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# 4-(Heteroarylaminomethyl)-*N*-(2-aminophenyl)-benzamides and their analogs as a novel class of histone deacetylase inhibitors

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**Abstract**—The synthesis and biological evaluation of a variety of 4-(heteroarylaminomethyl)-*N*-(2-aminophenyl)-benzamides and their analogs is described. Some of these compounds were shown to inhibit HDAC1 with $IC_{50}$ values below the micromolar range, induce hyperacetylation of histones, upregulate expression of the tumor suppressor $p21^{WAF1/Cip1}$, and inhibit proliferation of human cancer cells. In addition, certain compounds of this class were active in several human tumor xenograft models in vivo.


Histone deacetylases (HDACs) catalyze the hydrolysis of acetyl groups on the $NH_2$-terminal lysine residues of the core nucleosomal histones.[1] The acetylation status of the core histones correlates with transcriptional activity of certain genes. HDAC activity is generally associated with transcriptional repression. Abnormally increased HDAC activity has been associated with the development of certain human cancers.[2] In recent years, inhibition of HDACs has emerged as a potential strategy to reverse aberrant epigenetic changes associated with cancer.[3] Small molecules with hydroxamic acid functional groups such as natural product trichostatin A (TSA)[4] (**1**) and it's analogues,[5] suberoylanilide hydroxamic acid (SAHA, Zolinza™, Merck & Co., Inc.)[6] (**2**) and synthetic compounds such as the 2-aminoanilide MS-275[7] (**3**) and our isotype specific, oral product candidate **MGCD0103**,[8] are potent HDAC inhibitors (Fig. 1). Some of these compounds demonstrate in vivo anti-tumor activity and are currently under clinical evaluation and SAHA, has recently been approved for the treatment of advanced cutaneous T-cell lymphoma.

In the course of searching for novel HDAC inhibitors with high potency and good safety profiles, we recently designed 4-[(*s*-triazin-2-ylamino)methyl]-*N*-(2-aminophenyl)benzamides (**4**).[9] As a further development of HDAC inhibitors with better pharmaceutical and pharmacokinetic properties, we have synthesized 4-(heteroarylaminomethyl)-*N*-(2-aminophenyl)benzamides (**5**) bearing a 5-membered heteroaromatic ring which showed significant improvement in anti-tumor activities both in vitro and in vivo. The structure–activity relationships (SAR), the anti-proliferative activity and the in vivo efficacy of these novel HDAC inhibitors will be discussed.

The first series of compounds bearing a 5-membered heteroaromatic ring **6**–**12** (Table 1) was synthesized using two different approaches (Scheme 1). To generate

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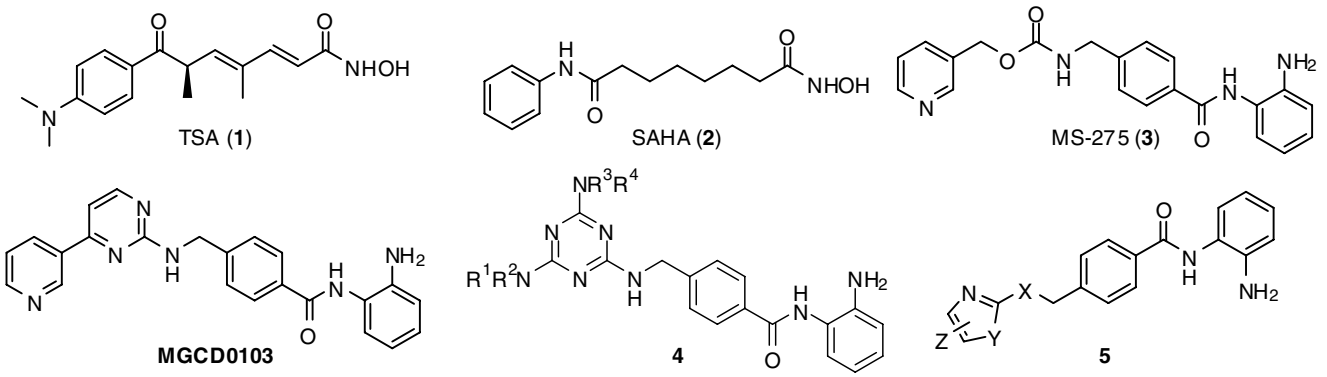
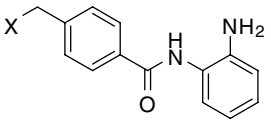
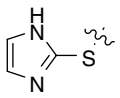
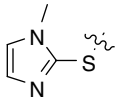
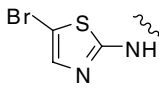
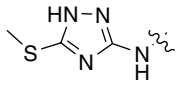
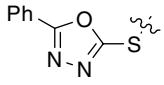
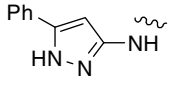
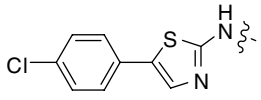



**Figure 1.** Small molecule HDAC inhibitors.

**Table 1.** In vitro activities of compounds **6**–**12**



| Compound | X | HDAC1[a] $IC_{50}$ (μM) | MTT HCT116 $IC_{50}$[b] (μM) |
|---|---|---|---|
| **6** |  | 0.5 | 5 |
| **7** |  | 1 | 5 |
| **8** |  | 0.4 | 0.4 |
| **9** |  | 0.2 | 0.6 |
| **10** |  | 0.08 | 0.4 |
| **11** |  | 0.07 | 0.3 |
| **12** |  | 0.3 | 0.3 |

[a] Inhibition of recombinant HDAC1.
[b] Cytotoxicity/proliferation of human cancer HCT116 cells.

the heteroarylthio derivatives, 1,2-phenylenediamine was monoprotected with a Boc-group and coupled with 4-(methoxycarbonyl)benzoic acid to generate amide **13**. The ester functionality was reduced to the alcohol and 1*H*-imidazole-2-thiol was introduced via a Mitsunobu reaction. The Boc-group deprotection with TFA afforded compound **6**. Compounds **7** and **10** were synthesized in a similar fashion. To generate the heteroarylamino derivatives a reductive amination between methyl 4-formylbenzoate and 5-bromothiazol-2-amine was used to generate compound **14**. The ester functionality was hydrolyzed and then coupled with 1,2-phenylenediamine using BOP[§] as a coupling agent to afford final product **8**. Compounds **9**, **11** and **12** were obtained similarly to compound **8**.

The second series was based on benzo-fused heteroaromatic systems (compounds **15**–**25**, Table 2). The reaction between 6-aminobenzothiazole-2-thiol and methyl 4-(bromomethyl)benzoate afforded compound **26** (Scheme 2). The amino group of this material was alkylated with 3-(bromomethyl)pyridine; the ester functionality was hydrolyzed to the corresponding acid which was then coupled with 1,2-phenylenediamine using BOP[§] as a coupling agent, to afford final product **22**. Other benzothiazol-2-ylthio derivatives (compounds **15**, **23** and **24**) and benzimidazol-2-ylthio derivatives (compounds **16** and **21**) were synthesized using the same approach. A reductive amination between 5-bromo-benzothiazol-2-amine and methyl 4-formylbenzoate generated compound **27**. This intermediate was hydrolyzed and the corresponding intermediate acid was coupled with 1,2-phenylenediamine to generate the final compound **19**. Compounds **17**, **18** and **20** were synthesized similarly to compound **19**. Compound **25** was obtained via a reductive amination followed by a Mitsunobu reaction on intermediate **28** and then completed the same way as the other compounds.

In our HDAC oncology program, we targeted HDAC1 in our design strategy since our work and that of others have clearly linked inhibition of this enzyme with histone hyperacetylation and inhibition of cell proliferation.[10] Thus, the series of compounds presented here are potent HDAC1 inhibitors. As Tables 1 and 2 show, the $IC_{50}$ values range from 30 nM to 1 μM, when tested

[§] Abbreviations: BOP, (benzotriazol-1-yloxy)tris (dimethyl-amino)-phosphoniumhexafluorophosphate; AMC, aminomethylcoumarin; MTT, 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide.