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Design, synthesis, and biological evaluation of aminothiazole derivatives against the fungal pathogens *Histoplasma capsulatum* and *Cryptococcus neoformans*

Ahmed Khalil [a,b], Jessica A. Edwards [c,d,e], Chad A. Rappleye [c,d,e], Werner Tjarks [a,e,*]

[a] Division of Medicinal Chemistry & Pharmacognosy, The Ohio State University, 500 West 12th Avenue, Columbus, OH 43210, USA
[b] Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt
[c] Department of Microbiology, The Ohio State University, USA
[d] Department of Microbial Infection and Immunity, The Ohio State University, USA
[e] The Center for Microbial Interface Biology, The Ohio State University, USA

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ABSTRACT

Invasive fungal disease constitutes a growing health burden and development of novel antifungal drugs with high potency and selectivity against new fungal molecular targets are urgently needed. Previously, an aminothiazole derivative, designated as 41F5, was identified in our laboratories as highly active against *Histoplasma* yeast (MIC_{50} 0.4–0.8 μM) through phenotypic high-throughput screening of a commercial library of 3600 purine mimicking compounds (*Antimicrob. Agents Chemother.* **2013**, *57*, 4349). Consequently, 68 analogues of 41F5 were designed and synthesized or obtained from commercial sources and their MIC_{50}s of growth inhibition were evaluated in *Histoplasma capsulatum* to establish a basic structure–activity-relationship (SAR) for this potentially new class of antifungals. The growth inhibiting potentials of smaller subsets of this library were also evaluated in *Cryptococcus neoformans* and human hepatocyte HepG2 cells, the latter to obtain selectivity indices (SIs). The results indicate that a thiazole core structure with a naphth-1-ylmethyl group at the 5-position and cyclohexylamide-, cyclohexylmethylamide-, or cyclohexylethylamide substituents at the 2-position caused the highest growth inhibition of *Histoplasma* yeast with MIC_{50}s of 0.4 μM. For these analogues, SIs of 92 to >100 indicated generally low host toxicity. Substitution at the 3- and 4-position decreased antifungal activity. Similarities and differences were observed between *Histoplasma* and *Cryptococcus* SARs. For *Cryptococcus*, the naphth-1-ylmethyl substituent at the 5-position and smaller cyclopentylamide- or cyclohexylamide groups at the 2-position were important for activity. In contrast, slightly larger cyclohexylmethyl- and cyclohexylethyl substituents markedly decreased activity.

1. Introduction

Over the past few decades, systemic and invasive fungal infections have emerged as a significant threat to public health. Invasive fungal infections cause more human deaths than tuberculosis, although the latter has gained more notoriety in the public eye.[1,2] *Cryptococcus* infections have been estimated to cause over 500,000 deaths annually among immunocompromised individuals.[2] Invasive fungal infections are not limited to individuals with compromised immune functions. For example, in the United States, infections with *Cryptococcus gattii* and *Histoplasma capsulatum* occur in immunocompetent as well as immunocompromised hosts, classifying these as primary, not just opportunistic, fungal pathogens.[3]

The shared eukaryotic nature of both the host and pathogen significantly complicates treatment options for fungal disease. Existing antifungals for systemic mycoses target either the fungal membrane sterol ergosterol or cell wall β-glucan.[4] Amphotericin B targets sterols directly and triazole-class antifungals impair

Abbreviations: ATCC, American type culture collection; DMAP, 4-dimethylaminopyridine; DMC, dichloromethane; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; EDAC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; FIC, fractional inhibitory concentration; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HMM, *Histoplasma*-macrophage media; HR-ESI, high resolution-electrospray ionization; MEM, minimum essential medium; MIC_{50}, minimal concentration that inhibits 50% of fungal growth; MIC, minimal inhibitory concentration; MW, molecular weight; PBS, phosphate-buffered saline; TEA, triethylamine; TFA, trifluoroacedic acid; TFAA, trifluoroacedic anhydride, THF, tetrahydrofuran; SI, selectivity index; SAR, structure–activity-relationship; YPD, yeast extract peptone dextrose.

* Corresponding author. Tel.: +1 614 292 7624; fax: +1 614 292 2435.
E-mail address: tjarks.1@osu.edu (W. Tjarks).

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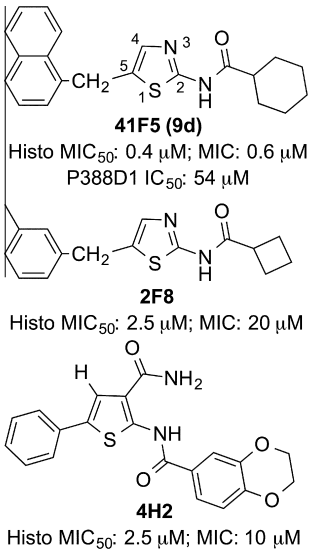


Figure 1. Structurally related thiazole/thiophene hit compounds 41F5, 2F8, and 4H2 identified in a phenotypic high-throughput screen of a purinome-focused library.[7]

sterol synthesis. However, both antifungal classes have significant host toxicity, which prohibits general prophylactic use of these antifungals.[5] The echinocandins are a third class of fungistatic antifungals recently developed, which target the synthesis of the essential fungal cell wall polysaccharide β-glucan. While better tolerated than amphotericin and the triazoles, the echinocandins lack efficacy against the more virulent fungal pathogens *Cryptococcus* and *Histoplasma*.[6] Further complicating antifungal treatment is the fact that *Cryptococcus* and *Histoplasma* yeasts invade immune cells (e.g., macrophages), and this intracellular location presents additional barriers to drug accessibility and efficacy. Thus, development of antifungal drugs with high potency and selectivity against new cellular targets are urgently needed to combat the growing health burden of invasive fungal disease.

Recently, our group performed a phenotypic high-throughput screen of a purinome-focused library of 3600 compounds with structural similarity to purines or any known purine analogue scaffold.[7] Inhibition of *Histoplasma* yeast growth was used as the screening phenotype. Concurrently, we measured mammalian cytotoxicity using a P388D1 macrophage cell line[8] since macrophages are the primary host cell for *Histoplasma* yeast. Among the 10 hits with the highest selectivity indices (SIs), a subgroup of three structurally related thiazole/thiophene derivatives (41F5, 2F8, 4H2, Fig. 1) were identified. The most active compound of this group was the aminothiazole 41F5, which had the lowest MIC_{50} (0.4–0.8 μM) and the highest SI (63–135) of all tested compounds relative to P388D1 macrophages. Preliminary studies also indicated selective toxicity of 41F5 against *Cryptococcus neoformans*.[7] Thus, the aminothiazole 41F5 has efficacy against *Histoplasma capsulatum* and *Cryptococcus neoformans*, two fungal pathogens that have natural resistance against the echinocandin class of antifungals.

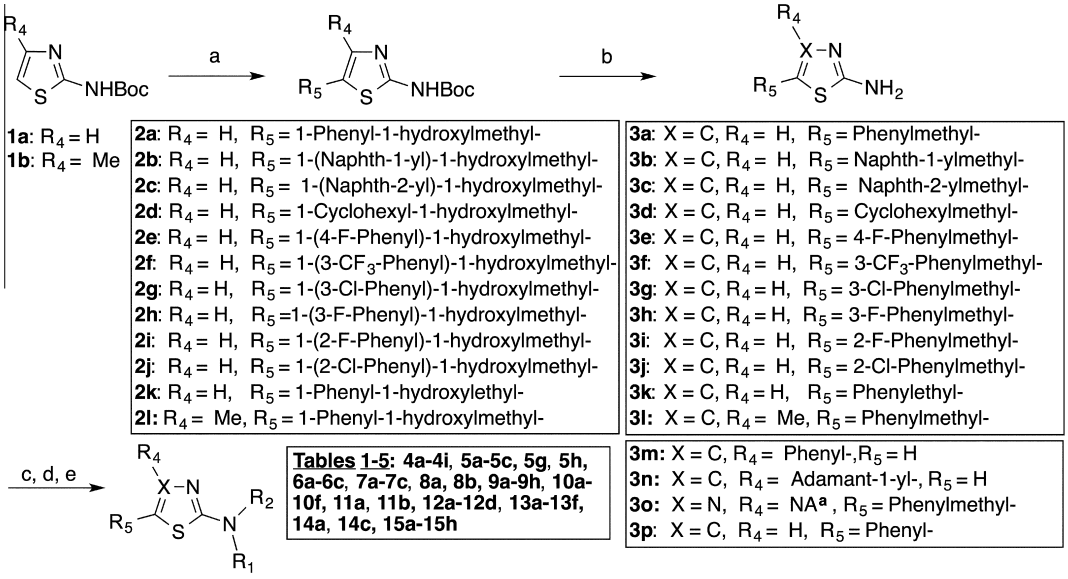
Compounds with aminothiazole scaffold display a wide range of biological activities,[9] including antiparasitic-,[10] antifungal-,[11] antibacterial-,[12] antitubucular-,[13] antiviral-,[14] anticancer-,[15,16] and antiprion[17] action. The study described here was carried out to establish the basic anti-*Histoplasma* and anti-*Cryptococcus* specific aminothiazole structure–activity relationships (SARs).

2. Results

2.1. Chemistry

The primary objective of our studies was to establish a *Histoplasma* SAR for aminothiazoles based on the 41F5 structure (Fig. 1). Other objectives were the development of a very basic *Cryptococcus* SAR for comparison and the evaluation of toxicity of promising novel compounds to hepatocyte (HepG2) cells. For this purpose we synthesized or purchased 68 compounds that are structurally related to 41F5. The thiazole core structure is easily amenable to modification. Due to its abundant use in drug design, numerous synthetic approaches have been developed and many synthetic precursor molecules for thiazole synthesis are commercially available or easily prepared.[15,16,18,19] Indeed, the design of this initial library was based to a significant extent on the synthetic feasibility and/or commercial availability of starting materials. Established synthetic procedures are shown in Scheme 1.

The reaction of compounds **1a** and **1b** with various aldehydes in presence of *n*-Buli at −78 °C afforded compounds **2a**–**2l** in yields



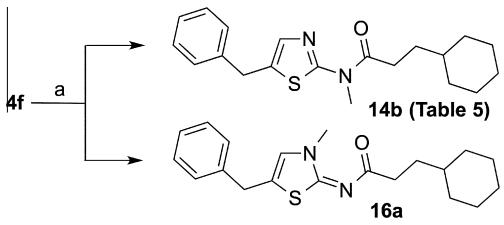
Scheme 1. Reagents and conditions: (a) R_5CHO, *n*-BuLi, THF, −78 °C, 2 h; (b) Et_3SiH, TFA, DCM, overnight, rt; (c) R_2COCl, Et_3N, THF, 15 min, rt or (d) R_2COOH, EDAC, DMAP, Et_3N, DMF/DCM (3:1, v/v), 2 h, rt or (e) TFAA, DCM, 30 min, rt. [a] Not applicable.

ranging from 22% to 59% (Scheme 1). The secondary alcohol functions of compounds **2a**–**2l** were reduced with triethylsilane (Et_3SiH) followed by in situ deprotection of the Boc group with trifluoroacetic acid (TFA) in DCM to give compounds **3a**–**3l** in yields ranging from 53% to 91%. It seems that this synthetic method has not been described previously for compounds **3a**–**3l**. Acylation of compounds **3a**–**3p** with various alkyl-, alicyclic-, or aryl acyl chlorides in the presence of triethylamine (TEA) gave products **4b**–**4f**, **4h**, **4i**, **5h**, **6a**–**6c**, **7a**–**7c**, **8a**, **8b**, **9b**–**9h**, **10a**–**10f**, **11a**, **11b**, **12a**–**12d**, **13a**–**13f**, **14a**, **14c**, and **15a**–**15h**.

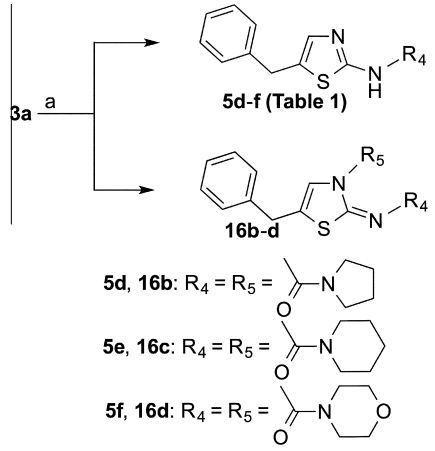
The reaction of **3a** or **3b** with trifluoroacetic anhydride (TFAA) at 0 °C followed by stirring for 30 min at room temperature yielded **4a** and **9a** in 56% and 93%, respectively. The reactions of compound **3a** with various alicyclic carboxylic acid in presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDAC) and dimethylaminopyridine (DMAP) gave compounds **4g**, **5a**–**5c**, and **5g** in yields ranging from 20% to 77%. Carboxylic acids instead of alicyclic acyl chlorides were used for the synthesis of **4g**, **5a**–**5c**, and **5g** because of their commercial availability.

In order to explore the effect of substituents at the N3 position of the thioazole ring on *Histoplasma* growth inhibition, compound **4f** was exposed to methyl iodide in the presence of sodium hydride according to previously described methods (Scheme 2).[20,21] Surprisingly, the reaction produced a mixture of two products, **14b** and **16a**, in 38% and 32% yield, respectively. Both compounds have similar HR-MS data indicating mono-methylation. However, for compound **16a**, a high field shift to 6.53 ppm was observed for the proton at the 4-position in the ^{1}H NMR spectrum, presumably due to lack of aromaticity in the thiazol-2(3H)-ylidene scaffold, compared to ~7.2 ppm for the same proton in **14b**.

In order to explore urea-type spacers and also the presence of heteroatoms in the ring system of the 2-position side chain, the reaction of compound **3a** with various *N*-acyl chlorides was carried out in the presence of DMAP (Scheme 3). In contrast to all reactions shown in Scheme 1, this reaction led to compounds that were mono substituted at the amino group at the 2-position (**5d**–**5f**) in low yields (5–8%) and compounds that were disubstituted both at the amino group in the 2-position and at the N3-position of thiazole ring (**16b**–**16d**) in yields ranging from 23% to 28%. The HR-MS data of compounds **5d**–**5f** and **16b**–**16d** are in agreement with mono- and disubstitution, respectively. In addition, the ^{1}H NMR spectra of **16b**–**16d** showed signals for the proton at the 4-position in the range of 6.5–6.6 ppm, which is consistent with the thiazol-2(3H)-ylidene scaffold whereas the signals for the same proton in the ^{1}H NMR spectra of compounds **5d**–**5f** were at 6.9–7.0 ppm, which indicates a thiazole ring system. Apparently the carbonyl carbon of the N-acyl chloride reagents is sufficiently electrophilic to allow nucleophilic attack both by the nitrogen of the amino group at the 2-position and that at the 3-position of thiazole ring.



Scheme 2. Reagents and conditions: (a) MeI, NaH, THF, 2 h, rt.



Scheme 3. Reagents and conditions: (a) 3-cyclohexylpropanoyl chloride, TEA, THF, rt.

2.2. Biology

Using 41F5 (Fig. 1) as the template, our primary intention was to develop an initial *Histoplasma* SAR for aminothiazole analogues (Fig. 2) by mapping the molecular target's binding pocket through varying dimensions and basic properties of substituents at the 2- and 5-positions of the aminothiazole core. Another objective was to determine the general effect of substitution at the 3- and 4-positions of the ring system on activity. Some other substitution effects were explored as well. For analogues with an *Histoplasma* MIC_{50} <3.5 μM, a very basic *Cryptococcus* SAR was also developed. In addition, for eleven compounds out of this group, we tested for potential liver toxicity in human hepatocyte HepG2 cells to establish selectivity indices (SIs).

Table 1 and Figure 1 summarize the biological data of aminothiazole derivatives with a benzyl substituent at the 5-position and various types of substituents at the 2-position. Within this group of compounds, those with cyclohexylmethylamide- (**4e**) and cyclohexylethylamide (**4f**) substituents at the 2-position had the lowest *Histoplasma* MIC_{50}- (0.7 μM) and MIC (1.3–2.5 μM) values. Cyclopentylamide- (**4c**), cyclohexylamide- (**4d**) and cyclobutylamide (**2F8**, Fig. 1) substituents caused slightly lower activity (MIC_{50} = 1.6–2.5 μM; MIC = 5 μM), whereas those with isopropylamide- (**4b**), tetrahydrothiopyran- (**5a**), and adamantylamide groups had markedly reduced activity (MIC_{50} = 4.8–6.7 μM; MIC = 10–20 μM). Interestingly, introduction of an *E*-ethene function between the amide and the cyclohexyl group (**4g**) reduced activity significantly compared with a cyclohexylethyl group (**4f**). Another noticeable finding was that the introduction of O- or N-heteroatoms at various positions of the ring systems at the 2-position reduced activity (**5b**–**5h**) even when the ring system was comparable in size to the cyclopentyl or cyclohexyl rings (**5b**–**5f**) (MIC_{50} >10 μM; MIC >20 μM). Other compounds in Table 1, that is, **3a** (unsubstituted 2-amino group), **4a** (2-trifluoromethylamide group) and **4h** (5-phenylamide group) had MIC_{50}- and MIC values >10 μM and >20 μM, respectively.

With the compounds shown in Table 2, we explored the effect of substitution at the 5-benzyl group on anti-*Histoplasma* activity.

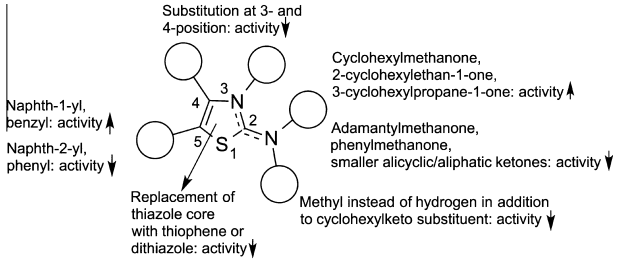
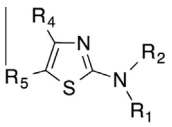
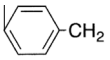
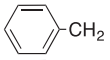
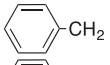
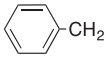
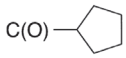
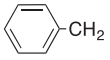
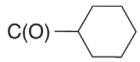
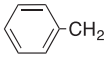
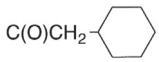
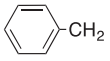
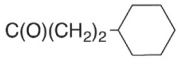
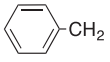
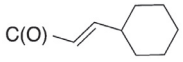
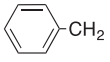
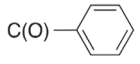
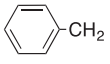
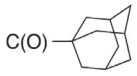
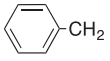
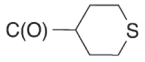
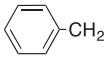
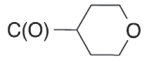
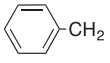
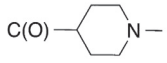
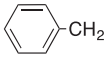
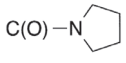
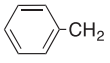
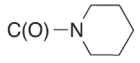
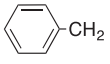
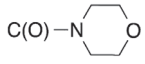
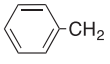
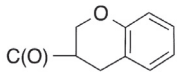
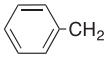
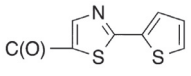


Figure 2. Basic *Histoplasma* SAR for aminothiazoles.

Table 1
5-Benzyl-substituted aminothiazole derivatives



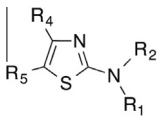
Compd	R_4	R_5	R_1	R_2	*Histoplasma capsulatum*		*Cryptococcus neoformans*		HepG2 cells	SI (Histo/HepG2)
					MIC_{50} (μM)	MIC (μM)	MIC_{50} (μM)	MIC (μM)	MIC_{50} (μM)	
3a	H		H	H	>10	>20	[a]nd	nd	nd	nd
4a	H		H	$C(O)CF_3$	>10	>20	nd	nd	nd	nd
4b	H		H	$C(O)CH(CH_3)_2$	6.7	20	nd	nd	nd	nd
4c	H		H		1.6 ± 0.1	5	3.6 ± 0.9	10	>40	>24
4d	H		H		1.6 ± 0.1	5	1.3 ± 0.2	5	>40	>21
4e	H		H		0.7 ± 0.1	2.5	>10	>20	>40	>44
4f	H		H		0.7 ± 0.1	1.3	>10	>20	>40	>44
4g	H		H		>10	>20	nd	nd	nd	nd
4h	H		H		>10	>20	nd	nd	nd	nd
4i	H		H		5.0	10	nd	nd	nd	nd
5a	H		H		4.8	10	nd	nd	nd	nd
5b	H		H		>10	>20	nd	nd	nd	nd
5c	H		H		>10	>20	nd	nd	nd	nd
5d	H		H		>10	>20	nd	nd	nd	nd
5e	H		H		>10	>20	nd	nd	nd	nd
5f	H		H		>10	>20	nd	nd	nd	nd
5g	H		H		>10	>20	nd	nd	nd	nd
5h	H		H		>10	>20	nd	nd	nd	nd

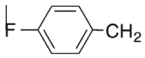
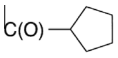
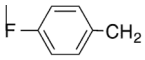
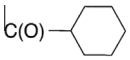
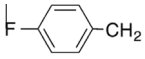
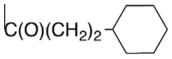
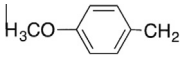
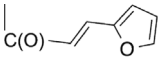
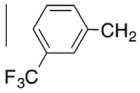
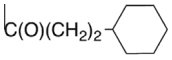
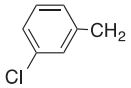
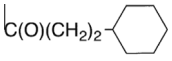
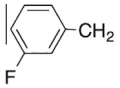
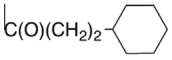
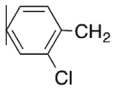
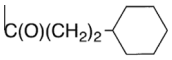
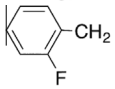
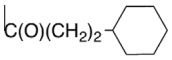
[a] Not determined.

Aromatic *ortho*- (**8a**, **8b**) and *meta*- (**7b**, **7c**) substitution with fluorine and chlorine did not substantially alter activity compared with unsubstituted **4c**–**4f** (Table 1) whereas *para*-substitution (**6a**–**6d**) had a negative impact. Noticeable is the lack of activity observed for **7a** with a trifluoromethyl group in *meta*-position.

Table 3 displays biological data for compounds with naphth-1-ylmethyl- or naphth-2-ylmethyl group at the 5-position. Within the group of aminothiazole derivatives with a naphth-1-ylmethyl substituent, a similar trend was observed as for compounds with 5-benzyl substituent (Table 1). Compounds with cyclohexylamide- (**9d**), cyclohexylmethylamide- (**9e**) and cyclohexylethylamide (**9f**) groups at the 2-position had the lowest *Histoplasma* IC_{50} values (MIC_{50} = 0.4 μM; MIC = 0.6–1.3 μM) whereas those with smaller isopropylamide- (**9b**) and cyclopentylamide (**9c**) substituents had slightly reduced activity. Trifluoromethylamide- (**9a**), phenylamide- (**9g**) and adamantylamide (**9h**) substituents at the 2-position caused markedly reduced activity (MIC_{50} >10 μM; MIC >20 μM). Except for compounds **10a**, with a 2-isopropylamide group (MIC_{50} = 4.5 μM; MIC = 20 μM), and **10c**, with 2-cyclohexylethylamide group (MIC_{50} = 5.7 μM; MIC = 20 μM), all aminothiazole derivatives with a naphth-2-ylmethyl group at the 5-position had MIC_{50} values >10 μM (MIC >20 μM). Comparing naphth-1-ylmethyl substitution at the 5-position with benzyl substitution at the same position, the isopropylamide group at the

Table 2
5-Benzyl-substituted aminothiazoles with differing substitution pattern at the 5-benzyl group



Compd	R_4	R_5	R_3	R_4	*Histoplasma capsulatum* MIC_{50} (μM)	*Histoplasma capsulatum* MIC (μM)	*Cryptococcus neoformans* MIC_{50} (μM)	*Cryptococcus neoformans* MIC (μM)	HepG2 cells MIC_{50} (μM)	SI Histo/HepG2)
6a	H		H		5.2	20	[a]nd	nd	nd	nd
6b	H		H		4.4 ± 1.0	20	nd	nd	nd	nd
6c	H		H		>10	>20	nd	nd	nd	nd
6d	H		H		>10	>20	nd	nd	nd	nd
7a	H		H		>10	>20	nd	nd	nd	nd
7b	H		H		1.1 ± 0.4	2.5	>10	>20	39 ± 2	65
7c	H		H		0.8 ± 0.1	2.5	>10	>20	40 ± 2	57
8a	H		H		0.9 ± 0.3	2.5	>10	>20	nd	nd
8b	H		H		1.0 ± 0.3	2.5	>10	>20	nd	nd

[a] Not determined.

2-position had a significant impact on activity, as evidenced by an MIC_{50} of 1.5 μM (MIC = 2.5 μM) for **9b** vs. an MIC_{50} of 6.7 μM (MIC = 20 μM) for **4b**. Overall, compounds **9d**–**9f**, with naphth-1-ylmethyl substituent at the 5-position combined with cyclohexylamide-, cyclohexylmethylamide-, and cyclohexylethylamide substituents, respectively, at the 2-position, had the highest anti-*Histoplasma* activities (MIC_{50} = 0.4 μM; MIC = 0.6–1.3 μM) of all tested compounds.

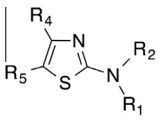
The compounds presented in Table 4 were evaluated to determine the effect of phenylethyl-, phenyl-, and cyclohexylmethyl substituents at the 5-position on *Histoplasma* growth. Phenylethyl- (**11a**, **11b**) substitution reduced activity only slightly compared to naphth-1-ylmethyl substitution (**9d**–**9f**, Table 3) whereas phenyl substitution (**12b**–**12d**) had a detrimental impact on activity. An interesting pattern was observed for compounds with cyclohexylmethyl substituent at the 5-position. Those with isopropylamide- (**13a**), cyclohexylmethylamide- (**13c**), and adamantylamide (**13f**) groups at the 2-position had no activity, whereas those with phenylamide (**13e**) substituent retained some activity (MIC_{50} = 4.6 μM; MIC = 10 μM). In contrast, cyclohexylamide- (**13b**) and cyclohexylethylamide- (**13d**) substitution produced high activity (MIC_{50} = 0.7–0.9 μM; MIC = 2.5–5.0 μM).

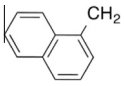
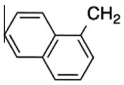
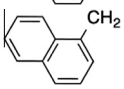
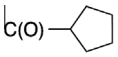
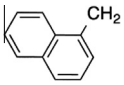
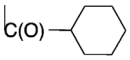
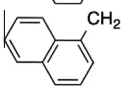
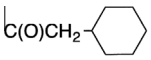
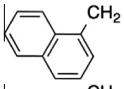
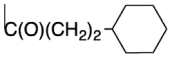
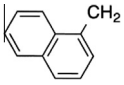
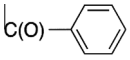
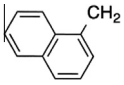
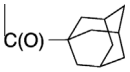
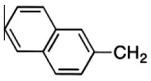
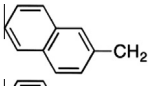
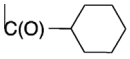
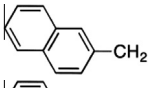
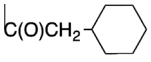
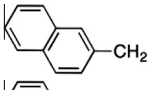
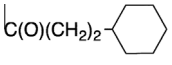
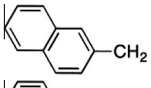
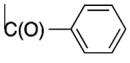
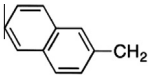
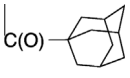
Biological data for compounds with varying substitution patterns, including groups at the 3- or 4-position, are shown in Table 5, Schemes 2, 3, and Figure 1. Compounds with substituents at the 3- (**16a**–**16d**, Schemes 2 and 3 [data not shown]) and 4- (**14c**, **15a**–**15h**, Table 5) positions had reduced anti-*Histoplasma* activity or were inactive. Some aminothiazole derivatives with bulky adamantyl substitution at the 4-position in combination with hydrogen at the 5-position retained moderate activity (**15d**, **15e**, **15g**, **15h**) with MIC_{50} values ranging from 2.5 μM to 7.4 μM (MIC = 5–20 μM). In contrast, compounds with 4-phenyl group and hydrogen at the 5-position (**15a**, **15b**) had no activity. Disubstitution at the amide nitrogen (**14b**) as well as replacement of thiazole with thiadiazole (**14a**), and possibly also thiophene (4H2, Fig. 1), abolished or reduced activity. In addition, the simultaneous presence of a hydroxymethyl linker at the 5-position and a Boc group at the 2-position (**2a**, Table 5) resulted in lack of activity. Interestingly, compounds **15e**–**15h** (Table 5) and **13b**–**13e** (Table 4) showed similar activity patterns. In both sub-series, 2-cyclohexylmethylamide substitution (**13c**, **15f**) abolished activity whereas the cyclohexylamide- (**13b**, **15e**), cyclohexylethylamide- (**13d**, **15g**), and phenyl (**13e**, **15h**) homologues retained activity.

Although only a very basic SAR was established for efficacy against *Cryptococcus*, we noted some similarities but also differences to the *Histoplasma* SAR. As in the case of the *Histoplasma* SAR, compounds with cyclopentaneamide- (**4c**, **9c**) and cyclohexaneamide groups (**4d**, **9d**) at the 2-position had anti-*Cryptococcus* activity. In contrast to the *Histoplasma* SAR, however, the compounds with larger cyclohexylmethylamide- (**4e**, **9e**) and cyclohexylethylamide (**4f**, **9f**) substituents had lost activity against *Cryptococcus*. The same is the case for the smaller isopropyl group (**9b**). At the 5-postion, the naphth-1-ylmethyl group (**9c**, **9d**) resulted in highest activity where as the benzyl- (**4c**, **4d**) and phenylethyl (**11a**) groups caused moderate loss of activity.

SIs between >21(**4d**) and >100(**9f**) indicate generally low host toxicity of the aminothiazole antifungals. Interestingly, commercially-available compound **6d** (Table 2) did not have any antifungal activity against *Histoplasma*. However, the same compound caused

Table 3
5-Napthyl-substituted aminothiazole derivatives



Compd	R_4	R_5	R_1	R_2	*Histoplasma capsulatum*		*Cryptococcus neoformans*		HepG2 cells	SI (Histo/HepG2)
					MIC_{50} (μM)	MIC (μM)	MIC_{50} (μM)	MIC (μM)	MIC_{50} (μM)	
9a	H		H	$C(O)CF_3$	>10	>20	[a]nd	nd	nd	nd
9b	H		H	$C(O)CH(CH_3)_2$	1.5 ± 0.1	2.5	>10	>20	nd	nd
9c	H		H		0.8 ± 0.1	1.3	0.8 ± 0.3	1.3	>40	>57
9d (**41F5**)	H		H		0.4 ± 0.01	0.6	0.4 ± 0.1	0.6	39 ± 1	97
9e	H		H		0.4 ± 0.01	0.6	>10	>20	37 ± 1	92
9f	H		H		0.4 ± 0.02	1.3	>10	>20	>40	>100
9g	H		H		>10	>20	nd	nd	nd	nd
9h	H		H		>10	>20	nd	nd	nd	nd
10a	H		H	$C(O)CH(CH_3)_2$	4.5	20	nd	nd	nd	nd
10b	H		H		>10	>20	nd	nd	nd	nd
10c	H		H		5.7	20	nd	nd	nd	nd
10d	H		H		>10	>20	nd	nd	nd	nd
10e	H		H		>10	>20	nd	nd	nd	nd
10f	H		H		>10	>20	nd	nd	nd	nd

[a] Not determined.

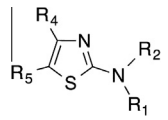
in vitro proliferation inhibition of DU-145 human prostate cancer cells with an IC_{50} of 15 nM.[15] This compound, with host cell toxicity but no antifungal activity, highlights the good specificity for fungi of the aminothiazole analogues presented here.

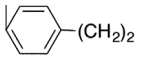
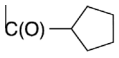
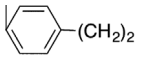
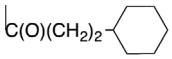
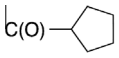
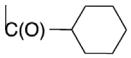
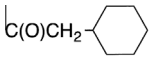
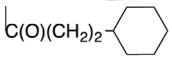
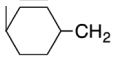
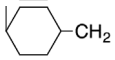
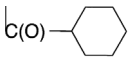
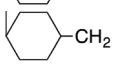
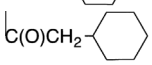
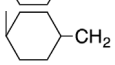
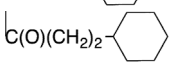
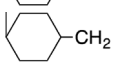
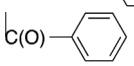
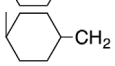
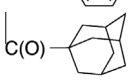
Most of the active aminothiazoles are very lipophilic and do not contain functional groups that are ionizable under physiological conditions. For example, **9d** has a *C*Log*P* of 5.67 (ChemBioDraw 13.0.2.3020). Thus, in the case of some of the compounds that were tested in more detail, slight (**4c**, **7c**, **9d**, **9e**) to moderate (**4e**, **7b**, **9c**) precipitation at high compound concentrations (generally >40 μM) was noticed during the antifungal assays in the test vials even though the media contained 1% DMSO. Solubility could be improved by increasing the DMSO concentrations. However, at concentrations above 1%, DMSO itself inhibited fungal growth.

3. Summary and conclusions

The *Histoplasma* SAR studies resulted in the lowest MIC_{50} and MIC values (0.4 μM; MIC = 0.6–1.3 μM) for compounds **9d** (41F5), **9e**, and **9f**. These compounds have a naphth-1-ylmethyl group at the 5-position and a cyclohexylamide-, cyclohexylmethylamide-, and cyclohexylethylamide substituent, respectively, at the 2-position. The MIC values of these compounds are approximately 1–2 μM (Fig. 3), which is in the range of effective in vitro concentrations of some clinically established antifungal[22] and antiparasitic drugs.[23] The highest SI (>100) was observed for compound **9f**. Overall, SIs ranged from >21 to >100, which indicates the possibility of low host toxicity of these novel aminothiazole antifungals and significant differences to, or even absence of, equivalent

Table 4
Aminothiazole derivatives with phenylethyl,- phenyl-, and cyclohexylmethyl substituents at the 5 position



Compd	R_4	R_5	R_1	R_2	*Histoplasma capsulatum*		*Cryptococcus neoformans*		HepG2 cells	SI (Histo/HepG2)
					MIC_{50} (μM)	MIC (μM)	MIC_{50} (μM)	MIC (μM)	MIC_{50} (μM)	
11a	H		H		0.9 ± 0.1	2.5	2.7 ± 0.6	5	[a]nd	nd
11b	H		H		0.7 ± 0.1	2.5	>10	>20	>40	>50
12a	H		H		>10	>20	nd	nd	nd	nd
12b	H		H		>10	>20	nd	nd	nd	nd
12c	H		H		>10	>20	nd	nd	nd	nd
12d	H		H		>10	>20	nd	nd	nd	nd
13a	H		H	$C(O)CH(CH_3)_2$	>10	>20	nd	nd	nd	nd
13b	H		H		0.7 ± 0.1	2.5	>10	>20	nd	nd
13c	H		H		>10	>20	nd	nd	nd	nd
13d	H		H		0.8 ± 0.1	5	9.6	>20	nd	nd
13e	H		H		4.6	10	nd	nd	nd	nd
13f	H		H		>10	>20	nd	nd	nd	nd

[a] Not determined.

mammalian targets for the tested aminothiazole antifungals. This hypothesis is also supported by the finding that compound **6d**, which is structurally related to 41F5, did not have antifungal activity although it proved to be a strong inhibitor of in vitro proliferation of DU-145 human prostate cancer cells.[15] It was previously observed that **9d** (41F5) has inhibitory rather than microbicidal action.[7] It remains to be determined whether the newly tested compounds have the same activity profile.

Previous studies have shown that **9d** (41F5) does not inhibit the in vitro growth of *Candida albicans*, *Aspergillus fumigatus*, and *Blastomyces dermatitidis*.[7] Strikingly, **9d** (41F5), and to a slightly lesser extend **9c**, have antifungal activity against two phylogenetically diverged organisms, that is, the basidiomycete *Cryptococcus* and the ascomycete *Histoplasma*, yet there are subtle differences in the SARs of these fungi. We suspect that aminothiazoles target a common molecule in both fungal species, but that the binding site has diverged between members of different phyla within the kingdom Fungi. This suggests the possibility that this class of antifungals has potential to inhibit the same molecular target also in other fungal pathogens (e.g., *Candida*, *Aspergillus*, or *Blastomyces*) based on appropriate structural modifications. Preliminary studies indicate that there is no synergism beyond additive effects between **9d** (41F5) and fluconazole (fractional inhibitory concentration index [FIC] ~0.7), nor between **9d** (41F5) and caspofungin (FIC ~1.1) suggesting that the aminothiazole antifungal target is not involved in ergosterol biosynthesis or cell wall β-glucan synthesis.[24] Thus, the possibility of a new molecular target in the area of fungal therapy seems likely, warranting further investigation.

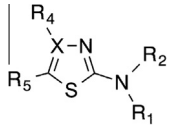
4. Experimental methods

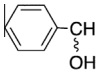
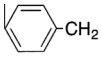
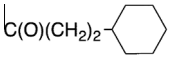
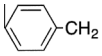
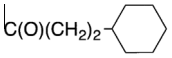
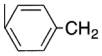
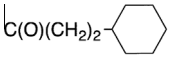
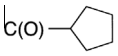
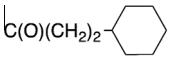
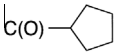
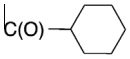
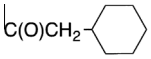
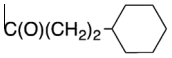
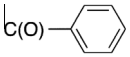
4.1. Chemistry

4.1.1. General chemical procedures

^1H and ^{13}C NMR spectra were obtained on a Bruker DRX 400 at The Ohio State University College of Pharmacy (400 MHz for ^1H and 100 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm from internal deuterated chloroform or methanol. Coupling constants are reported in Hz. ^{13}C NMR spectra are fully decoupled. High resolution-electrospray ionization (HR-ESI) mass spectra were obtained on a Micromass LCT spectrometer at The Ohio State University Campus Chemical Instrumentation Center, Columbus, OH. Silica gel 60 (0.063–0.200 mm), used for gravity column chromatography, and silica gel 60 (0.015–0.049 mm), used for flash column chromatography, were purchased from Dynamic Adsorbents Inc., Norcross, USA. Reagent-grade solvents were used for column chromatography. Pre-coated aluminum-backed TLC plates with silica gel 60 F254 (0.25-mm layer thickness) from Sigma-Aldrich were used for TLC. Compound visualization for TLC was achieved by UV light. Anhydrous solvents, starting materials, including compounds **1a**, **1b**, **3m**, **3n**, and **3o**, and other chemicals were purchased from standard commercial suppliers. 3-(2-Furyl)-N-[5-(4-methoxybenzyl)-1,3-thiazol-2-yl]acrylamide (**6d**) was purchased from Chembridge, San Diego, CA, USA. Compounds **3c**, **3d**, **4b**, **4d**, **6a**, **6b**, **9b**, **9d**, **12a**, **12b**, **14a**, and **15b** are commercially available. However, no synthetic procedures and analytical data are published. These compounds were synthesized and analyzed as described in Sections 4.1.3. and 4.1.4. Compounds **2f**,[25] **3a**,[26]

Table 5
Aminothiazole derivatives with varying substitution patterns



Compd	X	R_4	R_5	R_1	R_2	*Histoplasma capsulatum*		*Cryptococcus neoformans*	
						MIC_{50} (μM)	MIC (μM)	MIC_{50} (μM)	MIC (μM)
2a	C	H		H	$C(O)OC(CH_3)_3$	>10	>20	[a]nd	nd
14a	N	_		H		>10	>20	nd	nd
14b	C	H		Me		>10	>20	nd	nd
14c	C	Me		H		>10	>20	nd	nd
15a	C		H	H		>10	>20	nd	nd
15b	C		H	H		>10	>20	nd	nd
15c	C		H	H	$C(O)CH(CH_3)_2$	>10	>20	nd	nd
15d	C		H	H		7.4	20	nd	nd
15e	C		H	H		2.5 ± 0.1	5	>10	>20
15f	C		H	H		>10	>20	nd	nd
15g	C		H	H		5.2	20	nd	nd
15h	C		H	H		3.1 ± 0.1	10	8.3	20

[a] Not determined.

3b,[27] **3e**,[15] **3f**,[25] **3g**,[28] **3h**,[28] **3i**,[29] **3j**,[29] **3k**,[18] **3l**,[18] **4h**,[30] **15a**,[20] and **15h**[31] are commercially available and/or have been reported before. These compounds were synthesized and analyzed as described in Sections 4.1.2., 4.1.3. and 4.1.4. using partially different methods as described previously. Compound **3p** was prepared according to a procedure described by Hardgrave et al.[32] (2E)-3-Cyclohexyl-2-propenoic acid, used for the synthesis of **4g**, was prepared according to procedures previously described.[33] All reactions were carried under Argon atmosphere.

4.1.2. General procedure for the synthesis of compounds 2a–2l

n-BuLi (2.5 M in THF, 1.4 equiv) was added drop wise to a mixture of compound **1a** or **1b** (1 equiv) and aldehyde (1.2 equiv) in THF (~20 mL) at −78 °C for 2 h. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl, extracted with EtOAc, washed with water and then brine. The organic phase was dried over anhydrous Na_2SO_4, evaporated, and the residue was purified by silica gel column chromatography.

4.1.2.1. *tert*-Butyl{5-[hydroxy(phenyl)methyl]thiazol-2-yl}carbamate (2a). White solid; R_f 0.49 (DCM/MeOH, 19:1); yield 59%. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.48 (m, 5H), 7.07 (s, 1H), 6.01 (s, 1H), 2.20 (s, 1H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 152.8, 142.3, 135.2, 134.2, 128.8, 128.3, 126.2, 82.3, 70.6, 28.3. MS (HR-ESI) for $C_{15}H_{18}N_2O_3SNa$ [$(M+Na)^+$], calcd: *m*/*z* 329.0936, found: *m*/*z* 329.0917.

4.1.2.2. *tert*-Butyl{5-[hydroxy(naphthalen-1-yl)methyl]thiazol-2-yl}carbamate (2b). White solid; R_f 0.55 (DCM/MeOH, 19:1); yield 30%. ^1H NMR (400 MHz, $CDCl_3$): δ 11.71 (br s, 1H), 7.97 (m, 1H), 7.82 (m, 3H), 7.46 (m, 3H), 6.95 (s, 1H), 6.67 (s, 1H), 2.21 (s, 1H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 137.7, 135.0, 134.4, 134.0, 130.3, 129.0, 126.5, 125.9, 125.5, 123.8, 123.6, 82.0, 67.8, 28.2. MS (HR-ESI) for $C_{19}H_{20}N_2OSNa$ [$(M+Na)^+$], calcd: *m*/*z* 379.1092, found: *m*/*z* 379.1089.

4.1.2.3. *tert*-Butyl-{5-[hydroxy(naphthalen-2-yl)methyl]thiazol-2-yl}carbamate (2c). White solid; R_f 0.54 (DCM/MeOH, 19:1); yield 30%. NMR (400 MHz, $CDCl_3$): δ 11.83 (s, 1H), 7.93 (s, 1H), 7.84 (m, 3H), 7.49 (m, 3H), 7.06 (s, 1H), 6.14 (s, 1H), 2.17 (s, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 139.7, 135.1, 134.6, 133.3, 128.7, 128.3, 127.8, 126.5, 126.4, 124.9, 124.3, 82.2, 70.7, 28.2. MS (HR-ESI) for $C_{19}H_{20}N_2O_3SNa$ [$(M+Na)^+$], calcd: *m*/*z* 379.1092, found: *m*/*z* 379.1087.

4.1.2.4. *tert*-Butyl-{5-[hydroxy(cyclohexyl)methyl]thiazol-2-yl}-carbamate (2d). White solid; R_f 0.35 (DCM/MeOH, 9:1); yield 38%. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H), 4.61 (d, *J* = 6.83 Hz, 1H), 2.03 (m, 1H), 1.64–1.79 (m, 5H), 1.59 (s, 9H), 0.98–1.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 152.7, 134.4, 132.3, 82.7, 73.2, 45.2, 29.3, 29.0, 28.4, 26.0. MS (HR-ESI) for $C_{15}H_{24}N_2O_3SNa$ [$(M+Na)^+$], calcd: *m*/*z* 335.1405, found: *m*/*z* 335.1397.

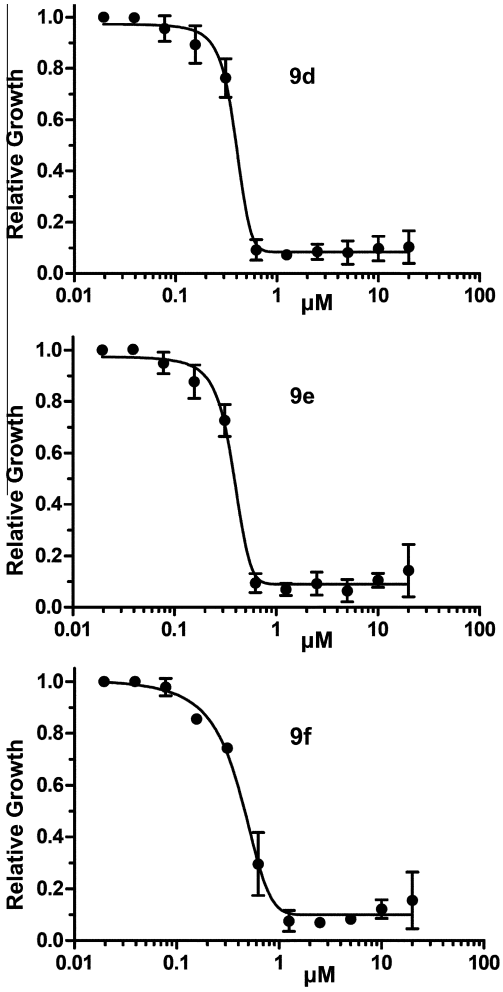


Figure 3. Dose-response curves for compounds **9d**–**9f** against *Histoplasma capsulatum* yeasts.

4.1.2.5. *tert*-Butyl-{5-[hydroxy-(4-fluorophenyl)methyl]thiazol-2-yl}carbamate (2e). White solid; R_f 0.5 (DCM/MeOH, 19:1); yield 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.85 (br s, 1H), 7.44 (m, 2H), 7.04–7.09 (m, 2H), 6.0 (s, 1H), 2.19 (s, 1H) 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 159.4, 143.5, 140.1, 139.4, 132.9, 119.3, 118.9, 82.7, 69.1, 24.3. MS (HR-ESI) for $C_{18}H_{22}N_2OSNa$ [(M+Na)$^+$], calcd: *m*/*z* 347.0842, found: *m*/*z* 347.0839.

4.1.2.6. *tert*-Butyl-{5-[hydroxy(3-trifluoromethylphenyl)methyl]-thiazol-2-yl}carbamate (2f). White solid; R_f 0.52 (DCM/MeOH, 19:1); yield 31%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.95 (br s, 1H), 7.75 (s, 1H), 7.67 (m, 1H), 7.59 (m, 1H), 7.52 (m, 1H), 7.04 (s, 1H), 6.08 (s, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 153.13, 143.6, 134.9, 134.6, 131.6, 131.2, 129.9, 129.5, 125.3, 123.3, 82.6, 70.1, 28.5. MS (HR-ESI) for $C_{16}H_{17}F_3N_2O_3S$ [(M+Na)$^+$], calcd: *m*/*z* 397.0812, found: *m*/*z* 397.0810.

4.1.2.7. *tert*-Butyl-{5-[hydroxy(3-chlorophenyl)methyl]thiazol-2-yl)carbamate (2g). White solid; R_f 0.51 (DCM/MeOH, 19:1); yield 53%.^{1}H NMR (400 MHz, $CDCl_3$): δ 11.91 (s, 1H), 7.39 (s, 1H), 7.33 (m, 3H), 6.01 (s, 1H), 2.19 (s, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 152.9, 144.4, 134.7, 134.6, 134.5, 130.0, 128.4, 126.4, 124.4, 82.3, 69.9, 28.3. MS (HR-ESI) for $C_{15}H_{17}ClN_2O_3S$ [(M+Na)$^+$], calcd: *m*/*z* 363.0546, found: *m*/*z* 363.0547.

4.1.2.8. *tert*-Butyl-{5-[hydroxy(3-fluorophenyl)methyl]thiazol-2-yl}carbamate (2h). White solid; R_f 0.5 (DCM/MeOH, 19:1); yield 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.68 (br s, 1H), 7.34 (m, 1H), 7.22 (m, 2H), 7.14 (s, 1H), 7.03 (m, 1H), 6.0 (s, 1H), 2.19 (s, 1H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 162.5, 161.9, 144.9, 134.6, 130.3, 121.8, 115.3, 115.0, 113.4, 113.2, 82.3, 69.9, 28.3. MS (HR-ESI) for $C_{15}H_{17}FN_2OS$ [(M+H)$^+$], calcd: *m*/*z* 347.0842, found: *m*/*z* 347.0845.

4.1.2.9. *tert*-Butyl-{5-[hydroxyl(2-fluorophenyl)methyl]thiazol-2-yl}carbamate (2i). White solid; R_f 0.51 (DCM/MeOH, 19:1); yield 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.95 (s, 1H), 7.64 (t, J = 7.61 Hz, 1H), 7.29–7.35 (m, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.03–7.10 (m, 2H), 6.29 (s, 1H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 161.0, 158.5, 152.9, 134.4, 133.8, 124.7, 124.6, 115.7, 115.5, 82.1, 64.7, 28.3. MS (HR-ESI) for $C_{15}H_{17}FN_2O_3S$ [(M+H)$^+$], calcd: *m*/*z* 325.1022, found: *m*/*z* 325.1024.

4.1.2.10. *tert*-Butyl-{5-[hydroxyl(2-chlorophenyl)methyl]thiazol-2-yl}carbamate (2j). White solid; R_f 0.49 (DCM/MeOH, 19:1); yield 48%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.97 (s, 1H), 7.81 (m, 1H), 7.33–7.44 (m, 2H), 7.21–7.32 (m, 1H), 7.09 (s, 1H), 6.41 (s, 1H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 152.9, 139.9, 134.9, 133.3, 132.1, 129.7, 129.3, 127.5, 127.5, 82.2, 67.2, 28.3. MS (HR-ESI) for $C_{15}H_{17}ClN_2O_3S$ [(M+Na)$^+$], calcd: *m*/*z* 363.0546, found: *m*/*z* 363.0551.

4.1.2.11. *tert*-Butyl-{5-[1-hydroxyl(2-phenyl)ethyl]thiazol-2-yl}-carbamate (2k). White solid; R_f 0.47 (DCM/MeOH, 19:1); yield 35%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.30 (m, 5H), 7.07 (s, 1H), 5.11 (t, J = 6.5 Hz, 1H), 3.13 (d, J = 6.8 Hz, 2H), 1.56 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 152.9, 137.3, 134.3, 133.5, 129.6, 128.8, 127.1, 82.3, 69.6, 45.7, 28.4. MS (HR-ESI) for $C_{16}H_{20}N_2O3S$ [(M+Na)$^+$], calcd: *m*/*z* 343.1092, found: *m*/*z* 343.1082.

4.1.2.12. *tert*-Butyl-{5-[hydroxy(phenyl)methyl]-4-methylthiazol-2-yl}carbamate (2l). White solid; R_f 0.53 (DCM/MeOH, 19:1); yield 22%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.44 (m, 5H), 6.03 (s, 1H), 2.29 (s, 3H), 2.01 (s, 1H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 152.6, 143.1, 142.9, 128.7, 128.3, 128.0, 126.0, 82.6, 69.6, 28.3, 15.1. MS (HR-ESI) for $C_{16}H_{20}N_2O_3S$ [(M+Na)$^+$], calcd: *m*/*z* 343.1092, found: *m*/*z* 343.1102.

4.1.3. General procedure of the synthesis of compounds 3a–3l

A mixture of compounds **2a**–**2l** (1 equiv), triethylsilane (8 equiv), and TFA (14 equiv) in DCM (~20 mL) was stirred overnight at room temperature. The mixture was evaporated and the residue was treated with a saturated solution of aqueous $NaHCO_3$. The aqueous layer was extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography.

4.1.3.1. 5-Benzyl-2-thiazolamine (3a). White solid; R_f 0.38 (DCM/MeOH, 19:1); yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.34 (m, 5H), 6.78 (s, 1H), 4.92 (br s, 2H), 3.88 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 139.9, 135.7, 128.7, 128.5, 128.2, 126.8, 33.5. MS (HR-ESI) for $C_{10}H_{10}N_2S$ [(M)$^+$], calcd: *m*/*z* 191.0643, found: *m*/*z* 191.0618.

4.1.3.2. 5-(1-Naphthalenylmethyl)-2-thiazolamine (3b). White solid; R_f 0.42 (DCM/MeOH, 19:1); yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 1H), 7.87 (m, 1H), 7.82 (m, 1H), 7.49 (m, 2H), 7.41 (m, 1H), 7.28 (m, 1H), 6.71 (s, 1H), 6.47 (br s, 2H), 4.31 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 134.4, 134.1, 131.6, 129.0, 128.2, 126.9, 126.6, 126.1, 125.7, 123.6, 30.8. MS (HR-ESI) for $C_{14}H_{12}N_2S$ [(M+H)$^+$], calcd: *m*/*z* 241.0799, found: *m*/*z* 241.0803.

4.1.3.3. 5-(2-Naphthalenylmethyl)-2-thiazolamine (3c). White solid; R_f 0.45 (DCM/MeOH, 19:1); yield 53%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.83 (m, 3H), 7.67 (s, 1H), 7.47 (m, 2H), 7.36 (d, J = 7.4 Hz, 1H), 6.87 (s, 1H), 4.82 (br s, 2H), 4.13 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 137.4, 136.0, 133.7, 132.5, 128.4, 127.8, 127.0, 126.8, 126.3, 125.8, 33.7. MS (HR-ESI) for $C_{14}H_{12}N_2S$ [(M+H)$^+$], calcd: m/z 241.0799, found: m/z 241.0796.

4.1.3.4. 5-(Cyclohexylmethyl)-2-thiazolamine (3d). White solid; R_f 0.31 (DCM/MeOH, 19:1); yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 1H), 4.92 (br s, 2H), 2.51 (d, J = 7.0 Hz, 2H), 1.67 (m, 5H), 1.43 (m, 1H), 1.09–1.32 (m, 3H), 0.91–1.04 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 135.5, 128.0, 39.7, 35.0, 33.0, 26.5, 26.3. MS (HR-ESI) for $C_{10}H_{16}N_2O$ [(M+H)$^+$], calcd: m/z 197.1112, found: m/z 197.1104.

4.1.3.5. 5-(4-Fluorobenzyl)-2-thiazolamine (3e). White solid; R_f 0.39 (DCM/MeOH, 19:1); yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (m, 2H), 7.03 (m, 2H), 6.78 (s, 1H), 4.83 (br s, 2H), 3.88 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 164.5, 162.0, 137.1, 131.1, 129.5, 117.0, 34.1 MS (HR-ESI) for $C_{10}H_9FN_2S$ [(M+H)$^+$], calcd: m/z 209.0549, found: m/z 209.0546.

4.1.3.6. 5-[3-(Trifluoromethyl)benzyl]-2-thiazolamine (3f). White solid; $\boldsymbol{R_f}$ 0.38 (DCM/MeOH, 19:1); yield 55%. $^{\mathbf{1}}$H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 7.41–7.53 (m, 4H), 6.79 (s, 1H), 5.21 (br s, 2H), 4.03 (s, 2H). $^{\mathbf{13}}$C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 168.0, 140.8, 136.24, 131.9, 131.2, 130.9, 129.2, 126.5, 125.2, 123.7, 33.2. MS (HR-ESI) for $C_{11}H_9F_3N_2S$ [(M+H)$^+$], calcd: $\boldsymbol{m/z}$ 259.0504, found: $\boldsymbol{m/z}$ 259.0517.

4.1.3.7. 5-(3-Chlorobenzyl)-2-thiazolamine (3g). White solid; R_f 0.37 (DCM/MeOH, 19:1); yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (m, 3H), 7.08 (s, 1H), 5.02 (br s, 2H), 4.01 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 141.9, 136.2, 134.5, 129.9, 128.6, 127.0, 126.6, 33.1. MS (HR-ESI) for $C_{10}H_9ClN_2S$ [(M+H)$^+$], calcd: m/z 225.0253, found: m/z 225.0252.

4.1.3.8. 5-(3-Fluorobenzyl)-2-thiazolamine (3h). White solid; R_f 0.39 (DCM/MeOH, 19:1); yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.31 (m, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.90–6.97 (m, 2H), 6.83 (s, 1H), 4.98 (br s, 2H), 3.97 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 164.6, 142.7, 136.5, 130.4, 127.4, 124.3, 115.8, 114.0, 33.4 MS (HR-ESI) for $C_{10}H_9FN_2S$ [(M+H)$^+$], calcd: m/z 209.0549, found: m/z 209.0547.

4.1.3.9. 5-(2-Fluorobenzyl)-2-thiazolamine (3i). White solid; R_f 0.38 (DCM/MeOH, 19:1) yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (m, 2H), 7.01–7.09 (m, 2H), 6.78 (s, 1H), 4.92 (br s, 2H), 4.03 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 162.0, 159.5, 136.2, 128.6, 126.5, 124.4, 115.6, 115.4, 26.4. MS (HR-ESI) for $C_{10}H_9FN_2S$ [(M+Na)$^+$], calcd: m/z 231.0368, found: m/z 231.0359.

4.1.3.10. 5-(2-Chlorobenzyl)-2-thiazolamine (3j). White solid; R_f 0.38 (DCM/MeOH, 19:1); yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 1H), 7.19–7.33 (m, 3H), 6.82 (s, 1H), 4.94 (br s, 2H), 4.11 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 137.6, 136.4, 133.8, 130.4, 129.7, 128.3, 127.2, 126.1, 31.0. MS (HR-ESI) for $C_{10}H_9ClN_2S$ [(M+H)$^+$], calcd: m/z 225.0253, found: m/z 225.0192.

4.1.3.11. 5-Phenethyl-2-thiazolamine (3k). White solid; R_f 0.38 (DCM/MeOH, 19:1); yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 2H), 7.24 (m, 3H), 6.67 (s,1H), 4.98(br s, 2H), 2.81–2.93 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 140.8, 134.7, 128.6, 128.5, 128.2, 126.3, 37.6, 29.1. MS (HR-ESI) for $C_{11}H_{12}N_2S$ [(M+H)$^+$], calcd: m/z 205.0799, found: m/z 205.0801.

4.1.3.12. 5-Benzyl-4-methyl-2-thiazolamine (3l). White solid; R_f 0.4 (DCM/MeOH, 19:1); yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.28 (m, 5H), 4.83 (br s, 2H), 3.91 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 143.6, 140.4, 128.7, 128.2, 126.6, 120.1, 32.3, 14.9 MS (HR-ESI) for $C_{11}H_{12}N_2S$ [(M+H)$^+$], calcd: m/z 205.0799, found: m/z 205.0789.

4.1.4. General procedure for the synthesis of compounds 4b–4f, 4h, 4i, 5h, 6a–6c, 7a–7c, 8a, 8b, 9b–9h, 10a–10f, 11a, 11b, 12a–12d, 13a–13f, 14a, 14c, and 15a–15h

To a mixture of compounds **3a**–**3p** (1 equiv) and acid chloride (1 equiv) in THF (~20 mL), triethylamine (3 equiv) was added. The mixture was stirred at room temperature for 15 min followed by filtration. The solvents were evaporated and the residue was purified by column chromatography.

4.1.4.1. *N*-(5-Benzylthiazol-2-yl)isobutyramide (4b). White solid; R_f 0.5 (DCM); yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.70 (s, 1H), 7.24–7.33 (m, 5H), 7.11 (s, 1H), 4.11 (s, 2H), 2.69 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 159.3, 139.5, 133.3, 132.3, 128.9, 128.6, 126.9, 35.4, 33.2, 19.4. MS (HR-ESI) for $C_{14}H_{16}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 283.0881, found: m/z 283.0881.

4.1.4.2. *N*-(5-Benzylthiazol-2-yl)cyclopentanecarboxamide (4c). White solid; $\boldsymbol{R_f}$ 0.53 (DCM); yield 60%. $^{\mathbf{1}}$H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 11.82 (s, 1H), 7.25–7.34 (m, 5H), 7.06 (s, 1H,), 4.10 (s, 2H), 2.82 (m, 1H), 1.90–1.95 (m, 4H), 1.78–1.80 (m, 2H), 1.62–1.65 (m, 2H). $^{\mathbf{13}}$C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 174.4, 159.4, 139.4, 133.2, 132.2, 128.9, 128.6, 126.9, 45.5, 33.2, 30.5, 26.1. MS (HR-ESI) for $C_{16}H_{18}N_2OSNa$ [(M+Na)$^+$], calcd: $\boldsymbol{m/z}$ 309.1038, found: $\boldsymbol{m/z}$ 309.1037.

4.1.4.3. *N*-(5-Benzylthiazol-2-yl)cyclohexanecarboxamide (4d). White solid; $\boldsymbol{R_f}$ 0.52 (DCM); yield 66%. $^{\mathbf{1}}$H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 11.97 (s, 1H), 7.24–7.32 (m, 5H), 7.05 (s, 1H), 4.08 (s, 2H), 2.33 (m, 1H), 1.81–1.93 (m, 4H), 1.71 (m, 1H), 1.52–1.64 (m, 2H), 1.15–1.28 (m, 3H). $^{\mathbf{13}}$C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 174.4, 159.5, 139.2, 133.1, 132.2, 128.9, 128.8, 126.9, 44.9, 33.2, 29.2, 25.7. MS (HR-ESI) for $C_{17}H_{20}N_2OSNa$ [(M+Na)$^+$], calcd: $\boldsymbol{m/z}$ 323.1194, found: $\boldsymbol{m/z}$ 323.1115.

4.1.4.4. *N*-(5-Benzylthiazol-2-yl)-2-cyclohexylacetamide (4e). White solid; $\boldsymbol{R_f}$ 0.51 (DCM); Yield 71%. $^{\mathbf{1}}$H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 11.69 (s, 1H), 7.18–7.33 (m, 5H), 7.08 (s, 1H), 4.10 (s, 2H), 2.32 (d, 1H, $\boldsymbol{J}$ = 7.13 Hz), 1.73–1.89 (m, 5H,), 0.91–1.34 (m, 6H). $^{\mathbf{13}}$C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 170.6, 159.3, 139.2, 132.6, 132.2, 128.9, 128.7, 127.0, 44.3, 35.3, 33.2, 26.3, 26.2, 26.1 MS (HR-ESI) for $C_{18}H_{22}N_2OSNa$ [(M+Na)$^+$], calcd: $\boldsymbol{m/z}$ 337.1350, found: $\boldsymbol{m/z}$ 337.1366.

4.1.4.5. *N*-(5-Benzylthiazol-2-yl)-3-cyclohexylpropanamide (4f). White solid; $\boldsymbol{R_f}$ 0.55 (DCM); yield 71%. $^{\mathbf{1}}$H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 7.21–7.29 (m, 5H), 7.07 (s, 1H), 4.13 (s, 2H), 2.51 (t, $\boldsymbol{J}$ = 7.9 Hz, 2H), 1.57–1.73 (m, 7H), 1.16–1.31 (m, 4H), 0.91–1.03 (m, 2H). $^{\mathbf{13}}$C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 179.8, 171.7, 138.9, 132.2, 131.4, 128.9, 128.6, 127.1, 37.4, 37.3, 32.3, 26.7, 26.6, 26.4, 26.3. MS (HR-ESI) for $C_{19}H_{24}N_2OS$ [(M+H)$^+$], calcd: $\boldsymbol{m/z}$ 329.1688, found: $\boldsymbol{m/z}$ 329.1686.

4.1.4.6. *N*-(5-Benzylthiazol-2-yl)benzamide (4h). White solid; R_f 0.71 (DCM); yield 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 and 7.21–7.64 (m, 10H), 6.78 (s, 1H), 4.06 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 159.4, 139.4, 133.9, 132.8, 129.1, 128.9, 128.8, 128.7, 128.6, 128.1, 126.9, 33.1. MS (HR-ESI) for $C_{17}H_{14}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 317.0724, found: m/z 317.0740.

4.1.4.7. *N*-(5-Benzylthiazol-2-yl)adamantane-1-carboxamide (4i). White solid; R_f 0.49 (DCM); yield 66%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.21–7.35 (m, 5H), 4.11 (s, 2H), 2.14 (m, 3H), 1.91 (m, 6H), 1.73 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.8, 158.4, 139.5, 133.8, 132.3, 128.8, 128.6, 126.9, 41.2, 38.9, 36.5, 33.1, 28.1. MS (HR-ESI) for $C_{21}H_{24}N_2OSNa$ [(M+Na)$^+$], calcd: *m*/*z* 375.1507, found: *m*/*z* 375.1515.

4.1.4.8. *N*-(5-Benzylthiazol-2-yl)-2-(thiophen-2-yl)thiazole-5-carboxamide (5h). White solid; R_f 0.58 (hexanes/EtOAc, 7:1); yield 65%.^{1}H NMR (400 MHz, $CDCl_3$): δ 10.43 (br s, 1H), 8.19 (s, 1H), 7.61 (d, *J* = 3.5 Hz, 1H), 7.47 (d, *J* = 4.8 Hz, 1H), 7.24–7.41 (m, 6H), 7.12 (d, *J* = 3.6 Hz, 1H), 4.11 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 156.5, 148.3, 139.5, 136.0, 135.2, 133.1, 129.3, 128.9, 128.7, 128.2, 128.1, 126.9, 33.2. MS (HR-ESI) for $C_{18}H_{13}N_3OS_3$[(-M+Na)$^+$], calcd: *m*/*z* 406.0118, found: *m*/*z* 406.0156.

4.1.4.9. *N*-[5-(4-Fluorobenzyl)thiazol-2-yl]cyclopentanecarboxamide (6a). White solid; R_f 0.47 (DCM); yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.83 (s, 1H), 7.18–7.21 (m, 2H), 6.96–7.03 (m, 3H), 4.03 (s, 2H), 2.8 (m, 1H), 1.92 (m, 4H), 1.77–1.79 (m, 2H), 1.60–1.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 163.1, 160.7, 136.2, 133.2, 132.1, 130.1, 115.7 45.5, 32.4, 30.5, 26.1. MS (HR-ESI) for $C_{16}H_{17}FN_2OS$ [(M+Na)$^+$], calcd: *m*/*z* 327.0943, found: *m*/*z* 327.0933.

4.1.4.10. *N*-[5-(4-Fluorobenzyl)thiazol-2-yl]cyclohexanecarboxamide (6b). White solid; R_f 0.43 (DCM); yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.02 (s, 1H), 7.2–7.26 (m, 2H), 6.97–7.02 (m, 3H), 4.05 (s, 2H), 2.36 (m, 1H), 1.79–1.89 (m, 4H), 1.67 (m, 1H), 1.49–1.62 (m, 2H), 1.11–1.30 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 163.2, 160.7, 135.0, 133.2, 132.1, 130.3, 115.6, 45.0, 32.4, 29.2, 28.3, 25.7. MS (HR-ESI) for $C_{17}H_{19}FN_2OS$ [(M+Na)$^+$], calcd: *m*/*z* 341.1100, found: *m*/*z* 341.1080.

4.1.4.11. *N*-[5-(4-Fluorobenzyl)thiazol-2-yl]-3-cyclohexanepropanamide (6c). White solid; R_f 0.44 (DCM); yield 66%.^{1}H NMR (400 MHz, $CDCl_3$): δ 12.11 (br s, 1H), 7.22 (m, 2H), 7.01 (m, 3H), 4.03 (s, 2H), 2.51 (m, 2H), 1.59–1.73 (m, 6H), 1.12–1.31 (m, 5H), 0.84–1.03 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 163.1, 160.6, 135.0, 132.9, 131.9, 130.1, 115.7, 37.3, 33.8, 33.1, 32.5, 32.2, 26.6, 26.3. MS (HR-ESI) for $C_{19}H_{23}FN_2OS$ [(M+Na)$^+$], calcd: *m*/*z* 369.1413, found: *m*/*z* 369.1427.

4.1.4.12. *N*-{5-[3-(Trifluoromethyl)benzyl]thiazol-2-yl}-3-cyclohexanepropanamide (7a). White solid; R_f 0.49 (DCM); yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.31 (br s, 1H), 7.39–7.52 (m, 4H), 7.11 (s, 1H), 4.08 (s. 2H), 2.51 (t, *J* = 8.0 Hz, 2H), 1.61–1.73 (m, 7H), 1.11–1.38 (m, 4H), 0.91–1.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 159.8, 140.3, 133.5, 132.0, 131.4, 131.1, 130.8, 129.3, 125.3, 123.9, 37.4, 33.8, 33.1, 32.9, 32.5, 26.6, 26.3. MS (HR-ESI) for $C_{20}H_{23}F_3N_2OS$ [(M+Na)$^+$], calcd: *m*/*z* 419.1378, found: *m*/*z* 419.1381.

4.1.4.13. *N*-[5-(3-Chlorobenzyl)thiazol-2-yl]-3-cyclohexanepropanamide (7b). White solid; R_f 0.55 (DCM); yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.36 (s, 1H), 7.24 (m, 3H), 7.13 (m, 2H), 4.07 (s, 2H), 2.5 (t, *J* = 7.6 Hz, 2H), 1.62–1.72 (m, 7H), 1.14–1.26 (m, 4H), 0.91–0.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 159.8, 134.7, 133.3, 131.0, 130.1, 128.7, 127.2, 126.7, 37.4, 33.8, 33.1, 32.7, 32.5, 26.6, 26.4, 26.3. MS (HR-ESI) for $C_{19}H_{23}ClN_2OS$ [(M+H)$^+$], calcd: *m*/*z* 363.1298, found: *m*/*z* 363.1302.

4.1.4.14. 3-Cyclohexane-*N*-[5-(3-fluorobenzyl)thiazol-2-yl]-propanamide (7c). White solid; R_f 0.51 (DCM); yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.37 (s, 1H), 7.32 (m, 1H), 7.13 (s, 1H), 7.01 (m, 1H), 6.92 (m, 2H), 4.06 (s, 2H), 2.5 (t, *J* = 7.7 Hz, 2H), 1.70 (m, 7H), 1.12–1.19 (m, 4H), 0.91–0.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 164.4, 161.9, 159.8, 141.8, 133.3, 131.1, 130.3, 124.2, 115.5, 114.0, 37.4, 33.8, 33.1, 32.8, 32.5, 26.6, 26.3. MS (HR-ESI) for $C_{19}H_{23}FN_2OS$ [(M+Na)$^+$], calcd: *m*/*z* 369.1413, found: *m*/*z* 369.1413.

4.1.4.15. *N*-[5-(2-Chlorobenzyl)thiazol-2-yl]-3-cyclohexanepropanamide (8a). White solid; R_f 0.53 (DCM); yield 76%.^{1}H NMR (400 MHz, $CDCl_3$): δ 12.01 (br s, 1H), 7.44 (m, 1H), 7.28 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 4.17 (s, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 1.61–1.69 (m, 7H), 1.23–1.31 (m, 4H), 0.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 159.2, 156.6, 137.2, 134.0, 133.7, 130.7, 129.9, 128.5, 127.3, 37.4, 33.8, 33.2, 32.5, 30.8, 26.6, 26.3. MS (HR-ESI) for $C_{19}H_{23}ClN_2OS$ [(M+H)$^+$], calcd: *m*/*z* 363.1298, found: *m*/*z* 363.1299.

4.1.4.16. 3-Cyclohexyl-*N*-[5-(2-fluorobenzyl)thiazol-2-yl]propanamide (8b). White solid; R_f 0.49 (DCM); yield 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.91 (s, 1H), 7.34 (m, 2H), 7.01–7.09 (m, 3H), 4.11 (s, 2H), 2.49 (m, 2H), 1.51–1.68 (m, 7H), 1.11–1.23 (m, 4H), 0.92–0.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 162.3, 159.5, 133.7, 130.9, 129.1, 126.7, 124.7, 116.0, 115.8, 37.6, 34.1, 33.4, 33.3, 32.8, 26.9, 26.6. MS (HR-ESI) for $C_{19}H_{23}FN_2OS$ [(M+Na)$^+$], calcd: *m*/*z* 369.1413, found: *m*/*z* 369.1404.

4.1.4.17. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]isobutyramide (9b). White solid; R_f 0.55 (DCM); yield 74%.^{1}H NMR (400 MHz, $CDCl_3$): δ 12.01 (s, 1H), 8.03 (m, 1H), 7.91 (m, 1H), 7.83 (m, 1H), 7.37–7.49 (m, 4H), 7.01 (s, 1H), 4.52 (s, 2H), 2.61 (m, 1H), 1.17 and 1.19(d s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 159.2, 135.2, 134.1, 133.4, 132.0, 131.7, 129.0, 128.0, 126.9, 126.4, 125.9, 125.7, 123.7, 35.2, 30.6, 19.3. MS (HR-ESI) for $C_{18}H_{18}N_2OSNa$ [(M+Na)$^+$], calcd: *m*/*z* 333.1038, found: *m*/*z* 333.1044.

4.1.4.18. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]cyclopentanecarboxamide (9c). White solid; R_f 0.52 (DCM); yield 68%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.93 (s, 1H), 8.02 (m, 1H), 7.91 (m, 1H), 7.79 (m, 1H), 7.38–7.51 (m, 4H), 7.03 (s, 1H), 4.54 (s, 2H), 2.71 (m, 1H), 1.69–1.77 (m, 6H), 1.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 159.1, 135.1, 134.2, 133.4, 131.9, 131.7, 129.0, 128.0, 126.4, 125.9, 125.7, 123.8, 45.4, 30.6, 30.4, 26.0. MS (HR-ESI) for $C_{20}H_{20}N_2OSNa$ [(M+Na)$^+$], calcd: *m*/*z* 359.1194, found: *m*/*z* 359.1200.

4.1.4.19. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (9d). White solid; R_f 0.53 (DCM); yield 63%.^{1}H NMR (400 MHz, $CDCl_3$): δ 12.33 (s, 1H), 8.04 (m, 1H), 7.93 (m, 1H), 7.81 (m, 1H), 7.44–7.48 (m, 4H), 6.81 (s, 1H), 4.53 (s, 2H), 2.21 (m, 1H), 1.69 (m, 2H), 1.41–1.77 (m, 5H), 1.11 (m, 1H), 0.83 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 159.3, 134.9, 134.2, 133.3, 131.7, 128.9, 127.2, 126.4, 125.9, 125.7, 123.9, 44.8, 30.5, 29.1, 25.6, 25.5. MS (HR-ESI) for $C_{21}H_{22}N_2OS$ [(M+H)$^+$], calcd: *m*/*z* 351.1531, found: *m*/*z* 351.1539.

4.1.4.20. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-2-cyclohexaneacetamide (9e). White solid; R_f 0.54 (DCM); yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.26 (s, 1H), 8.03 (m, 1H), 7.81–7.89 (m, 1H), 7.82 (m, 1H), 7.51 (m, 2H), 7.44 (m, 2H), 6.91 (s, 1H), 4.53 (s, 2H), 2.21 (d, *J* = 7.25 Hz, 2H), 1.81 (m, 1H), 1.63 (m, 5H), 1.01–1.23 (m, 3H), 0.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 159.1, 134.9, 134.2, 133.3, 131.7, 129.0, 128.0, 127.1, 126.4, 126.0, 125.7, 123.8, 44.1, 35.2, 33.1, 30.5, 26.2, 26.0. MS (HR-ESI) for $C_{22}H_{24}N_2OSNa$ [(M+Na)$^+$], calcd: *m*/*z* 387.1507, found: *m*/*z* 387.1499.

4.1.4.21. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (9f). White solid; R_f 0.56 (DCM); yield 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (m, 1H), 7.94 (m, 1H), 7.82 (m, 1H), 7.39–7.49 (m, 4H), 7.03 (s, 1H), 4.54 (s, 2H), 2.42 (t, J = 7.8 Hz, 2H), 1.51–1.73 (m, 7H), 1.21 (m, 4H), 0.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 159.4, 134.7, 134.2, 131.9, 131.6, 129.1, 128.2, 127.0, 126.5, 126.0, 125.7, 123.6, 37.2, 33.7, 33.1, 32.3, 30.5, 26.6, 26.2. MS (HR-ESI) for $C_{23}H_{26}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 401.1668, found: m/z 401.1675.

4.1.4.22. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]benzamide (9g). White solid; R_f 0.65 (DCM); yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.68 (s, 1H), 7.93–87.99 (m, 2H), 7.81 (m, 3H), 7.53 (m, 2H), 7.32–7.44 (m, 3H), 7.12–7.23 (m, 2H), 6.41 (s, 1H), 4.49 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 159.3, 135.0, 134.4, 134.2, 133.0, 132.5, 131.7, 129.0, 128.6, 128.1, 128.0, 127.1, 126.4, 125.9, 125.7, 123.9, 30.5. MS (HR-ESI) for $C_{21}H_{16}N_2OS$ [(M+H)$^+$], calcd: m/z 345.1062, found: m/z 345.1067.

4.1.4.23. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]adamantane-1-carboxamide (9h). White solid; R_f 0.55 (DCM); yield 65%.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.03 (m, 1H), 7.88 (m, 1H), 7.83 (m, 1H), 7.42–7.53 (m, 4H), 7.11 (s, 1H), 4.53 (s, 2H), 2.01 (m, 3H), 1.93 (m, 6H), 1.72 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 158.1, 135.2, 134.1, 132.0, 131.7, 128.9, 127.9, 127.0, 126.4, 125.9, 125.7, 123.8, 41.1, 38.8, 36.4, 30.5, 28.0. MS (HR-ESI) for $C_{25}H_{26}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 425.1664, found: m/z 425.1667.

4.1.4.24. *N*-(5-(2-Naphthalenylmethyl)thiazol-2-yl]isobutyramide (10a). White solid; R_f 0.55 (DCM); yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.03 (br s, 1H), 7.84 (m, 3H), 7.67 (s, 1H), 7.41–7.53 (m, 2H), 7.41 (dd, J = 8.4 Hz, J = 1.7 Hz, 1H), 7.21 (s, 1H), 4.32 (s, 2H), 2.71 (m, 1H), 1.26 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 160.0, 137.0, 133.7, 133.2, 132.5, 132.1, 128.6, 127.8, 126.9, 126.4, 125.9, 36.7, 34.7, 20.8. MS (HR-ESI) for $C_{18}H_{18}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 333.1038, found: m/z 333.1034.

4.1.4.25. *N*-[5-(2-Naphthalenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (10b). White solid; R_f 0.52 (DCM); yield 69%.^{1}H NMR (400 MHz, $CDCl_3$): δ 12.22, (br s, 1H), 7.81 (m, 3H), 7.74 (s, 1H), 7.52 (m, 2H), 7.32 (m, 1H), 7.04 (s, 1H), 4.21 (s, 2H), 2.33 (m, 1H), 1.76 (m, 2H), 1.70 (m, 2H), 1.51 (m, 3H), 1.03–1.21 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 159.8, 136.3, 133.7, 132.6, 132.2, 132.0, 128.7, 127.8, 127.7, 127.2, 127.0, 126.4, 125.9, 44.9, 33.3, 29.2, 25.6. MS (HR-ESI) for $C_{21}H_{22}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 373.1351, found: m/z 373.1364.

4.1.4.26. *N*-[5-(2-Naphthalenylmethyl)thiazol-2-yl]-2-cyclohexaneacetamide (10c). White solid; R_f 0.53 (DCM); yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.12 (s, 1H), 7.81 (m, 3H), 7.68 (s, 1H), 7.51 (m, 2H), 7.35 (d, J = 8.9, 1H), 7.09 (s, 1H), 4.21 (s, 2H), 2.31 (d, J = 7.2 Hz, 2H), 1.83 (m, 1H), 1.81–1.93 (m, 5H), 1.22 (m, 2H), 1.01 (m, 1H), 0.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 159.6, 136.4, 133.7, 132.6, 132.1, 128.7, 127.8, 127.1, 126.9, 126.4, 125.9, 44.2, 35.2, 33.3, 33.2, 26.2, 26.0. MS (HR-ESI) for $C_{22}H_{24}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 387.1507, found: m/z 387.1502.

4.1.4.27. *N*-[5-(2-Naphthalenylmethyl)thiazol-2-yl)-3-cyclohexanepropanamide (10d). White solid; R_f 0.54 (DCM); yield 76%.^{1}H NMR (400 MHz, $CDCl_3$): δ 12.17 (s, 1H), 7.82 (m, 3H), 7.72 (s, 1H), 7.49 (m, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.10 (s, 1H), 4.21 (s, 2H), 2.53 (t, J = 7.6 Hz, 2H), 1.62–1.73 (m, 7H), 1.14–1.21 (m, 4H), 0.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.16, 159.5, 136.8, 133.7, 133.1, 132.5, 132.0, 128.6, 127.8, 127.0, 126.9, 126.4, 125.9, 37.3, 33.8, 33.3, 33.1, 32.5, 26.6, 26.2. MS (HR-ESI) for $C_{23}H_{26}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 401.1668, found: m/z 401.1658.

4.1.4.28. *N*-[5-(2-Naphthalenylmethyl)thiazol-2-yl]benzamide (10e). White solid; R_f 0.56 (DCM); yield 72%.^{1}H NMR (400 MHz, $CDCl_3$): δ 12.53 (br s, 1H), 7.91–8.03 (m, 2H), 7.81 (m, 3H), 7.78 (s, 1H), 7.54 (m, 2H), 7.31 (m, 3H), 6.67 (s, 1H), 4.21 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 161.0, 138.2, 135.6, 135.1, 134.7, 134.2, 134.0, 133.9, 133.5, 131.5, 130.0, 129.5, 129.2, 128.5, 127.8, 127.3, 34.6. MS (HR-ESI) for $C_{21}H_{16}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 367.0881, found: m/z 367.0898.

4.1.4.29. *N*-[5-(2-Naphthalenylmethyl)thiazol-2-yl)adamantane-1-carboxamide (10f). White solid; R_f 0.64 (DCM); yield 77%.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 7.81 (m, 3H), 7.70 (s, 1H), 7.43–7.51 (m 2H), 7.39 (d, J = 8.6 Hz, 1H), 7.21 (s, 1H), 4.22 (s, 2H), 2.18 (m, 3H), 2.01 (s, 1H), 1.89 (s, 5H), 1.74 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ175.7, 158.4, 137.0, 134.1, 133.7, 132.5, 132.2, 128.6, 127.8, 127.0, 126.3, 125.8, 41.1, 38.9, 36.4, 33.3, 28.0. MS (HR-ESI) for $C_{25}H_{26}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 425.1664, found: m/z 425.1672.

4.1.4.30. *N*-(5-Phenethylthiazol-2-yl)cyclopentanecarboxamide (11a). White solid; R_f 0.45 (DCM); yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.11 (s, 1H), 7.33 (m, 2H), 7.21 (m, 3H), 6.93 (s, 1H), 3.12 (m, 2H), 3.01 (m, 2H), 2.85 (m, 1H), 1.91 (m, 4H), 1.82 (m, 2H), 1.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 158.8, 140.6, 132.5, 131.9, 128.6, 126.4, 45.4, 37.6, 30.5, 28.7, 26.2. MS (HR-ESI) for $C_{17}H_{20}N_2OS$ [(M+Na)$^+$], calcd: m/z 323.1194, found: m/z 323.1148.

4.1.4.31. *N*-(5-Phenethylthiazol-2-yl)-3-cyclohexanepropanamide (11b). White solid; R_f 0.47 (DCM); yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.24 (s, 1H), 7.21–7.33 (m, 5H), 7.03 (s, 1H), 3.11 (m, 2H), 3.01 (m, 2H), 2.53 (t, J = 7.6 Hz), 1.59–1.73 (m, 7H), 1.11–1.31 (m, 4H), 0.89–1.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 158.7, 140.6, 132.7, 132.0, 128.5, 126.5, 37.6, 37.4, 33.8, 33.2, 32.6, 28.8, 26.6, 26.3. MS (HR-ESI) for $C_{20}H_{26}N_2OS$ [(M+H)$^+$], calcd: m/z 365.1664, found: m/z 365.1664.

4.1.4.32. *N*-(5-Phenylthiazol-2-yl)cyclopentanecarboxamide (12a). White solid; $\boldsymbol{R_f}$ 0.43 (DCM); yield 75%. $^{\mathbf{1}}$H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 12.52 (s, 1H), 7.62 (m, 3H), 7.43 (t, $\boldsymbol{J}$ = 7.7 Hz, 2H), 7.31 (m, 1H), 3.01 (m, 1H), 2.05 (m, 4H), 1.78 (m, 2H), 1.70 (m, 2H). $^{\mathbf{13}}$C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 174.8, 159.5, 132.9, 131.9, 131.4, 129.3, 128.0, 126.3, 45.5, 30.6, 26.2. MS (HR-ESI) for $C_{15}H_{16}N_2OS$[(M+Na)$^+$], calcd: $\boldsymbol{m/z}$ 295.0881, found: $\boldsymbol{m/z}$ 295.0886.

4.1.4.33. *N*-(5-Phenylthiazol-2-yl)cyclohexanecarboxamide (12b). White solid; $\boldsymbol{R_f}$ 0.41 (DCM); yield 69%. $^{\mathbf{1}}$H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 12.33 (s, 1H), 7.51 (m, 2H), 7.43 (m, 2H), 7.30 (m, 1H), 2.53 (m, 1H), 2.01 (m, 2H), 1.89 (m, 2H), 1.61–1.78 (m, 3H), 1.19–1.51 (m, 3H). $^{\mathbf{13}}$C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 174.5, 159.4, 132.9, 131.8, 131.5, 129.3, 128.0, 126.2, 45.0, 29.3, 25.9, 25.7. MS (HR-ESI) for $C_{16}H_{18}N_2OS$ [(M+H)$^+$], calcd: $\boldsymbol{m/z}$ 309.1038, found: $\boldsymbol{m/z}$ 309.1037.

4.1.4.34. *N*-(5-Phenylthiazol-2-yl)-2-cyclohexaneacetamide (12c). White solid; $\boldsymbol{R_f}$ 0.43 (DCM); yield 78%. $^{\mathbf{1}}$H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 12.39 (s, 1H), 7.61 (s, 1H), 7.58 (d, $\boldsymbol{J}$ = 7.8 Hz, 2H), 7.45 (t, $\boldsymbol{J}$ = 6.8 Hz, 1H), 7.32 (t, $\boldsymbol{J}$ = 7.6 Hz, 1H), 2.50 (d, $\boldsymbol{J}$ = 7.12 Hz, 2H), 2.0 (m, 1H), 1.84 (d, $\boldsymbol{J}$ = 12.27 Hz, 2H), 1.72 (m, 3H), 1.01–1.39 (m, 6H). $^{\mathbf{13}}$C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 170.8, 159.2, 132.9, 131.6, 131.5, 129.3, 128.1, 126.3, 44.3, 36.4, 33.4, 26.2, 26.1. MS (HR-ESI) for $C_{17}H_{20}N_2OS$[(M+Na)$^+$], calcd: $\boldsymbol{m/z}$ 323.1194, found: $\boldsymbol{m/z}$ 323.1182.

4.1.4.35. *N*-(5-Phenylthiazol-2-yl)-3-cyclohexanepropanamide (12d). White solid; R_f 0.45 (DCM); yield 66%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.61 (s, 1H), 7.59 (s, 1H), 7.51 (d, J = 7.7 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.31 (m, 1H), 2.55 (t, J = 7.9 Hz, 2H), 1.61–1.84 (m, 7H), 1.09–1.41 (m, 4H), 0.89–1.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 159.5, 132.8, 131.6, 131.4, 129.3, 128.0, 126.2, 37.5, 34.0, 33.2, 32.6, 26.6, 26.3. MS (HR-ESI) for $C_{18}H_{13}N_2OS$ [(M+H)$^+$], calcd: m/z 315.1531, found: m/z 315.1517.

4.1.4.36. *N*-[5-(Cyclohexylmethyl)thiazol-2-yl]isobutyramide (13a). White solid; $\boldsymbol{R_f}$ 0.33 (DCM); yield 61%.^{1}H NMR (400 MHz, $\boldsymbol{CDCl_3}$): $\boldsymbol{\delta}$ 12.08 (br s, 1H), 7.01 (s, 1H), 2.73 (m, 1H), 2.60 (d, $\boldsymbol{J}$ = 7.01 Hz, 2H), 1.68–1.76 (m, 4H), 1.52 (m, 1H), 1.17–1.28 (m, 10H), 0.90–0.99 (m, 2H). ^{13}C NMR (100 MHz, $\boldsymbol{CDCl_3}$): $\boldsymbol{\delta}$ 175.2, 158.8, 133.0, 131.7, 39.8, 35.4, 34.6, 33.1, 26.5, 26.3, 19.4. MS (HR-ESI) for $\boldsymbol{C_{14}H_{22}N_2OSNa}$ [(M+Na)$^+$], calcd: $\boldsymbol{m/z}$ 289.1351, found: $\boldsymbol{m/z}$ 289.1352.

4.1.4.37. *N*-[5-(Cyclohexylmethyl)thiazol-2-yl]cyclohexanecarboxamide (13b). White solid; R_f 0.32 (DCM); yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.08 (s, 1H), 7.01 (s, 1H), 2.73 (d, J = 6.9 Hz, 2H), 2.43 (m, 1H), 1.78–2.02 (m, 4H), 1.51–1.79 (m, 8H), 1.11–1.29 (m, 7H), 1.0 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 158.8, 133.0, 131.6, 45.0, 39.7, 34.6, 33.1, 29.8, 29.3, 26.5, 26.3, 25.8. MS (HR-ESI) for $C_{17}H_{26}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 329.1664, found: m/z 329.1661.

4.1.4.38. *N*-[5-(Cyclohexylmethyl)thiazol-2-yl]-2-cyclohexaneacetamide (13c). White solid; R_f 0.35 (DCM); yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.19 (br s, 1H), 7.03 (s, 1H), 2.62 (d, J = 7.2 Hz, 2H), 2.39 (d, J = 6.7 Hz, 2H), 1.89 (m, 1H), 1.61–1.84 (m, 10H), 1.51 (m, 1H), 1.09–1.31 (m, 6H), 0.91–0.99 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 158.7, 133.0, 131.6, 44.3, 39.7, 35.4, 34.6, 33.3, 33.2, 33.1, 26.5, 26.3, 26.1. MS (HR-ESI) for $C_{18}H_{28}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 343.1820, found: m/z 343.1820.

4.1.4.39. *N*-[5-(Cyclohexylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (13d). White solid; R_f 0.36 (DCM); yield 60%.^{1}H NMR (400 MHz, $CDCl_3$): δ 12.29 (br s, 1H), 7.03 (s, 1H), 2.62 (d, J = 7.0 Hz, 2H), 2.52 (t, J = 7.6 Hz, 2H), 1.57–1.69 (m, 11H), 1.53 (m, 1H), 1.22–1.31 (m, 8H), 0.89–1.0 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 158.8, 133.0, 131.6, 39.7, 37.5, 34.6, 33.9, 33.2, 33.1, 32.7, 26.7, 26.5, 26.3, 26.2. MS (HR-ESI) for $C_{19}H_{30}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 335.2157, found: m/z 335.2164.

4.1.4.40. *N*-[5-(Cyclohexylmethyl)thiazol-2-yl]benzamide (13e). White solid; $\boldsymbol{R_f}$ 0.45 (DCM); yield 65%. ^{1}H NMR (400 MHz, $\boldsymbol{CDCl_3}$): $\boldsymbol{\delta}$ 8.11 (d, $\boldsymbol{J}$ = 7.5 Hz, 2H), 7.57 (m, 1H), 7.51 (m, 2H), 2.63 (d, $\boldsymbol{J}$ = 7.1 Hz, 2H), 1.71–1.84 (m, 4H), 1.52 (m, 1H), 1.11–1.29 (m, 4H), 0.92–1.0 (m, 2H). ^{13}C NMR (100 MHz, $\boldsymbol{CDCl_3}$): $\boldsymbol{\delta}$ 165.7, 158.9, 133.7, 132.7, 130.1, 128.9, 128.5, 128.2, 39.7, 34.5, 33.1, 26.5, 26.3. MS (HR-ESI) for $\boldsymbol{C_{17}H_{20}N_2OSNa}$ [(M+Na)$^+$], calcd: $\boldsymbol{m/z}$ 323.1194, found: $\boldsymbol{m/z}$ 323.1197.

4.1.4.41. *N*-[5-(Cyclohexylmethyl)thiazol-2-yl]adamantane-1-carboxamide (13f). White solid; R_f 0.34 (DCM); yield 72%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (s, 1H), 2.61 (d, J = 6.97 Hz, 2H), 2.11 (m, 3H), 1.93 (m, 6H), 1.62–1.84 (m, 9H), 1.22–1.33 (m, 6H), 0.81–1.0 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 158.3, 131.9, 131.3, 41.3, 39.7, 38.9, 36.4, 34.5, 33.0, 28.0, 26.4, 26.2. MS (HR-ESI) for $C_{21}H_{30}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 381.1977, found: m/z 381.1970.

4.1.4.42. *N*-(5-Benzyl-1,3,4-thiadiazol-2-yl)-3-cyclohexylpropanamide (14a). White solid; R_f 0.56 (DCM); yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.21 (s, 1H), 7.29–7.40 (m, 5H), 4.31 (s, 2H), 2.83 (m, 2H), 1.57–1.80 (m, 7H), 1.11–1.41 (m, 5H), 0.90–1.0 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 164.1, 161.3, 137.1, 129.1, 128.9, 127.6, 37.4, 36.4, 34.0, 33.1, 32.7, 32.1, 29.8, 26.7, 26.4. MS (HR-ESI) for $C_{18}H_{23}N_3OS$ [(M+Na)$^+$], calcd: m/z 352.1455, found: m/z 352.1460.

4.1.4.43. *N*-(5-Benzyl-4-methylthiazol-2-yl)-3-cyclohexylpropanamide (14c). White solid; R_f 0.5 (DCM); yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.33 (m, 5H), 4.0 (s, 2H), 2.41 (t, J = 7.8 Hz, 2H), 2.31 (s, 3H), 1.63–1.71 (m, 6H), 1.22–1.34 (m, 4H), 0.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 155.3, 141.8, 139.8, 128.8, 128.4, 126.8, 124.8, 37.2, 34.0, 33.1, 32.6 32.2, 29.9, 26.6, 26.3, 14.8. MS (HR-ESI) for $C_{20}H_{26}N_2OS$ [(M+Na)$^+$], calcd: m/z 365.1664, found: m/z 365.1665.

4.1.4.44. *N*-(4-Phenylthiazol-2-yl)cyclopentanecarboxamide (15a). White solid; $\boldsymbol{R_f}$ 0.44 (DCM); yield 63%. ^{1}H NMR (400 MHz, $\boldsymbol{CDCl_3}$): $\boldsymbol{\delta}$ 11.10 (s, 1H), 7.81 (d, $\boldsymbol{J}$ = 7.1, 2H), 7.41 (t, $\boldsymbol{J}$ = 7.5 Hz, 2H), 7.33 (t, $\boldsymbol{J}$ = 7.1, 1H), 7.11 (s, 1H), 2.32 (m, 1H), 1.54 (m, 4H), 1.51 (m, 2H), 1.34 (m, 2H). ^{13}C NMR (100 MHz, $\boldsymbol{CDCl_3}$): $\boldsymbol{\delta}$ 175.1, 159.8, 149.9, 134.5, 129.1, 128.4, 126.4, 108.0, 45.3, 30.4, 25.9. MS (HR-ESI) for $\boldsymbol{C_{18}H_{22}N_2OSNa}$ [(M+Na)$^+$], calcd: $\boldsymbol{m/z}$ 295.0881, found: $\boldsymbol{m/z}$ 295.0887.

4.1.4.45. *N*-(4-Phenylthiazol-2-yl)-3-cyclohexanepropanamide (15b). White solid; R_f 0.46 (DCM); yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.43 (s, 1H), 7.81 (d, J = 6.5 Hz, 2H),7.43 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 6.5 Hz, 1H), 7.19 (s, 1H), 2.01 (t, J = 7.7 Hz, 2H), 1.63 (m, 3H), 1.31–1.40 (m, 4H), 1.11 (m, 3H), 0.83 (m, 1H), 0.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 159.9, 149.6, 134.4, 129.1, 128.5, 126.3, 107.9, 37.1, 33.5, 32.8, 32.0, 26.5, 26.3. MS (HR-ESI) for $C_{18}H_{22}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 337.1351, found: m/z 337.1338.

4.1.4.46. *N*-[4-(Adamantan-1-yl)thiazol-2-yl]isobutyramide (15c). White solid; $\boldsymbol{R_f}$ 0.5 (DCM); yield 65%. ^{1}H NMR (400 MHz, $\boldsymbol{CDCl_3}$): $\boldsymbol{\delta}$ 8.81 (br s, 1H), 6.53 (s, 1H), 2.59 (m, 1H), 2.09 (m, 3H), 1.92 (m, 6H), 1.74 (m, 6H), 1.31 (d, $\boldsymbol{J}$ = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $\boldsymbol{CDCl_3}$): $\boldsymbol{\delta}$ 174.3, 161.3, 157.0, 106.2, 42.2, 36.9, 26.3, 35.8, 29.8, 28.1, 19.3. MS (HR-ESI) for $\boldsymbol{C_{17}H_{24}N_2OSNa}$ [(M+Na)$^+$], calcd: $\boldsymbol{m/z}$ 327.1507, found: $\boldsymbol{m/z}$ 327.1505.

4.1.4.47. *N*-[4-(Adamantan-1-yl)thiazol-2-yl]cyclopentanecarboxamide (15d). White solid; R_f 0.53 (DCM); yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (br s, 1H), 6.53 (s, 1H), 2.67 (m, 1H), 2.08 (m, 3H), 1.93 (m, 10H), 1.81 (m, 8H), 1.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 161.2, 157.2, 106.0, 45.8, 42.2, 36.9, 36.3, 30.4, 28.7, 26.1. MS (HR-ESI) for $C_{19}H_{26}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 353.1664, found: m/z 353.1675.

4.1.4.48. *N*-[4-(Adamantan-1-yl)thiazol-2-yl]cyclohexanecarboxamide (15e). White solid; R_f 0.55 (DCM); yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (br s, 1H), 6.51 (s, 1H), 2.32 (m, 1H), 1.83–2.11 (m, 20 H), 1.65–1.55 (m, 2H), 1.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 161.1, 157.5, 105.0, 45.3, 42.1, 36.9, 36.3, 29.4, 28.7, 25.7, 25.6. MS (HR-ESI) for $C_{20}H_{28}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 367.1820, found: m/z 367.1823.

4.1.4.49. *N*-[4-(Adamantan-1-yl)thiazol-2-yl]-2-cyclohexylacetamide (15f). White solid; R_f 0.54 (DCM); yield 68%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 6.53 (s, 1H), 2.28 (s, 2H), 2.11 (s, 3H), 1.87 (s, 6H), 1.76 (m, 14H), 1.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 164.0, 159.9, 107.8, 47.4, 45.0, 39.7, 39.1, 38.2, 36.0, 31.5, 28.9, 25.6. MS (HR-ESI) for $C_{21}H_{30}N_2OSNa$ [(M+Na)$^+$], calcd: m/z 381.1977, found: m/z 381.1989.

4.1.4.50. *N*-[4-(Adamantan-1-yl)thiazol-2-yl]-3-cyclohexylpropanamide (15g). White solid; R_f 0.51 (DCM); yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 6.51 (s, 1H), 2.44 (t, J = 8.1 Hz,2H), 2.11 (s, 3H), 1.91 (m, 6H), 1.64–1.79 (m, 12 H), 1.21–1.29 (m, 5H), 0.82–0.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 161.1, 157.5, 105.0, 42.1, 36.9, 36.3, 34.1, 33.1, 32.5, 28.9, 26.5, 26.3. MS (HR-ESI) for $C_{22}H_{32}N_2OSNa$ [$(M+Na)^+$], calcd: m/z 395.2133, found: m/z 395.2143.

4.1.4.51. *N*-[4-(Adamantan-1-yl)thiazol-2-yl]benzamide (15h). White solid; $\boldsymbol{R_f}$ 0.64 (DCM); yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 8.01 (d, $\boldsymbol{J}$ = 7,2 Hz, 2H), 7.41–7.63 (m, 3H), 6.61 (s, 1H), 2.07 (m, 3H), 2.01 (m, 6H), 1.83 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 164.6, 161.4, 157.9, 132.9, 132.4, 129.1, 127.6, 106.5, 42.14, 37.0, 36.4 28.7. MS (HR-ESI) for $\boldsymbol{C_{20}H_{22}N_2OSNa}$ [$(M+Na)^+$], calcd: $\boldsymbol{m/z}$ 361.1351, found: $\boldsymbol{m/z}$ 361.1350.

4.1.5. General procedure for the synthesis of compounds 4a and 9a

TFAA (1.4 equiv) was added drop wise to a solution of compound **3a** or **3b** (1 equiv) in DCM (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. Subsequently, the solvent was evaporated, the residue treated with a saturated aqueous solution of $NaHCO_3$, extracted with EtOAc, and washed with water and then brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography.

4.1.5.1. *N*-(5-Benzylthiazol-2-yl)trifluoroacetamide (4a). White solid; $\boldsymbol{R_f}$ 0.41 (DCM); yield 56%. ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 13.77 (br s, 1H), 7.18–7.31 (m, 5H), 7.11 (s, 1H), 4.09 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 167.2, 161.2, 137.8, 132.3, 129.2, 128.6, 127.5, 124.6, 115.4, 33.6. MS (HR-ESI) for $\boldsymbol{C_{12}H_9F_3N_2OS}$ [$(M+Na)^+$], calcd: $\boldsymbol{m/z}$ 309.0285, found: $\boldsymbol{m/z}$ 309.0278.

4.1.5.2. *N*-[5-(Naphthalen-1-ylmethyl)thiazol-2-yl]trifluoroacetamide (9a). White solid; R_f 0.55 (DCM); yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.86 (br s, 1H), 7.81–8.03 (m, 3H), 7.42–7.48 (m, 4H), 7.11 (s, 1H), 4.51, (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 161.5, 134.2, 133.6, 132.1, 131.4, 129.2, 128.6, 127.2, 126.7, 126.2, 125.7, 124.8, 123.3, 115.4, 30.9. MS (HR-ESI) for $C_{16}H_{11}F_3N_2OS$ [$(M+Na)^+$], calcd: m/z 359.0442, found: m/z 359.0440.

4.1.6. General procedure for the synthesis of compounds 4g, 5a–5c, and 5g

To a mixture of compound **3a** (1 equiv), alicyclic carboxylic acid (1.3 equiv), DMAP (0.45 equiv), triethylamine (1.8 equiv) in DCM/DMF (~2 mL 3:1, v:v) was added EDAC (1.8 equiv) at room temperature. The reaction mixture was stirred for 2 h, diluted with EtOAc, and washed with brine, aqueous HCl (0.2 N), and aqueous sodium bicarbonate solution. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography.

4.1.6.1. (*E*)-*N*-(5-Benzylthiazol-2-yl)-3-cyclohexylacrylamide (4g). White solid; $\boldsymbol{R_f}$ 0.69 (DCM/MeOH, 97:3); yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 11.92 (br s, 1H), 7.22–7.33 (m, 5H), 7.11 (s, 1H), 7.01 (dd, $\boldsymbol{J}$ = 15.5 Hz, $\boldsymbol{J}$ = 6.4 Hz, 1H), 6.03 (d, $\boldsymbol{J}$ = 15.2 Hz, 1H), 4.13 (s, 2H), 2.23 (m, 1H), 1.71–1.94 (m, 5H), 1.01–1.41 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 163.9, 154.0, 139.3, 133.5, 128.9, 128.7, 127.0, 119.5, 40.8, 33.2, 31.8, 26.1, 25.9. MS (HR-ESI) for $\boldsymbol{C_{19}H_{22}N_2OS}$ [$(M+Na)^+$], calcd: $\boldsymbol{m/z}$ 349.1351, found: $\boldsymbol{m/z}$ 349.1356.

4.1.6.2. *N*-(5-Benzylthiazol-2-yl)tetrahydro-2*H*-thiopyran-4-carboxamide (5a). White solid; R_f 0.55 (DCM/MeOH, 99:1); yield 39%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.31 (s, 1H), 7.32 (m, 2H), 7.21 (m, 3H), 7.03 (s, 1H), 4.09 (s, 1H), 2.71 (m, 2H), 2.53 (m, 2H), 2.38 (m, 2H), 2.19 (m, 1H), 1.91–2.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 159.5, 139.0, 133.0, 132.9, 129.0, 128.7, 127.1, 44.4, 33.2, 30.0, 27.8. MS (HR-ESI) for $C_{16}H_{18}N_2OS_2$ [$(M+H)^+$], calcd: m/z 341.0758, found: m/z 341.0745.

4.1.6.3. *N*-(5-Benzylthiazol-2-yl)tetrahydro-2*H*-pyran-4-carboxamide (5b). White solid; R_f 0.49 (DCM/MeOH, 19:1); yield 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.13 (s, 1H), 7.33–7.41 (m, 2H), 7.22 (m, 3H), 7.02 (s, 1H), 4.11 (s, 2H), 4.04 (d, J = 10.9 Hz, 2H), 3.33 (t, J = 10.9 Hz, 2H), 2.61–2.73 (m, 1H), 1.88–2.02 (m, 2H), 1.70 (d, J = 13.0 Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 159.4, 139.1, 132.9, 132.8, 129.0, 128.7, 127.1, 67.1, 41.88, 33.2, 28.8. MS (HR-ESI) for $C_{16}H_{18}N_2O_2S$ [$(M+Na)^+$], calcd: m/z 325.0987, found: m/z 325.0976.

4.1.6.4. *N*-(5-Benzylthiazol-2-yl)-1-methylpiperidine-4-carboxamide (5c). White solid; R_f 0.53 (DCM/MeOH, 4:1); yield 20%. ^{1}H NMR (400 MHz, CD_3OD): δ 7.21–7.34 (m, 5H), 7.11 (s, 1H), 4.03 (s, 2H), 2.91 (m, 2H), 2.48 (m, 1H), 2.31 (s, 3H), 2.11–2.21 (m, 2H), 1.78–1.91 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD): δ 175.0, 159.3, 141.4, 135.4, 133.9, 129.8, 129.5, 127.8, 55.8, 46.3, 42.6, 33.7, 29.2. MS (HR-ESI) for $C_{17}H_{21}N_3OS$ [$(M+H)^+$], calcd: m/z 316.1484, found: m/z 316.1479.

4.1.6.5. *N*-(5-Benzylthiazol-2-yl)chromane-3-carboxamide (5g). White solid; $\boldsymbol{R_f}$ 0.73 (DCM/MeOH, 97:3); yield 21%. ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 7.01–7.31 (m, 8H), 6.93 (m, 2H), 4.49 (m, 1H), 4.21 (t, $\boldsymbol{J}$ = 10.1 Hz, 1H), 4.01 (s, 2H), 3.23–3.31 (m, 1H), 3.11–3.219 (m, 1H), 3.0 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 171.3, 168.8, 159.9, 155.4, 140.7, 134.7, 134.4, 131.3, 129.9, 129.3, 128.4, 122.6, 121.6, 118.4, 68.3, 41.3, 34.5, 29.5. MS (HR-ESI) for $\boldsymbol{C_{20}H_{18}N_2O_2S}$ [$(M+Na)^+$], calcd: $\boldsymbol{m/z}$ 373.0987, found: $\boldsymbol{m/z}$ 373.0995.

4.1.7. Synthesis of compound 14b and 16a

To an ice-cooled mixture of NaH (40 mg, 60% in mineral oil, 1.6 mmol) in THF (10 mL) was added drop wise a solution of compound **4f** (0.25 g, 0.76 mmol) in THF (5 mL). The mixture was stirred at room temperature for 20 min, again cooled to 0 °C, and methyl iodide (120 μL, 1.9 mmol) was added drop wise. The mixture was then stirred at room temperature for 2 h. Water (5 mL) was added to quench the reaction and the mixture was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, evaporated, and the residue was separated/purified by silica gel chromatography to afford products **14b** and **16a**.

4.1.7.1. *N*-(5-Benzylthiazol-2-yl)-3-cyclohexyl-*N*-methylpropanamide (14b). White solid; R_f 0.69 (hexane/EtOAc, 7:3); yield 38%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.34 (m, 6H), 4.11 (s, 2H), 3.72 (s, 3H), 2.63 (m, 2H), 1.56–1.83 (m, 7H), 1.11–1.39 (m, 4H), 0.91–1.04 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 159.5, 139.9, 134.0, 133.9, 128.8. 128.6, 126.7, 37.3, 34.5, 33.2, 33.1, 32.3, 32.0, 26.6, 26.3. MS (HR-ESI) for $C_{20}H_{26}N_2OS$ [$(M+H)^+$], calcd: m/z 343.1844, found: m/z 343.1830.

4.1.7.2. (*E*)-*N*-(5-Benzyl-3-methylthiazol-2(3*H*)-ylidene)-3-cyclohexylpropanamide (16a). White solid; R_f 0.49 (hexane/EtOAc, 7:3); yield 32%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.43 (m, 5H), 6.53 (s, 1H), 3.89 (s, 2H), 3.62 (s, 3H), 2.51 (m, 2H), 1.62–1.83 (m, 7H), 1.09–1.34 (m, 4H), 0.81–1.0 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.3, 166.9, 138.1, 129.0, 128.8, 127.2, 125.7, 122.6, 37.6, 37.5, 35.4, 33.9, 33.5, 33.4, 26.8, 26.5. MS (HR-ESI) for $C_{20}H_{26}N_2S$ [$(M+H)^+$], calcd: m/z 343.1844, found: m/z 343.1827.

4.1.8. General procedure for the synthesis of compounds 5d–5f and 16b–16d

A mixture of compound **3a** (1 equiv), acid chloride (1 equiv), and DMAP (1.2 equiv) in DCM (~2 mL) was stirred for 2 h at room temperature. The solvent was evaporated and the residue was purified by silica gel column chromatography.

4.1.8.1. *N*-(5-Benzylthiazol-2-yl)pyrrolidine-1-carboxamide (5d). White solid; R_f 0.51 (EtOAc/hexanes, 1:1); yield 5%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (br s, 1H), 7.21–7.39 (m, 4H), 7.01 (s, 1H), 4.11 (s, 2H), 3.48 (s, 4H), 2.03 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 152.1, 139.8, 133.7, 131.31, 128.8, 128.6, 126.8, 46.0, 33.2, 29.9. MS (HR-ESI) for $C_{15}H_{17}N_3OS$ [$(M+Na)^+$], calcd: ***m/z*** 310.0990, found: ***m/z*** 310.0991.

4.1.8.2. *N*-(5-Benzylthiazol-2-yl)piperidine-1-carboxamide (5e). White solid; R_f 0.49 (EtOAc/hexanes, 1:1); yield 8%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.33 (m, 5H), 7.02 (s, 1H), 4.04 (s, 2H), 3.41 (m, 4H), 1.47–1.68 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 153.1, 139.7, 133.3, 128.8, 128.6, 126.8, 45.3, 33.2, 29.9, 25.7, 24.4. MS (HR-ESI) for $C_{16}H_{19}N_3OS$ [$(M+H)^+$], calcd: ***m/z*** 302.1327, found: ***m/z*** 302.1326.

4.1.8.3. *N*-(5-Benzylthiazol-2-yl)morpholine-4-carboxamide (5f). White solid; R_f 0.54 (DCM/MeOH, 19:1); yield 7%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (br s, 1H), 7.32 (m, 5H), 6.93 (s, 1H), 4.03 (s, 2H), 3.69 (m, 4H), 3.54 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 155.6, 140.9, 133.7, 132.8, 130.2, 130.0, 128.3, 68.0, 45.69, 34.5, 31.3. MS (HR-ESI) for $C_{15}H_{17}N_3O_2S$ [$(M+H)^+$], calcd: ***m/z*** 304.1120, found: ***m/z*** 304.1127.

4.1.8.4. *N*-[5-Benzyl-3-(pyrrolidine-1-carbonyl)thiazol-2(3*H*)-ylidene]pyrrolidine-1-carboxamide (16b). White solid; R_f 0.72 (EtOAc/hexanes, 1:1); yield 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.43 (m, 5H), 6.61 (s, 1H), 3.93 (s, 2H), 3.41–3.69 (m, 8H), 1.87–2.01 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 160.7, 150.4, 137.7, 129.0, 128.9, 127.1, 124.9, 117.9, 47.7, 46.6, 45.5, 34.2, 25.3, 24.9. MS (HR-ESI) for $C_{20}H_{24}N_4O_2S$ [$(M+Na)^+$], calcd: *m/z* 407.1518, found: *m/z* 407.1587.

4.1.8.5. *N*-[5-Benzyl-3-(piperidine-1-carbonyl)thiazol-2(3*H*)-ylidene]piperidine-1-carboxamide (16c). White solid; R_f 0.68 (EtOAc/hexanes, 1:1); yield 27%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.34 (m, 5H), 6.51 (s, 1H), 3.83 (s, 2H), 3.51–3.73 (m, 6H), 3.18 (m, 2H), 1.41–1.83 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 161.0, 150.9, 137.7, 128.9, 128.8, 127.1, 125.1, 118.2, 45.6, 43.8, 34.2, 26.4, 26.0, 24.9, 24.2. MS (HR-ESI) for $C_{22}H_{28}N_4O_2S$ [$(M+Na)^+$], calcd: *m/z* 435.1831, found: *m/z* 435.1821.

4.1.8.6. *N*-(5-Benzyl-3-(morpholine-4-carbonyl)thiazol-2(3*H*)-ylidene)morpholine-4-carboxamide (16d). White solid; R_f 0.64 (DCM/MeOH, 19:1) yield 23%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.34 (m, 5H), 6.56 (s, 1H), 3.81 (s, 2H), 3.49–3.77 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 161.1, 150.8, 137.4, 129.0, 128.9, 127.3, 125.8, 118.2, 67.0, 66.5, 45.1, 43.3, 34.2. MS (HR-ESI) for $C_{20}H_{24}N_4O_4S$ [$(M+Na)^+$], calcd: *m/z* 439.1416, found: *m/z* 439.1413.

4.2. Biology

4.2.1. Fungal strains and culture

The *Histoplasma capsulatum* strain used in this study was the wild-type strain G217B (ATCC 26032). *Histoplasma* cells were maintained as yeasts by growth in *Histoplasma*-macrophage media (HMM)[34] at 37 °C in 95% air/5% CO_2. The *Cryptococcus* strain used was the wild-type MATα serotype A strain H99 (kindly provided by Tamara Doering). *Cryptococcus* yeasts were cultured in YPD medium at 37 °C for routine maintenance or in HEPES-buffered RPMI for growth in microtiter plates for dose response measurements. For determination of the concentration of drug that inhibits 50% fungal growth (MIC_{50}), *Histoplasma* or *Cryptococcus* yeasts were cultured in 96-well microtiter plates with a two-fold dilution series of each compound from 40 μM to 0.078 μM in 100 μL of their respective growth medium. Wells were inoculated with 2×10^5 *Histoplasma* yeasts or 2×10^2 *Cryptococcus* yeasts (determined by hemocytometer counts) and plates were agitated twice daily for improved aeration. Yeast growth was monitored by absorbance at 595 nm over 5 days (*Histoplasma*) or 4 days (*Cryptococcus*) using a Synergy2 plate reader (BioTek). The turbidity in each well was normalized to control wells lacking the antifungal compound but with an equivalent amount of DMSO solvent (the 40 μM compound dilution contained 1% DMSO). Relative turbidity measurements at 4 days (*Histoplasma*) or 3 days (*Cryptococcus*) were used for linear regression analysis and MIC_{50} determination. The minimal inhibitory concentration preventing visible growth of fungi (MIC) was determined by inspection of plates and visual assessment of growth or no-growth. Compounds with an MIC_{50} <3.5 μM in *Histoplasma* yeasts were also evaluated in *Cryptococcus* yeasts. All compounds with an initial MIC_{50} <4.5 μM were evaluated in triplicate.

4.2.2. Evaluation of mammalian-cell toxicity

Cytotoxicity was evaluated using the human hepatocyte cell line HepG2 (ATCC HB-8065) for selected compounds with an $MIC_{50} \leqslant 1.6$ μM for *Histoplasma* yeasts. For mammalian cell culture, cells were maintained at 37 °C under 5% CO_2/95% air in Minimum Essential Medium (MEM) supplemented with 10% fetal bovine serum (FBS) and 2 mM L-glutamine. Mammalian cells were seeded into wells of a 96-well microtiter plate at 1×10^4 cells per well and allowed to adhere overnight. Antifungal compounds were subsequently added to cells in a concentration range from 80 μM to 0.3 μM. After 72 h, HepG2 cells were quantified by measuring cell mass by crystal violet staining.[35] Briefly, the growth medium was removed and cells washed once with phosphate-buffered saline (PBS). Cells were fixed in 3% paraformaldehyde, and stained with 0.1% crystal violet. Residual stain was removed by washing cells repeatedly with water and the retained crystal violet was solubilized in 10% acetic acid for 20 min with agitation. The retained dye was quantified by absorbance at 590 nm and normalized to untreated samples. Assays were performed on three replicates. Results were compared to control wells that lacked aminothiazole but contained an equivalent amount of DMSO as mammalian cell growth was decreased at solvent concentrations above 2%.

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References and notes

1. (a) Brown, G. D.; Denning, D. W.; Levitz, S. M. *Science* **2012**, *336*, 647; (b) Pfaller, M. A.; Diekema, D. J. *Crit. Rev. Microbiol.* **2010**, *36*, 1.
2. Park, B. J.; Wannemuehler, K. A.; Marston, B. J.; Govender, N.; Pappas, P. G.; Chiller, T. M. *AIDS* **2009**, *23*, 525.
3. (a) Galanis, E.; Hoang, L.; Kibsey, P.; Morshed, M.; Phillips, P. *Can. J. Infect. Dis. Med. Microbiol.* **2009**, *20*, 23; (b) Chu, J. H.; Feudtner, C.; Heydon, K.; Walsh, T. J.; Zaoutis, T. E. *Clin. Infect. Dis.* **2006**, *42*, 822.
4. Fera, M. T.; La Camera, E.; De Sarro, A. *Exp. Rev. Anti Infect. Ther.* **2009**, *7*, 981.
5. Maertens, J. *Eur. J. Haematol.* **2007**, *78*, 275.
6. (a) Messer, S. A.; Jones, R. N.; Moet, G. J.; Kirby, J. T.; Castanheira, M. *J. Clin. Microbiol.* **2010**, *48*, 2984; (b) Maligie, M. A.; Selitrennikoff, C. P. *Antimicrob. Agents Chemother.* **2005**, *49*, 2851; (c) Hage, C. A.; Connolly, P.; Horan, D.; Durkin, M.; Smedema, M.; Zarnowski, R.; Smith, P.; Wheat, L. J. *Antimicrob. Agents Chemother.* **2011**, *55*, 4447.
7. Edwards, J. A.; Kemski, M. M.; Rappleye, C. A. *Antimicrob. Agents Chemother.* **2013**, *57*, 4349.
8. Edwards, J. A.; Zemska, O.; Rappleye, C. A. *Infect. Immun.* **2011**, *79*, 3348.
9. (a) Kashyap, S. J.; Garg, V. K.; Sharma, P. K.; Kumar, N.; Dudhe, R.; Gupta, J. K. *Med. Chem. Res.* **2012**, *21*, 2123; (b) Siddiqui, N.; Arshad, M. F.; Ahsan, W.; Alam, M. S. *Int. J. Pharm. Sci. Drug Res.* **2009**, *1*, 136.
10. Gonzalez Cabrera, D.; Douelle, F.; Feng, T.-S.; Nchinda, A. T.; Younis, Y.; White, K. L.; Wu, Q.; Ryan, E.; Burrows, J. N.; Waterson, D.; Witty, M. J.; Wittlin, S.; Charman, S. A.; Chibale, K. *J. Med. Chem.* **2011**, *54*, 7713.
11. (a) Borelli, C.; Schaller, M.; Niewerth, M.; Nocker, K.; Baasner, B.; Berg, D.; Tiemann, R.; Tietjen, K.; Fugmann, B.; Lang-Fugmann, S.; Korting, H. C. *Antimicrob. Chemother.* **2008**, *54*, 245; (b) Narayana, B.; Vijaya Raj, K. K.; Ashalatha, B. V.; Kumari, N. S.; Sarojini, B. K. *Eur. J. Med. Chem.* **2004**, *39*, 867; (c) De Logu, A.; Saddi, M.; Cardia, M. C.; Borgna, R.; Sanna, C.; Saddi, B.; Maccioni, E. *J. Antimicrob. Chemother.* **2005**, *55*, 692.
12. Alwan, S. M. *Molecules* **2012**, *17*, 1025.
13. Al-Balas, Q.; Anthony, N. G.; Al-Jaidi, B.; Alnimr, A.; Abbott, G.; Brown, A. K.; Taylor, R. C.; Besra, G. S.; McHugh, T. D.; Gillespie, S. H.; Johnston, B. F.; Mackay, S. P.; Coxon, G. D. *PLoS ONE* **2009**, *4*.
14. Mayhoub, A. S.; Khaliq, M.; Kuhn, R. J.; Cushman, M. *J. Med. Chem.* **2011**, *54*, 1704.
15. Krasavin, M.; Karapetian, R.; Konstantinov, I.; Gezentsvey, Y.; Bukhryakov, K.; Godovykh, E.; Soldatkina, O.; Lavrovsky, Y.; Sosnov, A. V.; Gakh, A. A. *Arch. Pharm.* **2009**, *342*, 420.
16. Das, J.; Chen, P.; Norris, D.; Padmanabha, R.; Lin, J.; Moquin, R. V.; Shen, Z.; Cook, L. S.; Doweyko, A. M.; Pitt, S.; Pang, S.; Shen, D. R.; Fang, Q.; de Fex, H. F.; McIntyre, K. W.; Shuster, D. J.; Gillooly, K. M.; Behnia, K.; Schieven, G. L.; Wityak, J.; Barrish, J. C. *J. Med. Chem.* **2006**, *49*, 6819.
17. Gallardo-Godoy, A.; Gever, J.; Fife, K. L.; Silber, B. M.; Prusiner, S. B.; Renslo, A. R. *J. Med. Chem.* **2011**, *54*, 1010.
18. Daugan, A. C.-M.; Dean, A. W.; Fillmore, M. C. WO 2009/150196 A1, 2009.
19. (a) Florjancic, A. S.; Dart, M. J.; Ryther, K. B.; Perez-Medrano, A.; Carroll, W. A.; Patel, M. V.; Tietje, K. R.; Li, T.; Kolasa, T.; Gallagher, M. E.; Peddi, S.; Frost, J. M.; Nelson, D. W. US 2010/0093814 A1, 2010.; (b) Barda, D. A.; Burkholder, T. P.; Clayton, J. R.; Hao, Y.; Heath, P. C.; Henry, J. R.; Knobeloch, J. M.; Mendel, D.; McLean, J. A.; Remick, D. M.; Rempala, M. E.; Wang, Z.-Q.; Yip, Y. Y. M.; Zhong, B. WO 2006/091671 A1, 2006.
20. Zheng, S.; Zhong, Q.; Jiang, Q.; Mottamal, M.; Zhang, Q.; Zhu, N.; Burow, M. E.; Worthylake, R. A.; Wang, G. *ACS Med. Chem. Lett.* **2013**, *4*, 191.
21. Qiu, X.-L.; Li, G.; Wu, G.; Zhu, J.; Zhou, L.; Chen, P.-L.; Chamberlin, A. R.; Lee, W.-H. *J. Med. Chem.* **2009**, *52*, 1757.
22. (a) Espinel-Ingroff, A.; Fothergill, A.; Fuller, J.; Johnson, E.; Pelaez, T.; Turnidge, J. *Antimicrob. Agents Chemother.* **2011**, *55*, 2855; (b) Pfaller, M. A.; Castanheira, M.; Messer, S. A.; Moet, G. J.; Jones, R. N. *Diagn. Microbiol. Infect. Dis.* **2011**, *69*, 45; (c) Pfaller, M. A.; Diekema, D. J.; Andes, D.; Arendrup, M. C.; Brown, S. D.; Lockhart, S. R.; Motyl, M.; Perlin, D. S.; Testing, C. S. f. A *Drug Resist. Updat.* **2011**, *14*, 164; (d) Wheat, J.; Marichal, P.; Vanden Bossche, H.; Le Monte, A.; Connolly, P. *Antimicrob. Agents Chemother.* **1997**, *41*, 410.
23. (a) Callahan, H. L.; Portal, A. C.; Devereaux, R.; Grogl, M. *Antimicrob. Agents Chemother.* **1997**, *41*, 818; (b) Gomes, T. C.; de Andrade Junior, H. F.; Lescano, S. A.; Amato-Neto, V. *Rev. Soc. Bras. Med. Trop.* **2012**, *45*, 485; (c) Merschjohann, K.; Sporer, F.; Steverding, D.; Wink, M. *Planta Med.* **2001**, *67*, 623; (b) Lescano, S. A.; Amato-Neto, V. *Rev. Soc. Bras. Med. Trop.* **2012**, *45*, 485; (c) Merschjohann, K.; Sporer, F.; Steverding, D.; Wink, M. *Planta Med.* **2001**, *67*, 623.
24. (a) Odds, F. C. *J. Antimicrob. Chemother.* **2003**, *52*, 1; (b) Garcia, L. S. *Clinical Microbiology Procedures Handbook*, 3rd ed.; American Society for Microbiology: Washington, D.C., 2010.
25. Uto, Y.; Ogata, T.; Kiyotsuka, Y.; Miyazawa, Y.; Ueno, Y.; Kurata, H.; Deguchi, T.; Yamada, M.; Watanabe, N.; Takagi, T.; Wakimoto, S.; Okuyama, R.; Konishi, M.; Kurikawa, N.; Kono, K.; Osumi, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4159.
26. Pokhodylo, N.; Shyyka, O.; Matiychuk, V. *Med. Chem. Res.* **2014**, *23*, 2426.
27. Zimenkovskii, B. S.; Kutsyk, R. V.; Lesyk, R. B.; Matyichuk, V. S.; Obushak, N. D.; Klyufinska, T. I. *Pharm. Chem. J.* **2006**, *40*, 303.
28. Uto, Y.; Ogata, T.; Harada, J.; Kiyotsuka, Y.; Ueno, Y.; Miyazawa, Y.; Kurata, H.; Deguchi, T.; Watanabe, N.; Takagi, T.; Wakimoto, S.; Okuyama, R.; Abe, M.; Kurikawa, N.; Kawamura, S.; Yamato, M.; Osumi, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4151.
29. Biswal, S. S.; Singh, A.; Rastinehad, F.; Shen, M.; Boxer, M. B.; Zhang, Y.-Q.; Rohde, J. M.; Oh, K.; Venkannagari, S. WO 2014/145642 A2, 2014.
30. Zhao, H.; Caflisch, A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 523.
31. Ratan, R.; Gazaryan, I.; Smirnova, N. A. US 2013/0005666 A1, 2013.
32. Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158.
33. (a) Stiller, J.; Marques-Lopez, E.; Herrera, R. P.; Frohlich, R.; Strohmann, C.; Christmann, M. *Org. Lett.* **2011**, *13*, 70; (b) Alhamadsheh, M. M.; Palaniappan, N.; DasChouduri, S.; Reynolds, K. A. *J. Am. Chem. Soc.* **1910**, *2007*, 129.
34. Worsham, P. L.; Goldman, W. E. *J. Med. Vet. Mycol.* **1988**, *26*, 137.
35. Scragg, M. A.; Ferreira, L. R. *Anal. Biochem.* **1991**, *198*, 80.