ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett Letter

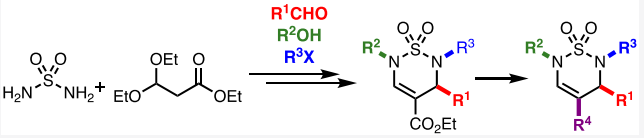
Synthesis and Selective Functionalization of Thiadiazine 1,1-Dioxides with Efficacy in a Model of Huntington's Disease[§]

Leila Terrab,[‖] Christopher J. Rosenker,[‖] Lisa Johnstone,[‖] Linh K. Ngo, Li Zhang, Nathaniel F. Ware, Bettina Miller, Andrea Z. Topacio, Sara Sannino, Jeffrey L. Brodsky, and Peter Wipf*

Cite This: *ACS Med. Chem. Lett.* 2020, 11, 984–990 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The scope of the acid-mediated 3-component synthesis of thiadiazines was investigated. A selective functionalization of the six-membered heterocyclic core structure was accomplished by sequential alkylations, saponifications, and coupling reactions. Several new analogs of a dihydropyrimidinone Hsp70 chaperone agonist, MAL1-271, showed promising activity in a cell based model of Huntington's disease.



KEYWORDS: *Thiadiazine, Hsp70, MAL1-271, Huntington's disease, molecular chaperone*

Sulfamide-based heterocycles are attractive synthetic targets in medicinal chemistry; while they have a wide variety of biological activities, they have been relatively neglected in SAR studies, in part due to a dearth of synthetic methods, and therefore cyclic sulfamides still offer considerable opportunities in patent space.[1−4] In addition to their function as urea bioisosteres,[5] agents containing these building blocks have been shown to exhibit antibacterial,[6,7] opioid receptor like-1 receptor (ORL1, NOP),[8] colony stimulating factor-1 (CSF-1, implied in rheumatoid arthritis and metastatic bone cancer),[9] and 11β-HSD1 (a target for type 2 diabetes) inhibitory activities.[10] A subclass of sulfamide-containing heterocycles, 1,2,6-thiadiazine 1,1-dioxides, has been shown to act as cannabinoid agonists and antagonists[11] and display modest antimicrobial activity,[12] smooth muscle relaxation,[13] and sedative effects.[14] Additionally, the structurally related 2,1,3-benzothiadiazine 2,2-dioxides, such as the commercial herbicide bentazon, have demonstrated herbicidal activity.[15]

The preparation of 1,2,6-thiadiazine 1,1-dioxides was first realized using an acid-mediated condensation of sulfamide and monoketones[16,17] or β-diketones.[18] Alternatively, functionalized thiadiazines have been prepared by base-mediated intramolecular cyclizations of sulfaminomethylene derivatives,[19,20] condensation with substituted sulfamides and ethyl 3,3-diethoxypropanoate (**1**),[21] condensation of sulfamide imines and **1**,[22] and the intramolecular Friedel−Crafts acylation of sulfamide iminium species.[23] More recently, thiadiazines were prepared by joining an *N,N′*-dibenzylated sulfamide with 2-(acetoxymethyl)buta-2,3-dienoate[24] and by a silver- and gold-catalyzed hydroamination of propargyl sulfamides;[25] but, overall, there is a surprising lack of 1,2,6-thiadiazine 1,1-dioxides with carboxylic acid substituents in the 4-position in the literature.

As part of our interest in the synthesis of novel heterocyclic compounds by multicomponent condensations (MCCs),[26,27] we envisioned 1,2,6-thiadiazine 1,1-dioxides to become readily available by a Biginelli-like MCC and represent versatile scaffolds wherein the core heterocycle could be functionalized at several positions. Specifically, we wanted to explore if thiadiazine 1,1-dioxides could serve as bioisosteric analogs of Biginelli dihydropyrimidinones such as **MAL1-271**, an agonist of Hsp70 that reduces protein aggregation associated with neurodegenerative diseases.[28] The thiadiazine 1,1-dioxide scaffold offers an attractive option to expand the hydrogen bond acceptor carbonyl moiety in the planar pyrimidinone urea moiety into three dimensions, as well as facilitate alkylation reactions for structure−activity relationship (SAR) purposes. We envisioned that a variety of novel thiadiazines could be prepared by selective *N*-alkylations[29] followed by functional group interconversions of the 4-carboxylate ester. To test this hypothesis, we set out to synthesize the thiadiazine 1,1-dioxide core, initially using literature conditions.[21,22] However, the use of neat TFA as a solvent required long reaction times and gave inconsistent yields in our hands (Scheme 1, eq 1). As a result, we initiated a search for optimal thiadiazine formation conditions. After considerable experimentation, we found that condensation of sulfamide (**2**) with **1** in a 1:5 mixture of TFA and CH_2Cl_2 resulted in the formation of stable, crystalline 8-membered ring dimer **3**[30] after 3 h at room temperature (Scheme 1, eq 2). The unusual

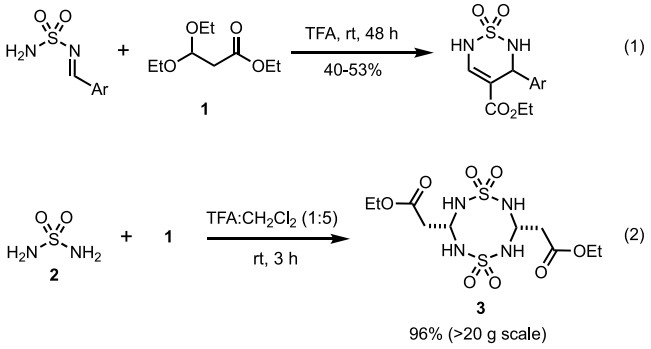
Special Issue: In Memory of Maurizio Botta: His Vision of Medicinal Chemistry

Received: January 13, 2020
Accepted: February 19, 2020
Published: February 20, 2020

ACS Publications © 2020 American Chemical Society

https://dx.doi.org/10.1021/acsmedchemlett.0c00018
ACS Med. Chem. Lett. 2020, 11, 984–990

Scheme 1. Literature Precedent for Thiadiazine 1,1-Dioxide Formation (Eq 1) and Preparation of Dithiatetrazocane 3 (Eq 2)



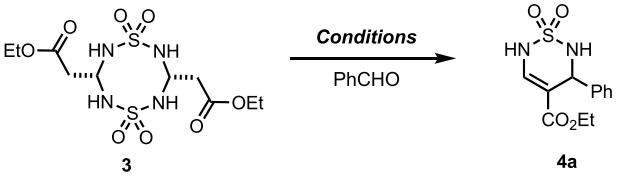
8-membered ring structure and *cis*-configuration of dithiatetrazocane **3** was assigned based on an X-ray structure analysis (Figure 1). Notably, there are very few compounds of similar connectivity in the literature.[31−33]

Figure 1. X-ray structure of 1,1,5,5-tetraoxido-1,5,2,4,6,8-dithiatetrazocane-3,7-diyl)diacetate **3** (CCDC 1972400).

Condensation of **3** with benzaldehyde in a 1:1 mixture of TFA and CH_2Cl_2 provided the desired thiadiazine **4a** in 61% yield (Table 1, entry 1). We also explored alternative acidic conditions that were milder and provided **4a** in a higher yield. Polyphosphate ester (PPE),[34] $BF_3{\cdot}Et_2O$, triflamide, anhydrous HCl, methanesulfonic acid, and TFA:CH_2Cl_2 (1:5) yielded thiadiazine **4a** in lower or comparable yields (entries 2−7). When the quantity of TFA was reduced to 10 mol equiv, product was obtained in 59% yield (entry 8). Further reduction of TFA to 2.5 mol equiv was sufficient to obtain **4a** in 57% yield if the reaction concentration was increased to 0.5 M and the mixture was heated to 40 °C for 30 h (entry 9). Due to the limited solubility of the sulfamide dimer **3** in CH_2Cl_2 and our desire to increase the reaction rate, the solvent was changed to hexafluoroisopropanol (HFIP). We envisioned this non-nucleophilic alcohol with its remarkable hydrogen bond donor/acceptor capabilities would increase the dissolution of **3** and stabilize ionic intermediates, thus improving the conversion rate and product yield. However, the use of HFIP as a solvent in the presence of 2.5 equiv of TFA provided a modest decrease of the reaction time while producing **4a** in comparable yields (entry 10).

Based on these optimizations, we selected 10−20 mol equiv of TFA in a solution of CH_2Cl_2 for further investigations of the scope of compatible aldehydes in the thiadiazine 1,2-dioxide formation with **3** (Table 2). Aliphatic aldehydes (entries 2−3),

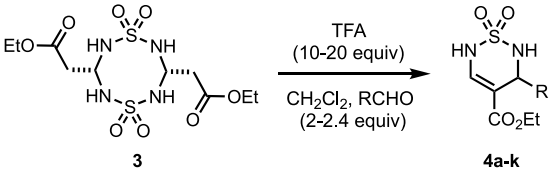
Table 1. Optimization of Thiadiazine 4a Formation from 3



Entry	Conditions	Yield[a]
1	TFA:CH_2Cl_2 (1:1), rt, 30 min	61%
2	PPE, THF, reflux, 40 min	45%
3	$BF_3{\cdot}OEt_2$ (2 equiv), CH_2Cl_2, rt, 6 h	65%
4	10% Tf_2NH, CH_2Cl_2, rt, 2.5 h	42%
5	4 M HCl (10 equiv), dioxane, rt, 14 h	47%[b]
6	$MeSO_3H$ (5.7 equiv), CH_2Cl_2, 0 °C, 40 min	39%
7	TFA:CH_2Cl_2 (1:5), rt, 3 h	61%
8	TFA (10 equiv), CH_2Cl_2, rt, 60 h	59%
9	TFA (2.5 equiv), CH_2Cl_2, 40 °C, 30 h	57%[c]
10	TFA (2.5 equiv), HFIP, 35−40 °C, 17 h	66%[d]

[a]Isolated yield after chromatography on SiO_2. [b]Isolated in 85% purity. [c]Reaction was performed at 0.51 M. [d]Reaction was performed at 0.50 M. [e]Reaction in the absence of TFA led to the recovery of 81% of **3**.

Table 2. Thiadiazine Formation with 3 and Various Aldehydes



Entry	R	4a−j	Yield[a]
1	Ph	**4a**	66%[b]
2	Me	**4b**	59%
3	Et	**4c**	56%
4	2,4-$Cl_2C_6H_3$	**4d**	70%
5	4-NCC_6H_4	**4e**	41%
6	4-$MeCO_2C_6H_4$	**4f**	57%
7	4-$CF_3C_6H_4$	**4g**	65%
8	2-BrC_6H_4	**4h**	45%
9	4-$AcOC_6H_4$	**4i**	48%
10	3-$MeOC_6H_4$	**4j**	62%
11	3-thiophene	**4k**	30%

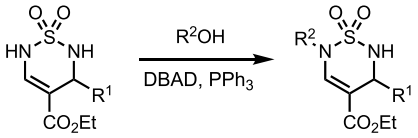
[a]Isolated yield after chromatography on SiO_2. [b]Reaction was performed using TFA (2.5 equiv), HFIP, 35−40 °C, 17 h.

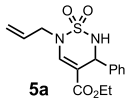
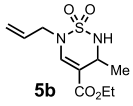
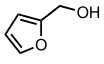
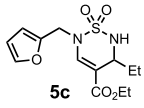
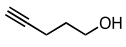
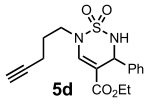
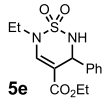
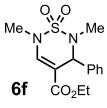
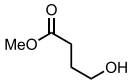
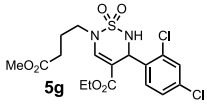
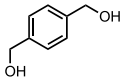
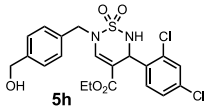
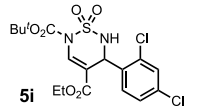
as well as electron deficient (entries 4−8) and electron-rich aryl aldehydes (entries 9−10), provided the cyclocondensation products **4a−4j** in 40−70% yield. The heterocyclic thiophene-3-carboxaldehyde provided **4k** in a modest 30% yield (entry 11). Other heterocyclic aldehydes (furans, quinolines, and pyridines) resulted in the formation of complex mixtures and were not further analyzed.

Next, we examined the possibility of regioselective sequential *N*-alkylation of the two sulfamide nitrogens by exploiting their inherent difference in acidity (pK_a^1 ca. 9.2 vs pK_a^2 ca. 9.5; that is, the vinylogous carbamate sulfamide N(6)-H is calculated to be slightly more acidic)[35] as well as their steric environment. Treatment of thiadiazine **4a** with NaH followed by allyl iodide led to a mixture of mono- and dialkylated products. In contrast, Mitsunobu[36] conditions with allyl alcohol using DBAD led to a selective (*N*)6-monoalkylation of thiadiazines **4a** and **4b** in good yields (Table 3, entries 1−2). The regiochemistry was determined by NOESY correlations between the methylene hydrogens of the allyl group and the hydrogen of the thiadiazine alkene.

https://dx.doi.org/10.1021/acsmedchemlett.0c00018
ACS Med. Chem. Lett. 2020, 11, 984−990

Table 3. Regioselective *N*(6)-Alkylation of Thiadiazines 4a–d



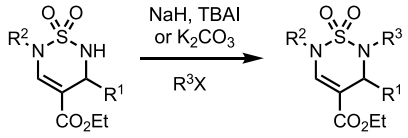
Entry	4	R^2OH	Yield	Product
1	**4a**		77%	 **5a**
2	**4b**		72%	 **5b**
3	**4c**		37%[a]	 **5c**
4	**4a**		58%	 **5d**
5	**4a**	EtOH	75%	 **5e**
6	**4a**	MeI	Quant[b]	 **6f**
7	**4d**		53%	 **5g**
8	**4d**		52%	 **5h**
9	**4d**	Boc_2O	86%[c]	 **5i**

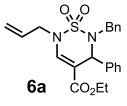
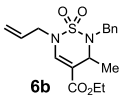
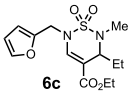
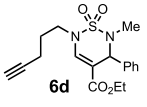
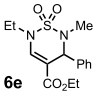
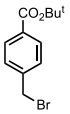
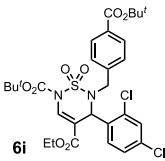
[a]DEAD was used in place of DBAD. [b]**4a** was treated with MeI (5 equiv), K_2CO_3, and MeCN. [c]Reaction with **4d** (1.1 equiv), Boc_2O (1 equiv), and K_2CO_3 (2.5 equiv).

Furanylmethanol required a change of the dialkylazodicarboxylate to DEAD, which simplified the purification (entry 3). Simple or functionalized alkyl alcohols also gave good conversions (entries 4, 5, and 7). While the yield was slightly lower with 1,4-phenylenedimethanol, monoalkylated product **5h** was readily isolated (entry 8), and a Boc-protection was also highly selective and generated thiadiazine 1,2-dioxide **5i** in 86% yield (entry 9). A symmetrical dialkylation was straightforward by treating **4a** with an excess of MeI in the presence of K_2CO_3 to give **6f** in excellent yield (entry 6).

The alkylation of the thiadiazine *N*(2) amide was investigated next. Benzylations of **5a** and **5b** were accomplished in the presence of NaH and TBAI to provide **6a** and **6b** in 68 and 71% yield, respectively (Table 4, entries 1–2).

Table 4. N(2)-Alkylation of Thiadiazines 5



Entry	5	R^3X	Yield	Product 6
1	**5a**	BnBr	68%[a]	 **6a**
2	**5b**	BnBr	71%[a]	 **6b**
3	**5c**	MeI	91%[b]	 **6c**
4	**5d**	MeI	98%[b]	 **6d**
5	**5e**	MeI	Quant[b]	 **6e**
6	**5i**		79%[b]	 **6i**

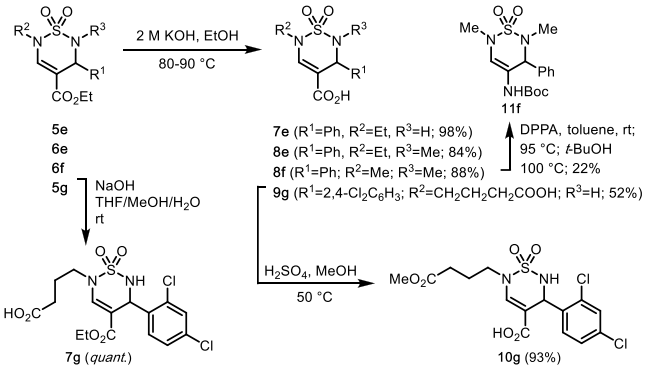
[a]NaH, TBAI, THF. [b]K_2CO_3, MeCN.

N-Methylations of **5c–e** were achieved with K_2CO_3 in MeCN and produced **6c–e** in high yields (Table 4, entries 3–5). An ester-functionalized benzyl bromide was similarly and successfully introduced to generate the Boc-protected diester **6i** (entry 6).

For additional chemical scaffold diversifications, we focused on selective conversions of the C(4)-esters (Scheme 2). Initial attempts at a Lewis acid mediated transesterification, or a mild hydrolysis using TMSOK or Bu_3SnOH, were unsuccessful. Gratifyingly, ester hydrolysis was achieved by heating **5e**, **6e**, **6f**, and **5g** in 2 M KOH in EtOH to provide acids **7e**, **8e**, **8f**, and **9g**, respectively. Under milder conditions with NaOH in THF, MeOH, and water at room temperature, the aliphatic carboxylate in **5g** was saponified selectively, and **7g** was isolated in quantitative yield. Furthermore, diacid **9g** could be selectively re-esterified to the monomethyl ester **10g** under Fischer conditions, thus allowing for a regiospecific conversion of the carboxylate functional groups in diester **5g**. Finally, a Curtius rearrangement of thiadiazine **8f** with DPPA[37] afforded

https://dx.doi.org/10.1021/acsmedchemlett.0c00018
ACS Med. Chem. Lett. 2020, 11, 984–990

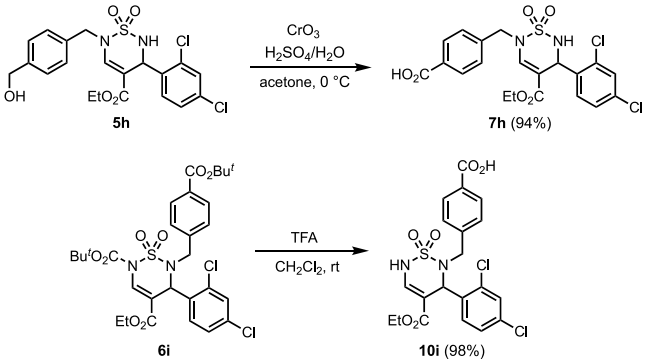
Scheme 2. Saponification of Mono- and Dialkylated Thiadiazines and Curtius Rearrangement of Carboxylate 8f



the *tert*-butyl carbamate **11f**, providing the first entry to this unprecedented thiadiazine 1,1-dioxide substitution pattern.

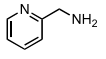
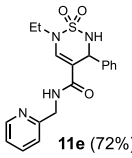
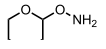
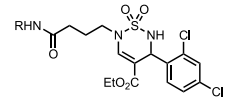
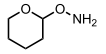
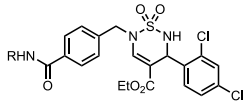
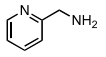
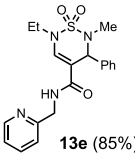
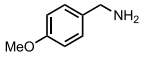
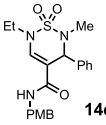
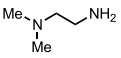
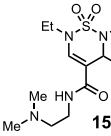
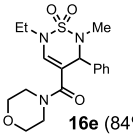
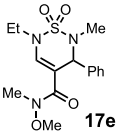
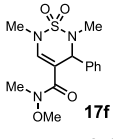
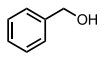
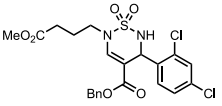
Jones oxidation of the side chain alcohol in **5h** provided benzoic acid **7h** in 94% yield, and treatment of **6i** with TFA generated the regioisomeric benzoate **10i** with concomitant removal of the Boc-group (Scheme 3). These transformations added additional versatility and valuable sites for diversifications to the collection of thiadiazine 1,1-dioxide building blocks.

Scheme 3. Selective Formations of Monoacid Thiadiazine 1,1-Dioxides



In order to demonstrate the utility of these building blocks for the preparation of bioactive screening samples, we generated a series of amide and ester analogs and subjected them to a representative biological assay. Amide bond formation using PyBOP and DIPEA, or EDCI, DMAP, and DIPEA, with pyridinyl methanamine proceeded in good yield with thiadiazines **7e** and **8e** to give **11e** and **13e** (Table 5, entries 1 and 4). Hydroxamic acids **12g** and **12h** were obtained by coupling of carboxylic acids **7g** and **7h**, respectively, with THP-protected hydroxylamine in the presence of T_3P and TEA, followed by cleavage of the THP group with Amberlyst-15 resin (entries 2 and 3). *p*-Methoxybenzylamine, *N*,*N*-dimethylethylenediamine, and morpholine yielded amides **14e**, **15e**, and **16e** (entries 5−7). The formation of hydroxamic esters **17e** and **17f** and benzyl ester **18g** also occurred in moderate to high yield (entries 8−10). Furthermore, methyl hydroxamate **17f** was selectively reduced to the aldehyde **19f** (Scheme 4). We anticipated that this aldehyde would allow access to secondary amines by reductive amination. While one-pot imine formation−reduction conditions were unsuccessful, sequential imine formation using Ti(*i*-PrO)$_4$ followed by

Table 5. Amidation and Esterification of Acids 7, 8, and 10

Entry	Acid	Amine/Alcohol	Amide/Ester **11-18**
1	**7e**		 **11e** (72%)[a]
2	**7g**		 c → **11g** (R=OTHP, 77%)[b] **12g** (R=OH, 53%)
3	**7h**		 c → **11h** (R=OTHP, 81%)[b] **12h** (R=OH, 82%)
4	**8e**		 **13e** (85%)[d]
5	**8e**		 **14e** (83%)[d]
6	**8e**		 **15e** (76%)[d]
7	**8e**		 **16e** (84%)[d]
8	**8e**	MeNH(OMe) •HCl	 **17e** (90%)[d]
9	**8f**	MeNH(OMe) •HCl	 **17f** (94%)[d]
10	**10g**		 **18g** (60%)[a]

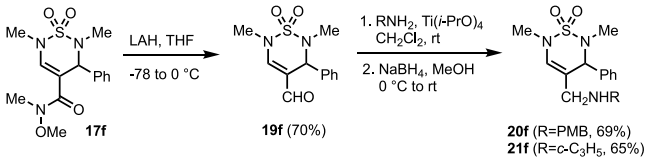
[a]Coupling with EDCI, DMAP, DIPEA. [b]T_3P and TEA. [c]Amberlyst-15, MeOH, rt. [d]coupling with PyBOP, DIPEA

reduction with $NaBH_4$ provided amines **20f** and **21f** in 69% and 65% overall yield from **19f**.

After developing a versatile strategy and reaction conditions for the preparation and sequential functionalization of thiadiazine 1,1-dioxides, we investigated our hypothesis that

https://dx.doi.org/10.1021/acsmedchemlett.0c00018
ACS Med. Chem. Lett. 2020, 11, 984−990

Scheme 4. Reduction of Hydroxamide 17f and Reductive Amination of Aldehyde 19f



this heterocyclic core could be a suitable replacement for a dihydropyrimidine-2-one and show similar efficacy in a model of neurodegenerative disease.[38,39] Therefore, ten structurally related analogs of the Biginelli product **MAL1-271** were selected for a cell-based screen in a Huntington's disease (HD) model (Figure 2).

HD is an ultimately fatal neurodegenerative disorder that is caused by a polyglutamine repeat expansion in the Huntingtin protein (HTT). Studies in model systems indicate that Hsp70 overexpression reduces the cellular levels of toxic HTT aggregates, and in animals Hsp70 induction can even suppress some of the negative consequences of polyglutamine expansion.[40] Based on the fact that **MAL1-271** functions as an Hsp70 agonist, we examined ten diverse analogs, i.e. **5g**, **5h**, **6i**, **7h**, **9g**, **10g**, **10i**, **12g**, **12h**, and **18g**, for their ability to blunt the formation of toxic aggregates in HEK293 cells that express an HTT exon containing 17 glutamine repeats. Among these compounds, **5g**, **9g**, **10g**, **12g**, and **18g** show a closer structural resemblance to **MAL1-271** than **5h**, **6i**, **7h**, **10i**, and **12h**. We discovered that several analogs reduced the number of cellular puncta/aggregates compared to the DMSO control. Cells were stained for confocal microscope imaging with 4′,6-diamidino-2-phenylindole (DAPI), a fluorescent dye with high affinity to adenine−thymine rich DNA regions. A bright spot detection tool was used to identify and quantify the number of protein aggregates ("dots") per cell.

Compared to the **MAL1-271** positive control, **5g**, **9g**, **18g**, **5h**, **7h**, **12h**, and **6i** were less effective ($p < 0.0001$), whereas **10g** and **10i** were equally effective (Figure 2). Thiadiazine **12g** exhibited even a slightly greater effect on aggregate suppression than **MAL1-271** ($p < 0.05$). Interestingly, the chemotype of **10g** and **12g** is closely related to **MAL1-271**, but **10i** represents a novel heterocycle substitution pattern that can serve as a starting point for new structure−activity studies (Figure 3).

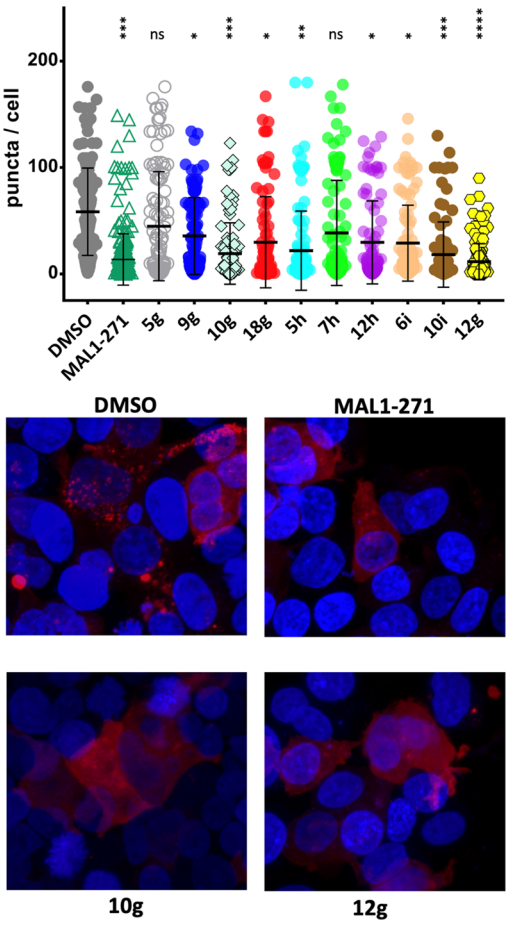


Figure 2. HEK293H cells were transfected with 4 μg of an HTT17Q-mCherry construct,[41] and 24 h after transfection cells were treated with 10 μM compound or DMSO for 6 h. Top panel: number of puncta per cell. Statistically significant differences between control and treated samples are indicated by asterisks. * $p < 0.05$; ** $p < 0.005$; *** $p < 0.0005$; **** $p < 0.00005$ compared to the DMSO control. Bottom panel: representative cell images for negative control (DMSO), positive control (**MAL1-271**), and analogs **10g** and **12g**. Toxic aggregates are shown as red dots. See SI for additional information.

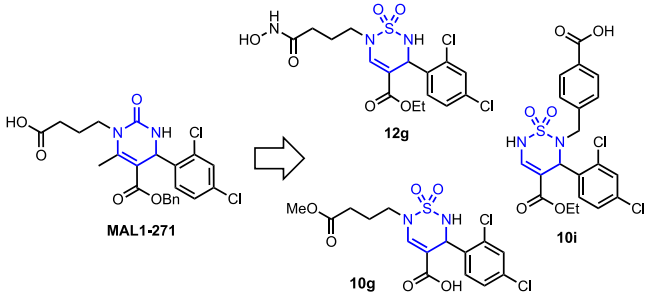


Figure 3. Structures of Hsp70 agonist **MAL1-271** and thiadiazine 1,1-dioxide analogs that showed similar activity in the HD model assay. The respective Biginelli (dihydropyrimidinone) and thiadiazine scaffolds are highlighted in blue.

It is interesting to note that **12g** is a hydroxamic acid analog of **MAL1-271**; in order to address the possibility that **12g** or another analog exerted antiaggregation effects due to inhibition of a histone deacetylase (HDAC),[42] we counter-screened actives **10g**, **10i**, **12g**, and **12h** (negative control) against HDAC 1−8 (Table 1 in the Supporting Information). None of the active compounds, in particular not even the hydroxamic acid **12g**, displayed significant HDAC 1−6 inhibition at 0.1−1 μM concentrations. Only hydroxamic acid **12h** showed 40% inhibition of HDAC 7 at 1 μM, and all compounds showed moderate inhibition (35−60%) of HDAC 8 at 1 μM concentration in the assay. The absence of a clear correlation between HDAC inhibition and activity in the HD assay for hydroxamates **12g** and **12h** suggests that the active hit compound **12g** does not reduce cellular HTT aggregates due to direct HDAC inhibition. Moreover, HDAC6, which has been implicated in heat shock protein gene expression,[43] was also not inhibited by hydroxamates **12g** and **12h** at 0.2 μM concentration. However, since the biochemical assays at higher concentrations were prevented by low aqueous solubility, we cannot exclude the possibility of some HDAC inhibition in HEK293H cells at 10 μM concentration.

https://dx.doi.org/10.1021/acsmedchemlett.0c00018
ACS Med. Chem. Lett. 2020, 11, 984−990

In summary, we have developed a versatile strategy for the preparation and selective functionalization of thiadiazine 1,1-dioxides, a relatively rare heterocycle that has previously been underutilized in medicinal chemistry screening campaigns. In addition, we have demonstrated the utility of this scaffold as a potential biomimetic of the privileged Biginelli heterocycle, the dihydropyrimidinone. The identification of active analogs of the Hsp70 agonist dihydropyrimidinone **MAL1-271**, i.e. thiadiazines **10g**, **10i**, and **12g**, in a relevant cell based biological assay highlights the potential application of thiadiazine 1,1-dioxides in hit identification in general, and specifically in Huntington's disease and perhaps other neurodegenerative diseases associated with the accumulation of toxic protein aggregates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.0c00018.

Experimental details and ^{1}H and ^{13}C NMR spectra for new synthetic intermediates and products. Assay information. (PDF)

Accession Codes

CCDC 1972400 contains the supplementary crystallographic data for compound **3** in this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Peter Wipf − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States;* orcid.org/0000-0001-7693-5863; Email: pwipf@pitt.edu

Authors

Leila Terrab − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Christopher J. Rosenker − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Lisa Johnstone − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Linh K. Ngo − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Li Zhang − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Nathaniel F. Ware − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Bettina Miller − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Andrea Z. Topacio − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Sara Sannino − *Department of Biological Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Jeffrey L. Brodsky − *Department of Biological Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.0c00018

Author Contributions

‖L. Terrab, C. J. Rosenker, and L. Johnstone contributed equally to this work and should be considered cofirst authors. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

This work was supported in part by grants P50 GM067082, R35 GM131732, and P30 DK79307 from the National Institutes of Health and a generous donation from the Moravitz family.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank T. S. Maskrey, I. Mager, and A. Cervi (University of Pittsburgh) for project management (TSM) and technical assistance (TSM, IM, AC), S. J. Geib (University of Pittsburgh) for the X-ray analysis of **3**, P. Needham (University of Pittsburgh) for technical assistance with the HD assay, and U. Pandey (University of Pittsburgh) and Alice Migazzi (University of Trento) for reagents for the HD assay.

■ ABBREVIATIONS

DAPI, 4′,6-diamidino-2-phenylindole; DBAD, di-*tert*-butyl azodicarboxylate; DEAD, diethyl azodicarboxylate; DIPEA, diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DPPA, diphenylphosphoryl azide; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HD, Huntington's disease; HDAC, histone deacetylase; HFIP, hexafluoroisopropanol; PPE, polyphosphate ester; HSF1, heat shock factor 1; Hsp70, heat shock protein 70 kDa; HTT, Huntingtin protein; PyBOP, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate; TBAI, tetrabutylammonium iodide; TEA, triethylamine; T_3P, propanephosphonic acid anhydride

■ REFERENCES

(1) Lawson, A.; Tinkler, R. B. Chemistry of Thiadiazole and Thiadiazine S-Oxides. *Chem. Rev.* **1970**, *70*, 593−618.

(2) Petersen, H. Syntheses of Cyclic Ureas by α-Ureidoalkylation. *Synthesis* **1973**, *1973*, 243−292.

(3) McDermott, S. D.; Spillane, W. J. Synthesis and Reactions of Sulfamides. A Review. *Org. Prep. Proced. Int.* **1984**, *16*, 49−77.

(4) Gazieva, G. A.; Kravchenko, A. N.; Lebedev, O. V. Sulfamides in the Synthesis of Heterocyclic Compounds. *Russ. Chem. Rev.* **2000**, *69*, 221−230.

(5) Ghosh, A. K.; Brindisi, M. Urea Derivatives in Modern Drug Discovery and Medicinal Chemistry. *J. Med. Chem.* **2019**, DOI: 10.1021/acs.jmedchem.9b01541

(6) Kim, S. J.; Jung, M.-H.; Yoo, K. H.; Cho, J.-H.; Oh, C.-H. Synthesis and Antibacterial Activities of Novel Oxazolidinones Having Cyclic Sulfonamide Moieties. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5815−5818.

(7) Kim, S. J.; Cho, J.-H.; Oh, C.-H. Novel 1β-Methylcarbapenems Having Cyclic Sulfonamide Moieties: Synthesis and Evaluation of in-Vitro Biological Activity - Part II. *Arch. Pharm.* **2009**, *342*, 528−532.

(8) Palin, R.; Clark, J. K.; Evans, L.; Feilden, H.; Fletcher, D.; Hamilton, N. M.; Houghton, A. K.; Jones, P. S.; McArthur, D.; Montgomery, B.; Ratcliffe, P. D.; Smith, A. R. C.; Sutherland, A.; Weston, M. A.; Wishart, G. Rapid Access Towards Follow-up NOP Receptor Agonists Using a Knowledge Based Approach. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6441−6446.

(9) Wilson, K. J.; Illig, C. R.; Chen, J.; Wall, M. J.; Ballentine, S. K.; Des Jarlais, R. L.; Chen, Y.; Schubert, C.; Donatelli, R.; Petrounia, I.; Crysler, C. S.; Molloy, C. J.; Chaikin, M. A.; Manthey, C. L.; Player,

M. R.; Tomczuk, B. E.; Meegalla, S. K. Reducing Ion Channel Activity in a Series of 4-Heterocyclic Arylamide FMS Inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3925−3929.
(10) Kim, S. H.; Bok, J. H.; Lee, J. H.; Kim, I. H.; Kwon, S. W.; Lee, G. B.; Kang, S. K.; Park, J. S.; Jung, W. H.; Kim, H. Y.; Rhee, S. D.; Ahn, S. H.; Bae, M. A.; Ha, D. C.; Kim, K. Y.; Ahn, J. H. Synthesis and Biological Evaluation of Cyclic Sulfamide Derivatives as 11β-Hydroxysteroid Dehydrogenase 1 Inhibitors. *ACS Med. Chem. Lett.* **2012**, *3*, 88−93.
(11) Cano, C.; Goya, P.; Paez, J. A.; Giron, R.; Sanchez, E.; Martin, M. I. Discovery of 1,1-Dioxo-1,2,6-Thiadiazine-5-Carboxamide Derivatives as Cannabinoid-Like Molecules with Agonist and Antagonist Activity. *Bioorg. Med. Chem.* **2007**, *15*, 7480−7493.
(12) Bhatt, N.; Vyas, K.; Joshi, K.; Nimavat, K. Synthesis and Biological Screening of Alkyl 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl)benzoate. *Asian J. Biochem. Pharm. Res.* **2011**, *1*, 464−469.
(13) Castro, A.; Martinez, A.; Cardelus, I.; Llenas, J. Dioxides of Bicyclic Thiadiazines: A New Family of Smooth Muscle Relaxants. *Bioorg. Med. Chem.* **1995**, *3* (2), 179−185.
(14) Houlihan, W. J. Dioxobenzothiadiazines. US Patent 3278532, 1966.
(15) Lamberth, C. Pyrimidine Chemistry in Crop Protection. *Heterocycles* **2006**, *68*, 561−603.
(16) Degering, E. F.; Wilson, J. E. Derivatives of Sulfamide. *J. Org. Chem.* **1952**, *17*, 339−341.
(17) Ouchi, A.; Moeller, T. The Condensation Reaction between Sulfamide and Monoketones. *J. Org. Chem.* **1964**, *29*, 1865−1867.
(18) Wright, J. B. The Reaction of Sulfamide with Alpha- and Beta-Diketones. The Preparation of 1,2,5-Thiadiazole 1,1-Dioxides and 1,2,6-Thiadiazine 1,1-Dioxides. *J. Org. Chem.* **1964**, *29*, 1905−1909.
(19) Goya, P.; Stud, M. Synthesis of 4-Substituted 3-Hydroxy- and 3-Amino-6H-1,2,6-Thiadiazine 1,1-Dioxides. *J. Heterocycl. Chem.* **1978**, *15*, 253−256.
(20) Hansen, H.; Koenig, K. H.; Rohr, W. Synthesis and Reactions of Substituted 3-Oxo-1,2,6-Thiadiazine 1,1-Dioxides. *Liebigs Ann. Chem.* **1979**, *1979*, 950−958.
(21) Lee, C. H.; Kohn, H. Functionalized 5,6-Dihydro-2H-1,2,6-Thiadiazine 1,1-Dioxides. Synthesis, Structure and Chemistry. *J. Heterocycl. Chem.* **1990**, *27*, 2107−2111.
(22) Lee, C. H.; Lee, Y. H.; Choi, W. S.; Chung, B. Y. Synthesis of 4-Carbethoxy-5-Aryl-5,6-Dihydro-2H-1,2,6-Thiadiazine 1,1-Dioxides. *Bull. Korean Chem. Soc.* **1992**, *13*, 462−463.
(23) Lee, C.-H.; Jin, G. F.; Lim, H. W.; Yang, E. H.; Lee, J.-D.; Nakamura, H.; Ban, H. S.; Kang, S. O. Facile Synthesis of 4-Substituted 3,4-Dihydro-1H-2,1,3-Benzothiadiazine 2,2-Dioxides. *Heteroat. Chem.* **2011**, *22*, 192−197.
(24) Li, C.; Zhang, Q.; Tong, X. Amine-Catalyzed (3+n) Annulations of 2-(Acetoxymethyl)Buta-2,3-Dienoates with 1,n-Bisnucleophiles (n = 3−5). *Chem. Commun.* **2010**, *46*, 7828−7830.
(25) Veguillas, M.; Rosair, G. M.; Bebbington, M. W. P.; Lee, A.-L. Silver Effect in Regiodivergent Gold-Catalyzed Hydroaminations. *ACS Catal.* **2019**, *9*, 2552−2557.
(26) Maskrey, T. S.; Frischling, M. C.; Rice, M. L.; Wipf, P. A Five-Component Biginelli-Diels-Alder Cascade Reaction. *Front. Chem.* **2018**, *6*, 376.
(27) Huryn, D. M.; Brodsky, J. L.; Brummond, K. M.; Chambers, P. G.; Eyer, B.; Ireland, A. W.; Kawasumi, M.; LaPorte, M. G.; Lloyd, K.; Manteau, B.; Nghiem, P.; Quade, B.; Seguin, S. P.; Wipf, P. Chemical Methodology as a Source of Small-Molecule Checkpoint Inhibitors and Heat Shock Protein 70 (Hsp70) Modulators. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6757−6762.
(28) Terrab, L.; Wipf, P. Hsp70 and the Unfolded Protein Response as a Challenging Drug Target and an Inspiration for Probe Molecule Development. *ACS Med. Chem. Lett.* **2020**, in press.
(29) For an example of a selective methylation, see: Goya, P.; Martinez, P.; Ochoa, C.; Stud, M. Regioselective N-Alkylation of 1,2,6-Thiadiazine 1,1-Dioxide Derivatives. *J. Heterocycl. Chem.* **1981**, *18*, 459−462.
(30) Goya, P.; Stud, M. Synthesis of 4-Substituted 3-Hydroxy- and 3-Amino-6H-1,2,6-Thiadiazine 1,1-Dioxides. *J. Heterocycl. Chem.* **1978**, *15*, 253−256.
(31) Dusemund, J. Reaction of Sulfamide with Aldehydes and Acetals. *Arch. Pharm.* **1974**, *307*, 881−883.
(32) Lee, C. H.; Kohn, H. 3,7-Bis(Carboethoxy)Perhydro-1,5,2,4,6,8-Dithiatetrazocine 1,1,5,5-Tetroxide. Synthesis, Structure and Chemistry. *Heterocycles* **1988**, *27*, 2581−2588.
(33) Lee, C. H.; Kohn, H. Intra- and Intermolecular α-Sulfamidoalkylation Reactions. *J. Org. Chem.* **1990**, *55*, 6098−6104.
(34) Cava, M. P.; Lakshmikantham, M. V.; Mitchell, M. J. Synthesis of Caseadine Methyl Ether. *J. Org. Chem.* **1969**, *34*, 2665−2667.
(35) pKa and LogD values were calculated with Instant JChem 19.19.0, downloaded on 9/9/2019 (ChemAxon; http://www.chemaxon.com).
(36) Mitsunobu, O.; Yamada, M. Preparation of Esters of Carboxylic and Phosphoric Acid Via Quaternary Phosphonium Salts. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380−2382.
(37) Shioiri, T.; Ninomiya, K.; Yamada, S. Diphenylphosphoryl Azide: A New Convenient Reagent for a Modified Curtius Reaction and for the Peptide Synthesis. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205.
(38) Chiang, A. N.; Liang, M.; Dominguez-Meijide, A.; Masaracchia, C.; Goeckeler-Fried, J. L.; Mazzone, C. S.; Newhouse, D. W.; Kendsersky, N. M.; Yates, M. E.; Manos-Turvey, A.; Needham, P. G.; Outeiro, T. F.; Wipf, P.; Brodsky, J. L. Synthesis and Evaluation of Esterified Hsp70 Agonists in Cellular Models of Protein Aggregation and Folding. *Bioorg. Med. Chem.* **2019**, *27*, 79−91.
(39) Kilpatrick, K.; Novoa, J. A.; Hancock, T.; Guerriero, C. J.; Wipf, P.; Brodsky, J. L.; Segatori, L. Chemical Induction of Hsp70 Reduces α-Synuclein Aggregation in Neuroglioma Cells. *ACS Chem. Biol.* **2013**, *8*, 1460−1468.
(40) Davis, A. K.; Pratt, W. B.; Lieberman, A. P.; Osawa, Y. Targeting Hsp70 Facilitated Protein Quality Control for Treatment of Polyglutamine Diseases. *Cell. Mol. Life Sci.* **2019**, DOI: 10.1007/s00018-019-03302-2.
(41) Crotti, A.; Benner, C.; Kerman, B. E.; Gosselin, D.; Lagier-Tourenne, C.; Zuccato, C.; Cattaneo, E.; Gage, F. H.; Cleveland, D. W.; Glass, C. K. Mutant Huntingtin Promotes Autonomous Microglia Activation Via Myeloid Lineage-Determining Factors. *Nat. Neurosci.* **2014**, *17*, 513−521.
(42) Siebzehnruebl, F. A.; Raber, K. A.; Urbach, Y. K.; Schulze-Krebs, A.; Canneva, F.; Moceri, S.; Habermeyer, J.; Achoui, D.; Gupta, B.; Steindler, D. A.; Stephan, M.; Nguyen, H. P.; Bonin, M.; Riess, O.; Bauer, A.; Aigner, L.; Couillard-Despres, S.; Paucar, M. A.; Svenningsson, P.; Osmand, A.; Andreew, A.; Zabel, C.; Weiss, A.; Kuhn, R.; Moussaoui, S.; Blockx, I.; Van der Linden, A.; Cheong, R. Y.; Roybon, L.; Petersen, A.; von Hoersten, S. Early Postnatal Behavioral, Cellular, and Molecular Changes in Models of Huntington Disease Are Reversible by HDAC Inhibition. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, E8765−E8774.
(43) Pernet, L.; Faure, V.; Gilquin, B.; Dufour-Guerin, S.; Khochbin, S.; Vourc'h, C. HDAC6-Ubiquitin Interaction Controls the Duration of HSF1 Activation after Heat Shock. *Mol. Biol. Cell* **2014**, *25*, 4187−4194.

https://dx.doi.org/10.1021/acsmedchemlett.0c00018
ACS Med. Chem. Lett. 2020, 11, 984−990