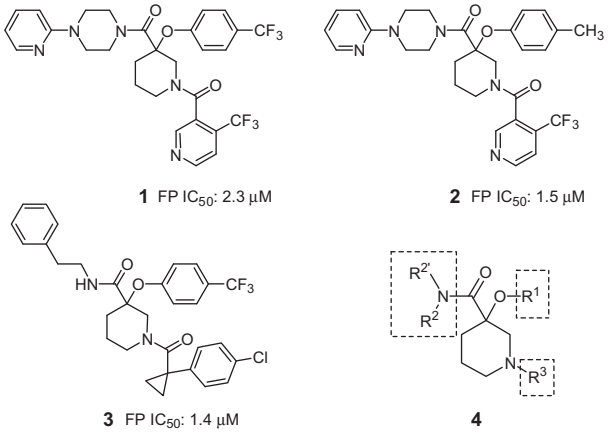
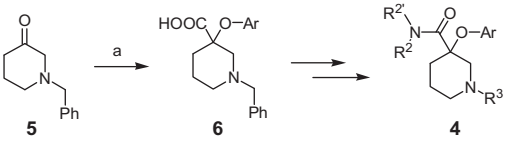


Figure 1. Substituted piperidines as novel HDM2 inhibitors.

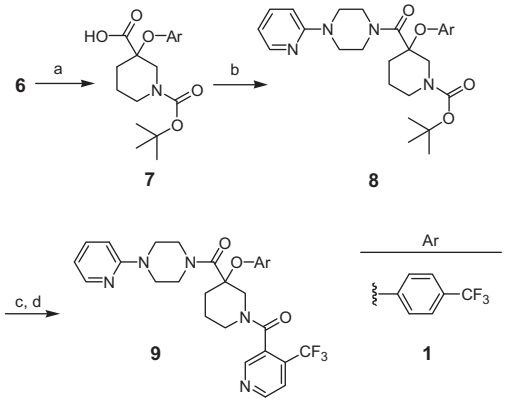


Scheme 1. Synthesis of substituted piperidine **4**. Reagents and conditions: (a) phenol (ArOH), $CHCl_3$, NaOH, 0–40 °C.

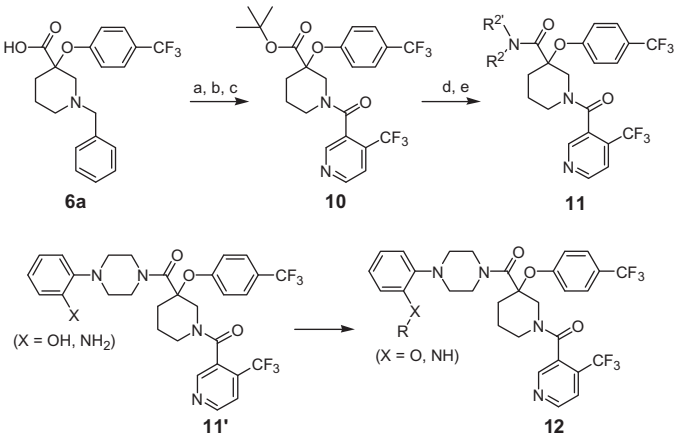
yl)piperazine to give **8** (Scheme 2). Further elaboration by acidic BOC deprotection and subsequent amide formation with 4-(trifluoromethyl)nicotinic acid led to final compounds **9**.

For ease of handling and purification as well as to enable rapid optimization at $R^2/R^{2'}$ (see **4**), intermediate acid **6a** was esterified[18] which, after hydrogenolysis of the benzyl group and amide formation with 4-(trifluoromethyl)nicotinic acid, gave intermediate **10** (Scheme 3). Ester hydrolysis of **10** with HCl produced the corresponding acid which underwent EDC-promoted amidation with various amines to generate diamides **11**. Further $R^2/R^{2'}$ optimization was carried out through extension of a sidechain off the *ortho* position of the piperazine-linked phenyl ring (**11′**), most effectively by O-alkylation or N-acylation leading to final compounds **12**.

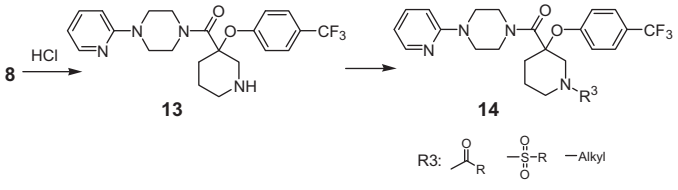
Similarly, common intermediate **13**, used for R^3 optimization, was synthesized by BOC de-protection of the corresponding piperazine amide **8** (Scheme 4). The resulting free amine enabled the broad profiling of R^3 substituents and the generation of SAR



Scheme 2. R^1 (aryl) optimization. Reagents and conditions: (a) 5% Pd/C, H_2, BOC_2O, $^iPr_2NEt$ (b) Carbonyldiimidazole, polymer-supported (PS-CDI), HOBt, 1-(pyridin-2-yl)piperazine, THF (c) 4 N HCl in 1,4-dioxane (d) PS-CDI, HOBt, 4-(trifluoromethyl)nicotinic acid, DMF.

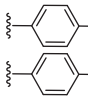
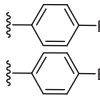
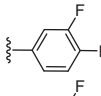
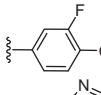
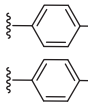


Scheme 3. $R^2/R^{2'}$ (amine and sidechain) optimization. Reagents and conditions: (a) (*Z*)-*tert*-butyl *N,N′*-diisopropylcarbamimidate; (b) H_2, Pd/C; (c) acid, EDC, HOBt; (d) 4 N HCl in 1,4-dioxane; (e) PS-CDI; HOBt, amine.



Scheme 4. R^3 optimization.

Table 1
R^1 SAR: In vitro activity (refer to general structures **9**)

Compound	R^1	IC_{50} (μM)
9a		21
9b		5.2
9c		6.7
9d		6
9e		1.9
9f		2.9
9g		1.4
9h		41
9i		48
9j		33
2		1.5
1		2.3

(a) All compounds were tested as HCl salts; (b) Fluorescent polarization was measured by reading the plate using the Analyst AD (Molecular Device). IC_{50} was determined as described in Zhang et al.[14]