Synthesis of thiazolyl-based hydroxamic acids as histone deacetylase inhibitors

Yodita Asfaha, Alexander Jan Skerhut, Leandro A. Alves-Avelar, Nadine Horstick-Muche, Beate Lungerich, Stefan Klinken, Matthias U. Kassack,* and Thomas Kurz*

Institut für Pharmazeutische und Medizinische Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätstr.1, 40225 Düsseldorf, Germany

Email: thomas.kurz@hhu.de, matthias.kassack@hhu.de

Dedicated to Professor Jan Bergman with respect and best wishes for the occasion of his 80th birthday

Received 06-25-2020 Accepted 10-30-2020 Published on line 11-19-2020

Abstract

Herein we report the synthesis of 4-phenyl substituted thiazolyl-based hydroxamates as histone deacetylase inhibitors. The synthesis of the target compounds is comprised of a Hantzsch-thiazole reaction, a HATU-mediated acylation and a hydroxamic acid synthesis. Preliminary docking results indicated an isozyme selectivity by addressing the lower pocket of HDAC4 with 4-phenyl thiazoles. Surprisingly, this new series of thiazolyl based hydroxamates revealed a moderate HDAC6 inhibitory activity in the low micromolar range. Two of the hydroxamic acids did not show an HDAC4 inhibition up to 100 µM, whilst a third with a 4-pyridinyl CAP moiety displayed a moderate HDAC4 inhibitory activity in the micromolar range.

Keywords: Thiazole synthesis, histone deacetylase inhibitors, ester cleavage, hydroxamic acids
Introduction

The term epigenetic refers to inheritable changes in gene expression without altering the underlying DNA sequence.\(^1\) Epigenetic mechanisms are subdivided into four different classes: (1) posttranslational modifications of histones, (2) chemical modifications of DNA (3) chromatin-remodeling complexes, and (4) regulatory non-coding RNAs. An essential post-translational modification is protein acetylation/deacetylation, which is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). The human zinc dependent HDACs are classified into three classes: class I (HDACs 1-3, 8), class II (IIa: HDACs 4, 5, 7, 9; IIb: HDACs 6, 10) and class IV (HDAC 11).\(^2\) Various studies demonstrated that HDACs are overexpressed in a broad spectrum of cancer cells.\(^3\)–\(^6\) Their inhibition provides a promising strategy for the development of novel epigenetic anticancer drugs. Until now, the natural product romidepsin and four trichostatin A derived HDAC inhibitors (vorinostat, belinostat, panobinostat, tucidinostat) are approved for the treatment of lymphoma and myeloma (Figure 1).\(^7\)–\(^12\) The common pharmacophore model for HDACi consists of the following four elements: a zinc binding group (ZBG), a linker and a connecting unit (CU), that interact with the substrate binding tunnel and a cap, also known as surface recognition domain.\(^13,14\) According to their ZBG, HDACi can be subdivided into 4 main chemical classes: hydroxamic acids, thiols, carboxylic acids and o-amino anilides.\(^15\)

![Figure 1](image_url)

**Figure 1.** General pharmacophore model of HDACi and chemical structures of FDA approved HDAC inhibitors 1-4 and their indications. CTCL: cutaneous T-cell lymphoma, MM: multiple myeloma, PTCL: peripheral T-cell lymphoma.\(^7\)–\(^12\)

Thiazoles are privileged structures in medicinal chemistry. Its core scaffold is found in many natural products such as alkaloids, secondary metabolites and cyclopeptides.\(^16\) The thiazole moiety is also present in several active pharmaceutical ingredients with anticancer, anti-inflammatory, antibacterial, CNS-regulatory, anti-Parkinson, and antidiuretic properties (Figure 2).\(^17\)–\(^20\)
Initial studies for the development of thiazolyl-based HDAC inhibitors were performed by Anandan et al. (Figure 3). In the reported HDAC inhibitors, the thiazole moiety acts as a linker that bridges the ZBG with the cap group. These HDAC inhibitors displayed in vitro HDAC inhibitory activity in HeLa cell nuclear extracts and antiproliferative effects towards the breast cancer cell line MCF7 in the micromolar range.

Results and Discussion

Design of 4-phenyl substituted thiazolyl hydroxamates as HDAC inhibitors
Recent studies have shown that HDAC class IIa enzymes might be associated with neurodegenerative diseases and cancer. So far, only trifluoromethylxadiazoles (TFMO), cyclopropane hydroxamates as well as benzhydryl based class IIa HDAC inhibitors have been reported. In published crystal structures of class IIa HDACs, the so-called lower pocket was identified as a distinctive structural feature. Bürli et al. and Luckhurst et al. showed that tri- and tetrasubstituted cyclopropanes, providing a scaffold with a suitable 3D-geometry that occupy the lower pocket with their phenyl moiety (Scheme 1, circled in red). Here, we report the synthesis of trisubstituted thiazolyl-based hydroxamates as potential class IIa HDAC inhibitors.
Scheme 1. Pharmacophore model of class IIa selective HDACi (above) and design of target structures as class IIa selective HDAC.

In order to evaluate whether the 4-phenyl-substituent of compound 9a might occupy the lower pocket of class IIa HDACs, we performed docking studies. Molecular docking studies of the thiazole derivative 9a, in various HDAC-isozymes were performed using a previously validated docking protocol employing Autodock 4.2 as docking engine.\textsuperscript{31} 9a, as thiazolyl-based HDACi representative, was docked in HDAC2 (PDB 5IWG)\textsuperscript{32}, HDAC8 (PDB 5CFW)\textsuperscript{33}, HDAC4 (PDB 5A2S)\textsuperscript{30} and HDAC6 (PDB 5EDU)\textsuperscript{34}.

The analysis of the docking conformation of compound 9a in HDAC4 suggests that, as envisioned, the hydroxamate moiety of 9a can coordinate with the zinc cation in a bidentate manner (Figure 4). In addition, the phenyl substituent of 9a occupied the lower pocket in a similar binding mode as the phenyl moiety of compound 14 (Figure 4). The thiazolyl-based hydroxamate 9a did not generate valid docking poses in the other HDACs as no docking pose was observed that showed a complexation of the zinc ion by the hydroxamic acid moiety.

Figure 4. Proposed binding mode of compound 9a (light blue) in HDAC4 (PDB 5A2S)\textsuperscript{30}. The docking pose of compound 9a is superimposed with the HDAC4 cocrystallised compound 14 (pink).

Chemistry

The starting material of the Hantzsch thiazole synthesis was the α-bromoester 10 that was prepared according to Borowiecki et al.\textsuperscript{35} After the treatment of 10 with thiourea, the thiazole 11 was formed. In the following step, 11 and the respective carboxylic acids were coupled using HATU under basic conditions yielding the corresponding amides 12a-c. The direct hydroxylaminolysis of the esters 12a-c to the corresponding
hydroxamic acids 9a-c applying various literature procedures did not provide the expected products. Therefore, the hydroxamic acids 9a-c were synthesized by ester hydrolysis and subsequent conversion of the respective carboxylic acids with HATU, DIPEA and hydroxylamine hydrochloride (Scheme 2). The ester hydrolysis was achieved by the addition of an excess of potassium hydroxide. However, the same protocol was unsuccessful when applied for the cleavage of the corresponding ethyl esters. This finding underscores that the hydrolysis depends on the nature of the alkyl substituent of the ester moiety.

Scheme 2. Synthesis of the target structures 9a-c.

Biological Evaluation
The synthesised compounds 9a-c were assessed for their antiproliferative activity and for their HDAC inhibitory activity in the human monocytic cell line THP-1 using class-distinguishing substrates (Boc-Lys(Ac)-AMC: class I and IIb HDACs; Boc-Lys(TFAc)-AMC: class IIa, HDAC8). The results are depicted in Table 1 with vorinostat as reference compound. Among the tested compounds, 9b exhibited the highest antiproliferative activity with 61.5% of growth inhibition at 100 µM concentration. The introduction of a 3,5-dimethoxyphenyl (9a) or biphenyl (9c) CAP moiety led to a decreased cytotoxicity with antiproliferative effects below 50% at 100 µM. In a whole-cell HDAC inhibition assay using the Boc-Lys(Ac)-AMC-HDAC substrate, all screened hydroxamic acids 9a-c displayed inhibitory activities below 40% at 100 µM. However, the cellular HDAC inhibition assay using the Boc-Lys(TFAc)-AMC-HDAC substrate revealed a slightly increased inhibition with over 45% at 100 µM for 9a and 9b.

Overall there is a good correlation between the antiproliferative activity and the cellular HDAC inhibition. All tested compounds 9a-c showed a moderate cytotoxicity and cellular HDAC inhibition.

For further evaluation, the synthesized compounds 9a-c were screened against recombinant human HDAC2, HDAC4, HDAC6 and HDAC8 (Table 2). Vorinostat was included as a pan-HDACi reference compound. Interestingly, the new thiazolyl-based hydroxamates 9a-c were identified as moderate HDAC6 inhibitors in the low micromolar range. In contrast to our preliminary in-silico data, the hydroxamic acids 9a and 9c displayed no HDAC4 inhibition in the tested concentration range (≤ 100 µM). However, the hydroxamic acid 9b exhibiting a 4-pyridinyl CAP moiety demonstrated a moderate micromolar activity against HDAC4 (IC_{50}(HDAC4) = 48.8 µM).
Table 1. Cell viability (MTT assay) and whole-cell HDAC inhibition assay in the human monocytic cell line THP-1

<table>
<thead>
<tr>
<th>R in Cpd 9</th>
<th>cell viability (MTT)</th>
<th>HDAC inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% inhibition of 100 µM</td>
<td>IC₅₀ [µM]</td>
</tr>
<tr>
<td>9a</td>
<td>47.1%</td>
<td>&gt;100</td>
</tr>
<tr>
<td>9b</td>
<td>61.5%</td>
<td>(82.1</td>
</tr>
<tr>
<td>9c</td>
<td>44.5%</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>96.6%</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Presented data are calculated from at least two experiments each performed in duplicates. IC₅₀ values were calculated for compounds with an inhibition of more than 50%. Standard deviation of percent inhibition values is less than 14%. Vehicle control was defined as 0% inhibition.
Table 2. Inhibitory activity of 9a-c and Vorinostat on recombinant human HDAC2, HDAC4, HDAC6 and HDAC8

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>IC50 [µM] (pIC50 ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDAC2</td>
</tr>
<tr>
<td>9a</td>
<td>&gt;100</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>9b</td>
<td>&gt;100</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>9c</td>
<td>&gt;100</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorinostat</td>
<td>0.096</td>
</tr>
<tr>
<td></td>
<td>(7.02 ± 0.04)</td>
</tr>
</tbody>
</table>

Data shown are from at least two experiments each performed at least as duplicates and the IC50 value of pooled data is reported when IC50 < 100 µM.

Conclusions

Histone deacetylases are zinc-dependent metalloproteases that catalyse the removal of acetyl functional groups from lysine residues of both histone and nonhistone proteins. HDACs are involved in a multitude of biological processes e.g. in cell cycle progression, cell survival, apoptosis and differentiation. They are clinically validated targets for the treatment of cancer. Selective HDAC inhibitors may serve as important tools for elucidating the role of specific HDACs in certain diseases. Contrary to our preliminary qualitative in-silico screening, all synthesized compounds 9a-c exhibited a moderate HDAC6 inhibitory activity in the low micromolar range. Only the hydroxamic acid 9b exhibiting a 4-pyridinyl CAP moiety displayed a moderate micromolar activity against HDAC4 (IC50(HDAC4) = 48.8 µM).

Experimental Section

General. All chemicals and solvents were purchased from commercial suppliers (Sigma Aldrich, Alfa Aesar, Fluorochem, TCI, abcr and Acros Organics) and used without further purification. All anhydrous reactions were carried out in flame-dried Schlenk-flasks and under argon atmosphere. Dry solvents were used directly from Seal® bottles from Acros Organics. Analytic Thin Layer Chromatography (TLC) was carried out with Macherey
Nagel precoated silica gel plates (ALUGRAM® Xtra SIL G/UV254). Detection was achieved with ultraviolet irradiation (254 nm) and/or staining with potassium permanganate solution (9 g KMnO₄, 60 g K₂CO₃, 15 mL of a 5% aqueous NaOH-solution, and 900 mL demineralised water). Flash column chromatography was performed with CombiFlashRf200 (TeleDyneIsco) with the solvent mixtures specified in the corresponding procedure.

Physical data. Proton (¹H) and carbon (¹³C) NMR spectra were recorded on Bruker Avance III – 300, Bruker Avance DRX – 500 or Bruker Avance III – 600. Spectra were referenced to the residual non-deuterated solvent signal (¹H-NMR: DMSO-d₆ (2.50 ppm), ¹³C-NMR: DMSO-d₆ (39.52 ppm); ¹H-NMR: CDCl₃ (7.26 ppm), ¹³C-NMR: CDCl₃ (77.16 ppm)). Chemical shifts are quoted in parts per million (ppm). Signal patterns are indicated as: singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Coupling constants, J, are measured in Hz. Proton (¹H) and carbon (¹³C) NMR spectra were recorded by the NMR-Divisions of the Department of Chemistry (Heinrich-Heine-University Düsseldorf). Electrospray Ionisation (ESI) mass spectra were carried out by the Mass spectrometry-Division of the Heinrich-Heine-University Düsseldorf, using Bruker Daltonics UHR-QTOF maXis 4G (Bruker Daltonics). Melting points (mp.) were determined using a Büchi M-565 melting point apparatus and are uncorrected.

Analytical HPLC analysis were carried out on a Knauer HPLC system comprising an Azura P 6.1L pump, an Optimas 800 autosampler, a Fast Scanning Spectro-Photometer K-2600 and Knauer Reversed Phase column (SN: FK36). UV absorption was detected at 254 nm. The purity of all final compounds was 95% or higher.

### Table 3. The solvent gradient table for analytic HPLC analysis

<table>
<thead>
<tr>
<th>Time / min</th>
<th>Water + 0.1% TFA</th>
<th>ACN + 0.1% TFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>0.50</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>20.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>30.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>31.0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>40.0</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

Synthesis of methyl 2-bromo-3-oxo-3-phenylpropanoate (10). A solution of methyl 3-oxo-3-propanoate (2.67 g, 15.0 mmol, 1.00 eq) in methanol (40.0 mL) was cooled to 0 °C and sodium methoxide (30 wt. % in methanol, 3.43 mL, 18.0 mmol, 1.20 eq) was added dropwise. After stirring for further 5 min, bromine (0.92 mL, 18.0 mmol, 1.20 eq) in methanol (20.0 mL) was added dropwise to the reaction. The resulting mixture was stirred overnight at rt. The solvent was removed in vacuo, and the crude solid was resuspended in ethyl acetate. The organic layer was washed with water (3 × 25 mL), dried over Na₂SO₄ and filtered. After removing the solvent, the crude product was purified by flash column chromatography (prepacked silica cartridge, n-hexane/ethyl acetate) to provide 2-bromo-3-oxo-3-phenylpropanoate (10) (2.85 g, 11.1 mmol, 74%) as a yellow oil. ¹H NMR (300 MHz, DMSO-d₆) δ = 3.75 (s, 3H), 6.70 (s, 1H), 7.60 (t, J 7.6 Hz, 2H), 7.69 – 7.78 (m, 1H), 8.04 (dd, J 8.4, 1.3 Hz, 2H) ppm. ¹³C NMR (75 MHz, DMSO-d₆) δ = 46.86, 53.67, 129.10, 133.08, 134.58, 165.89, 189.37 ppm. HPLC analysis: Rᵣ = 12.150 min, 98.2%. HRMS (ESI+) = calcd. for C₁₀H₁₀BrO₃[M+H]⁺ = 256.9808, found: 256.9806.
Synthesis of methyl 2-amino-4-phenylthiazole-5-carboxylate (11). To a solution of methyl 2-bromo-3-oxo-3-phenylpropanoate (10) (2.53 g, 6.70 mmol, 1.00 eq) in methanol (40.0 mL), thiourea (0.52 g, 6.70 mmol, 1.00 eq) was added and the resulting solution was refluxed for 6 h. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc, washed with saturated NaHCO₃ solution (3x 50 mL) and dried over Na₂SO₄. After filtration, the solvent was removed in vacuo to yield the crude product which was purified by flash column chromatography (prepacked silica cartridge, n-hexane/ethyl acetate) to provide methyl 2-amino-4-phenylthiazole-5-carboxylate (11) (0.70 g, 2.90 mmol, 43%) as a yellow solid. M.p.: 183-186°C. ¹H NMR (300 MHz, DMSO-d₆) δ = 3.62 (s, 3H), 7.29 – 7.46 (m, 3H), 7.60 – 7.68 (m, 2H), 7.86 (s, 2H) ppm. ¹³C NMR (75 MHz, DMSO-d₆) δ = 51.40, 107.65, 127.33, 128.69, 129.58, 134.51, 159.02, 161.53, 169.89 ppm. HPLC analysis: Rₜ = 7.533 min, 97.2%. HRMS (ESI⁺) = calcd. for C₁₁H₁₁N₂O₃S [M+H]⁺ = 323.0536, found: 323.0535.

General procedure 1. HATU-coupling
For the synthesis of the amides 12a-c, 1.00 eq of the respective carboxylic acid was dissolved in dry DMF (0.1 mmol/mL) and 1.00 eq HATU and 2.00 eq DIPEA were added. After stirring for 15 min at rt, methyl 2-amino-4-phenylthiazole-5-carboxylate (11) (1.00 eq) was added and the resulting mixture was stirred for 16h at 60 °C. The solvent was removed in vacuo and the residue was diluted with EtOAc. The organic layer was washed with saturated NaHCO₃ (3x 50 mL), brine (1x 50 mL), dried over Na₂SO₄ and filtered. After the removal of the solvent, the crude product was purified by flash column chromatography (prepacked silica cartridge, n-hexane/ethyl acetate) to provide the amides 12a-c.

Methyl 2-(3,5-dimethoxybenzamido)-4-phenyl-thiazole-5-carboxylate (12a). 3,5-Dimethoxybenzoic acid (1.01 g, 5.50 mmol, 1.00 eq) was subjected to General Procedure 1. The crude product was purified by flash column chromatography (n-hexane/EtOAc) to furnish methyl 2-(3,5-dimethoxybenzamido)-4-phenyl-thiazole-5-carboxylate (12a) (1.95 g, 4.90 mmol, 98%) as a white solid. M.p.: 170-174°C. ¹H NMR (300 MHz, DMSO-d₆) δ = 3.74 (s, 3H), 3.83 (s, 6H), 6.76 (t, J 2.2 Hz, 1H), 7.33 (d, J 2.3 Hz, 2H), 7.41 – 7.51 (m, 3H), 7.74 (dd, J 6.0, 0.9 Hz, 2H), 13.15 (s, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆) δ = 51.90, 55.59, 105.49, 106.02, 127.55, 128.91, 129.63, 133.15, 134.01, 155.96, 160.19, 160.52, 161.80, 165.33 ppm. HPLC analysis: Rₜ = 15.883 min, >99%. HRMS (ESI⁺): calcd. for C₂₀H₂₀N₂O₃S [M+H]⁺ = 399.1009, found: 399.1008.

Methyl 2-(isonicotinamido)-4-phenyl-thiazole-5-carboxylate (12b). Isonicotinic acid (373 mg, 3.00 mmol, 1.00 eq) was subjected to General Procedure 1. The crude product was purified by flash column chromatography (n-hexane/EtOAc) to furnish methyl 2-(isonicotinamido)-4-phenyl-thiazole-5-carboxylate (12b) (0.62 g, 1.80 mmol, 61%) as a white solid. M.p.: 225-229°C. ¹H NMR (300 MHz, DMSO-d₆) δ = 3.73 (s, 3H), 7.30 – 7.53 (m, 3H), 7.69 – 7.79 (m, 2H), 7.97 – 8.04 (m, 2H), 8.75 – 8.85 (m, 2H), 13.47 (s, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆) δ = 52.03, 115.13, 121.81, 127.62, 129.04, 129.69, 133.78, 138.51, 150.46, 155.87, 159.81, 161.68, 164.67 ppm. HPLC analysis: Rₜ = 9.667 min, >99%. HRMS (ESI⁺): calcd. for C₁₇H₁₄N₃O₃S [M+H]⁺ = 340.0750, found: 340.0753.

Methyl 2-([1,1'-biphenyl]-4-carboxamido)-4-phenylthiazole-5-carboxylate (12c). Biphenyl-4-carboxylic acid (595 mg, 3.00 mmol, 1.00 eq) was subjected to General Procedure 1. The crude product was purified by flash column chromatography (n-hexane/EtOAc) to furnish methyl 2-([1,1'-biphenyl]-4-carboxamido)-4-phenylthiazole-5-carboxylate (12c) (0.58 g, 1.40 mmol, 47%) as a white solid. M.p.: 267-270°C. ¹H NMR (600 MHz, DMSO-d₆) δ = 3.75 (s, 3H), 7.41 – 7.47 (m, 4H), 7.51 (dd, J 8.4, 6.9 Hz, 2H), 7.71 – 7.82 (m, 4H), 7.83 – 7.90 (m, 2H), 8.19 – 8.27 (m, 2H), 13.24 (s, 1H) ppm. ¹³C NMR (151 MHz, DMSO-d₆) δ = 52.01, 114.70, 126.80, 126.99, 127.63, 128.43, 129.00, 129.10, 129.12, 129.70, 130.12, 134.01, 138.74, 144.40, 156.06, 160.34, 161.85, 165.56 ppm. HPLC analysis: Rₜ = 17.983 min, 98.3%. HRMS (ESI⁺): calcd. for C₂₄H₁₉N₂O₃S [M+H]⁺ = 415.1111, found: 415.1114.
General procedure 2: Methyl ester hydrolysis

For the synthesis of the carboxylic acids 13a-c, 1.00 eq of the methyl ester 12a-c was dissolved in THF (0.1 mmol/mL) and 30.0 eq potassium hydroxide was added. The resulting mixture was refluxed for 16 h. The solvent was removed in vacuo and the residue was resuspended with EtOAc. The organic layer was washed with saturated NaHCO₃ (3x 50 mL). The combined aqueous phases were acidified (pH = 2-3) and the resulting precipitate (product) was filtered off and washed with water.

2-(3,5-Dimethoxybenzamido)-4-phenylthiazole-5-carboxylic acid (13a). Methyl 2-(3,5-dimethoxybenzamido)-4-phenyl-thiazole-5-carboxylate (12a) (0.51 g, 1.28 mmol, 1.00 eq) was subjected to General Procedure 2. The acid 13a (0.27 g, 0.71 mmol, 55%) was obtained as a white solid. M.p.: 187-191°C. ¹H NMR (600 MHz, DMSO-d₆) δ = 3.83 (s, 6H), 6.76 (t, J 2.3 Hz, 1H), 7.33 (d, J 2.3 Hz, 2H), 7.39 – 7.45 (m, 3H), 7.71 – 7.78 (m, 2H), 13.05 (s, 2H) ppm. ¹³C NMR (151 MHz, DMSO-d₆) δ = 55.62, 105.46, 105.94, 116.78, 127.53, 129.78, 132.73, 129.78, 133.24, 134.25, 155.10, 159.73, 160.49, 162.83, 165.22 ppm. HPLC analysis: Rᵣ = 13.00 min, 96.4%. HRMS (ESI⁺) = calcd. for C₁₉H₁₇N₂O₅S [M+H]⁺ = 385.0853, found: 385.0852.

2-(Isonicotinamido)-4-phenylthiazole-5-carboxylic acid (13b). Methyl 2-(isonicotinamido)-4-phenylthiazole-5-carboxylate (12b) (338 mg, 1.04 mmol, 1.00 eq) was subjected to General Procedure 2. The acid 13b (228 mg, 0.70 mmol, 67%) was obtained as a white solid. M.p.: 246-250°C. ¹H NMR (300 MHz, DMSO-d₆) δ = 1.23 (t, J 7.1 Hz, 3H), 4.22 (q, J 7.1 Hz, 2H), 7.40 – 7.55 (m, 3H), 7.68 – 7.81 (m, 2H), 7.98 – 8.08 (m, 2H), 8.78 – 8.90 (m, 2H), 13.50 (s, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆) δ = 13.91, 60.85, 115.62, 121.78, 127.56, 128.99, 129.71, 133.80, 135.05, 150.46, 155.66, 159.74, 161.24, 164.64 ppm. HPLC analysis: Rᵣ = 6.883 min, 98.4%. HRMS (ESI⁺) = calcd. for C₁₆H₁₅N₂O₅ [M+H]⁺ = 326.0594, found: 326.0597.

2-[[1,1'-Biphenyl]-4-carboxamido]-4-phenylthiazole-5-carboxylic acid (13c). Methyl 2-[[1,1'-biphenyl]-4-carboxamido]-4-phenylthiazole-5-carboxylate (12c) (0.35 g, 0.84 mmol, 1.00 eq) was subjected to General Procedure 2. The acid 13c (0.31 g, 0.77 mmol, 92%) was obtained as a white solid. M.p.: 225 °C (decomp.). ¹H NMR (600 MHz, DMSO-d₆) δ = 7.40 – 7.46 (m, 4H), 7.51 (t, J 7.7 Hz, 2H), 7.72 – 7.81 (m, 4H), 7.85 – 7.89 (m, 2H), 8.22 – 8.26 (m, 2H), 13.13 (s, 1H) ppm. ¹³C NMR (151 MHz, DMSO-d₆) δ = 126.83, 127.01, 127.56, 128.44, 128.77, 129.09, 129.12, 129.81, 133.78, 144.39, 162.86, 165.44 ppm. HPLC analysis: Rᵣ = 14.933 min, 92.0%. HRMS (ESI⁺) = calcd. for C₂₃H₂₁N₂O₅S [M+H]⁺ = 401.0954, found: 401.0953.

General procedure 3. Hydroxamic acid formation

For the synthesis of the hydroxamic acids 9a-c, 1.00 eq of the respective carboxylic acid 13a-c was dissolved in dry DMF (0.1 mmol/mL), 1.00 eq HATU and 3.20 eq DIPEA were added. After stirring for 15 min at rt, 1.20 eq hydroxylamine hydrochloride was added and the resulting mixture was stirred for further 16 h at 60 °C. The reaction mixture was then poured into water and the resulting participate was then filtered and washed with aqueous HCl-solution (pH = 4) and water. The crude product was purified by flash column chromatography (prepacked silica cartridge, DCM/30% methanol in DCM) to provide the corresponding hydroxamic acids.

2-(3,5-Dimethoxybenzamido)-N-hydroxy-4-phenylthiazole-5-carboxamide (9a). 2-(3,5-Dimethoxybenzamido)-4-phenylthiazole-5-carboxylic acid (13a) (199 mg, 0.50 mmol, 1.00 eq) was subjected to General Procedure 3. The hydroxamic acid 9a (50.0 mg, 0.12 mmol, 25%) was obtained as a white solid. M.p. 225 °C (decomp.) ¹H NMR (300 MHz, DMSO-d₆) δ = 3.84 (s, 6H), 6.76 (s, 1H), 7.34 (d, J 2.2 Hz, 2H), 7.38 – 7.52 (m, 3H), 7.77 (d, J 6.8 Hz, 2H), 9.28 (s, 1H), 11.07 (s, 1H), 12.98 (s, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆) δ = 55.61, 105.35, 105.96, 128.13, 128.28, 128.70, 129.70, 129.71, 133.40, 134.10, 154.81, 160.52, 161.78, 165.01. HPLC analysis: Rᵣ = 10.383 min, 95.0%. HRMS (ESI⁺) = calcd. for C₁₉H₁₇N₂O₅S [M+H]⁺ = 400.0962, found: 400.0960.
**N-Hydroxy-2-((isonicotinamido)-4-phenylthiazole-5-carboxamide (9b).** 2-(Isonicotinamido)-4-phenylthiazole-5-carboxylic acid (13b) (595 mg, 1.83 mmol, 1.00 eq) was subjected to General Procedure 3. The hydroxamic acid 9b (0.200 g, 0.59 mmol, 32%) was obtained as an orange solid. M.p. 210-214°C. $^1$H NMR (300 MHz, DMSO-d$_6$) δ = 7.42 (dq, J 13.5, 6.8 Hz, 3H), 7.76 (d, J 7.3 Hz, 2H), 8.01 (d, J 5.2 Hz, 2H), 8.82 (d, J 5.1 Hz, 2H), 9.34 (s, 1H), 11.12 (s, 1H) ppm. $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ = 117.92, 121.95, 128.40, 128.59, 133.95, 138.88, 150.59, 156.94, 164.49 ppm. HPLC analysis: R$_t$ = 4.817 min, 97.3%. HRMS (ESI+) = calcd. for C$_{16}$H$_{13}$N$_4$O$_3$S [M+H]$^+$ = 341.0703, found: 304.0706.

**2-((1,1'-Biphenyl)-4-carboxamido)-N-hydroxy-4-phenylthiazole-5-carboxamide (9c).** 2-((1,1'-Biphenyl)-4-carboxamido)-4-phenylthiazole-5-carboxylic acid (13c) (260 mg, 0.65 mmol, 1.00 eq) was subjected to General Procedure 3. The hydroxamic acid 9c (0.165 g, 0.40 mmol, 61%) was obtained as a white solid. M.p. 225 °C (decomp.) $^1$H NMR (600 MHz, DMSO-d$_6$) δ = 7.38 – 7.47 (m, 4H), 7.52 (t, J 7.6 Hz, 2H), 7.79 (d, J 7.6 Hz, 4H), 7.88 (d, J 8.0 Hz, 2H), 8.25 (d, J 8.1 Hz, 2H), 9.29 (s, 1H), 11.09 (s, 1H), 13.05 (s, 1H) ppm. $^{13}$C NMR (151 MHz, DMSO-d$_6$) δ = 126.81, 127.00, 127.55, 128.22, 128.32, 128.41, 129.02, 129.11, 130.26, 134.05, 138.79, 144.30, 148.59, 157.20, 159.67, 165.16 ppm. HPLC analysis: R$_t$ = t = 12.633 min, 95.7%. HRMS (ESI+) = calcd. for C$_{23}$H$_{18}$N$_3$O$_5$S O$_3$[M+H]$^+$ = 416.1063, found: 416.1055.

### Acknowledgements

YA, AJS, MUK, and TK gratefully acknowledge support from the Deutsche Forschungsgemeinschaft (DFG) for grant number KA 1942/1-1 to MUK and grant number KU 1577/2-1 to TK, and the support from the DFG research training group 270650915/GRK2158. We further acknowledge the CHDI Foundation Inc. for providing the compound CHDI-00390576-0000-004.

### Supplementary Material

The performed docking studies and the experimental procedures for the biological evaluation are provided as supplementary material.

### References

1. Bird, A. Nature 2007, 447 (7143), 396–398. [https://doi.org/10.1038/nature05913](https://doi.org/10.1038/nature05913)


5. Ropero, S.; Esteller, M. Mol. Oncol. 2007, 1, 19–25. [https://doi.org/10.1016/j.molonc.2007.01.001](https://doi.org/10.1016/j.molonc.2007.01.001)
https://doi.org/10.2174/0929867013372058

https://doi.org/10.1038/nbt1272

https://doi.org/10.1182/blood-2006-06-025999

https://doi.org/10.1038/nrc1779

https://doi.org/10.1073/pnas.95.6.3003

https://doi.org/10.1097/cad.0b013e32832e14e1

https://doi.org/10.1016/j.canlet.2009.02.019

https://doi.org/10.4155/fmc-2018-0125

https://doi.org/10.1038/nrd2133

https://doi.org/10.1007/s12263-012-0283-9

https://doi.org/10.1002/jhet.2827

https://doi.org/10.1016/j.ejmech.2011.01.013

https://doi.org/10.1016/j.ejmech.2007.03.014

https://doi.org/10.1016/j.ejmech.2005.01.013

https://doi.org/10.1016/j.mrrev.2004.11.001

https://doi.org/10.1016/S1474-4422(10)70106-X

https://doi.org/10.1371/journal.pone.0185321

https://doi.org/10.1016/j.ahj.2012.04.011


   [https://doi.org/10.1016/j.tet.2016.11.039](https://doi.org/10.1016/j.tet.2016.11.039)

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license ([http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/))