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Article

Identification and Optimization of Novel Small-Molecule Cas9 Inhibitors by Cell-Based High-Throughput Screening

Sang-Woo Lee,[¶] Kim Tai Tran,[¶] Ruben Vazquez-Uribe, Charlotte Held Gotfredsen, Mads Hartvig Clausen, Blanca Lopez Mendez, Guillermo Montoya, Anders Bach,* and Morten Otto Alexander Sommer*

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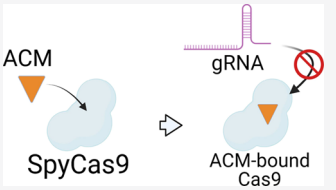
ABSTRACT: CRISPR/Cas9 has revolutionized several areas of life science; however, methods to control the Cas9 activity are needed for both scientific and therapeutic applications. Anti-CRISPR proteins are known to inhibit the CRISPR/Cas adaptive immunity; however, *in vivo* delivery of such proteins is problematic. Instead, small-molecule Cas9 inhibitors could serve as useful tools due to their permeable, proteolytically stable, and non-immunogenic nature. Here, we identified a small-molecule ligand with anti-CRISPR/Cas9 activity through a high-throughput screening utilizing an *Escherichia coli* selection system. Extensive structure−activity relationship studies, which involved a deconstruction−reconstruction strategy, resulted in a range of analogues with significant improvements in the inhibitory activity. Based on NMR and electrophoretic mobility shift assays, we propose that the inhibitory action of these compounds likely results from direct binding to apo-Cas9, preventing Cas9:gRNA complex formation. These molecules may find use as Cas9 modulators in various applications.



INTRODUCTION

Since their discovery, CRISPR/Cas systems have revolutionized gene editing in various species.[1,2] Among the different CRISPR/Cas systems, Cas9 has become the most popular tool owing to its simplicity and well-studied characteristics.[3,4] However, applications such as gene editing utilizing Cas9 activity require specific targeting; otherwise, non-specific targeting on off-target sites will cause unwanted mutations and pose potential risks.[5−8] Therefore, the activity and specificity of Cas9 should be carefully modulated, and developing fail-safe methods is crucial for Cas9-based editing.[9] Such anti-CRISPR reagent can also be used to detect Cas9 levels in the environment[10] or to improve phage therapy to treat drug-resistant bacteria harboring the CRISPR system.[11] Accordingly, identifying new classes of Cas9 inhibitors will further broaden numerous CRISPR/Cas9 applications.

Anti-CRISPR proteins have been found in nature as natural defense mechanisms against CRISPR/Cas systems.[12−14] The genes encoding these proteins are commonly found in phages, plasmids, and mobile elements to counteract CRISPR/Cas-based immunity in the host cell.[15−17] By their natural properties, anti-CRISPR proteins have been used for optimizing CRISPR-based applications. Anti-CRISPR proteins were used to reduce off-targeting by Cas9 in human cells[8] and to suppress a gene drive in yeast.[18] While protein-based anti-CRISPRs are useful tools to control the activity of Cas9, they have some limitations: (1) proteins are relatively large and thus cell membrane permeability is limited,[19,20] (2) proteins and small peptides tend to be quickly degraded *in vivo* by endogenous proteases, reducing their half-life and bioavailability,[20] and (3) proteins administered *in vivo* can potentially trigger undesired immune responses.[21,22] Small molecules may be an attractive alternative to protein-based anti-CRISPR agents in some applications. Small molecules are relatively more permeable across the membrane,[23] proteolytically stable *in vivo*,[24] and generally non-immunogenic[25] compared to protein counterparts; hence, they are more promising as tools or drugs for modulating the Cas9 activity. Recently, one small-molecule Cas9 inhibitor was identified by fluorescence polarization-based high-throughput screening (HTS);[26] however, identifying new classes of Cas9 inhibitors with a different mechanism of action can also benefit and expand potential Cas9 applications in the future.

In this work, we deployed an *Escherichia coli* selection system[27] to functionally identify small molecules with anti-CRISPR/Cas9 activity. Based on these hits, we investigated the structure−activity relationship (SAR) and synthesized a series of small molecules with inhibitory activity against *Streptococcus pyogenes* Cas9 (SpyCas9). These compounds were tested in various assays to further validate and investigate their mechanism of action.

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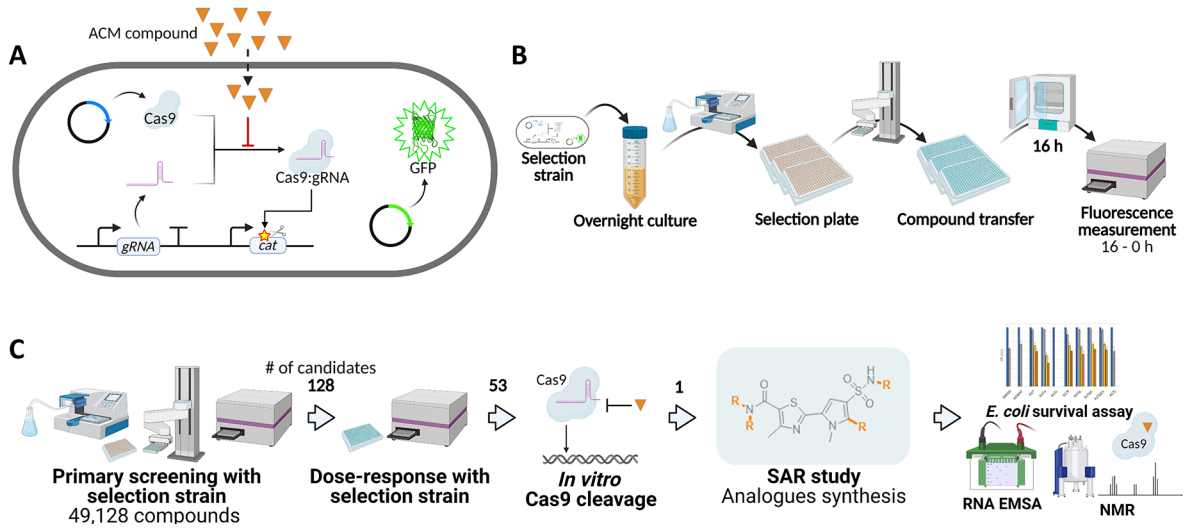

Figure 1. Design scheme and workflow of cell-based HTS in this study. (A) Design scheme of *E. coli* selection strain for HTS. SpyCas9 and gRNA are expressed under inducible promoter and target *cat* locus conferring chloramphenicol resistance. Small molecules with anti-CRISPR activity can inhibit cell death by chloramphenicol. Constitutively expressed GFP was measured as an indicator of cell growth. (B) Overall scheme of the primary screening in this study. Fresh selection strain grown overnight was dispersed in 384-well selection plates before automated compound transfer. The selection plates were incubated for 16 h at 37 °C to measure the fluorescence increase. (C) Overall workflow of this study. A total of 128 hits were selected after primary screening. We confirmed 128 hits in a similar setup with various concentrations and chose 53 hits for the next step. Only **compound 2** showed proper inhibition *in vitro*. After an extensive SAR study, we further validated **compound 2** and derivatives with various methods, including *E. coli* survival assay, NMR, and RNA EMSA.

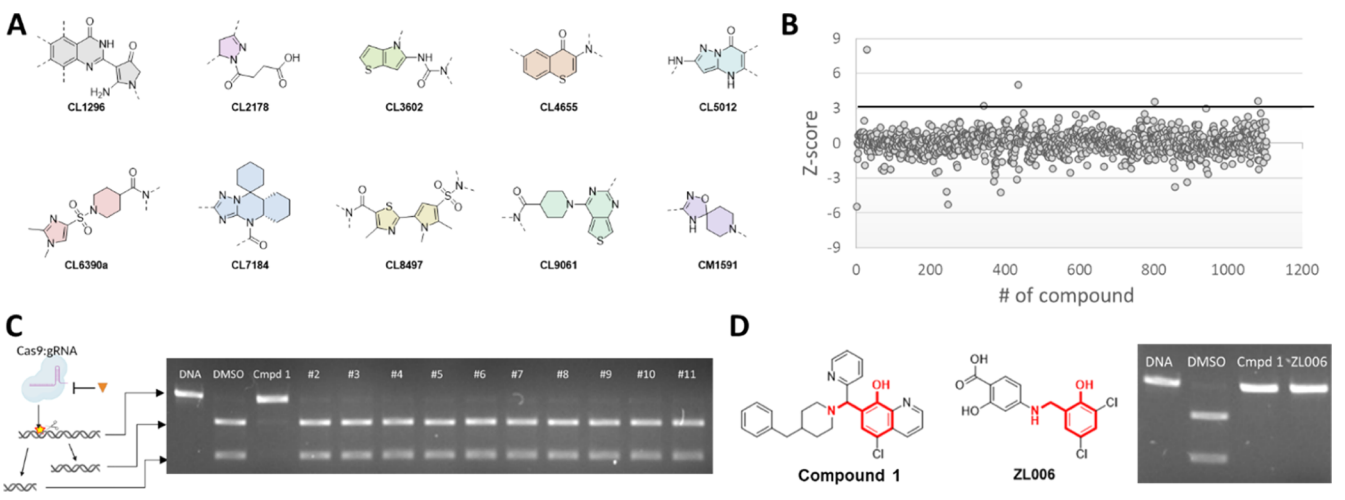

Figure 2. Initial scaffold selection for SAR study after the primary screening. (A) Structures and IDs of selected representative scaffolds from the ChemDiv Targeted Diversity Library. Stippled lines indicate variable R groups. **Compound 2** belongs in the CL8497 group. (B) Example of hit selection from primary screening. Candidates showing more than 3 times fluorescence increase than standard deviation (Z-score > 3) were chosen for the next step. (C) Example of *in vitro* Cas9 cleavage assay for validation. We tested the inhibitory activity of compounds by visualizing DNA cleavage by SpyCas9 *in vitro*. DMSO without any dissolved compound was used as a negative control. 53 candidates at 500 μM were tested, and only **compound 1** and **compound 2** showed inhibitory activity against SpyCas9. (D) **Compound 1** inactivates SpyCas9 similar to **ZL006**. Both are phenolic Mannich bases which are commonly described as PAINS.

RESULTS AND DISCUSSION

Selection Strain for Cell-Based Small-Molecule SpyCas9 Inhibitor Screening. For cell-based HTS, we designed an *E. coli* selection strain for screening the SpyCas9 inhibitory activity (Figure 1A).[27] SpyCas9 and gRNA are expressed from plasmids and form the Cas9:gRNA complex. This complex targets DNA encoding chloramphenicol resistance marker *cat*, leading to direct coupling of chloramphenicol resistance and SpyCas9 activity. In the absence of a SpyCas9 inhibitor, the cell will be susceptible to chloramphenicol, but with the inhibition of SpyCas9, the cell becomes resistant to chloramphenicol. Previously, we employed our selection strain to functionally identify anti-CRISPRs from metagenomic libraries and showed *in vivo* activity of anti-CRISPRs.[27] Here, we expected that HTS with our selection strain would also be applicable on small-molecule libraries. Since many compounds may precipitate in an aqueous cell growth medium, measuring optical density to monitor cell growth could be problematic. To circumvent this, we additionally expressed green fluorescent protein (GFP) in our selection strain as a sensitive indicator of cell growth, which was measured in the primary screening process instead

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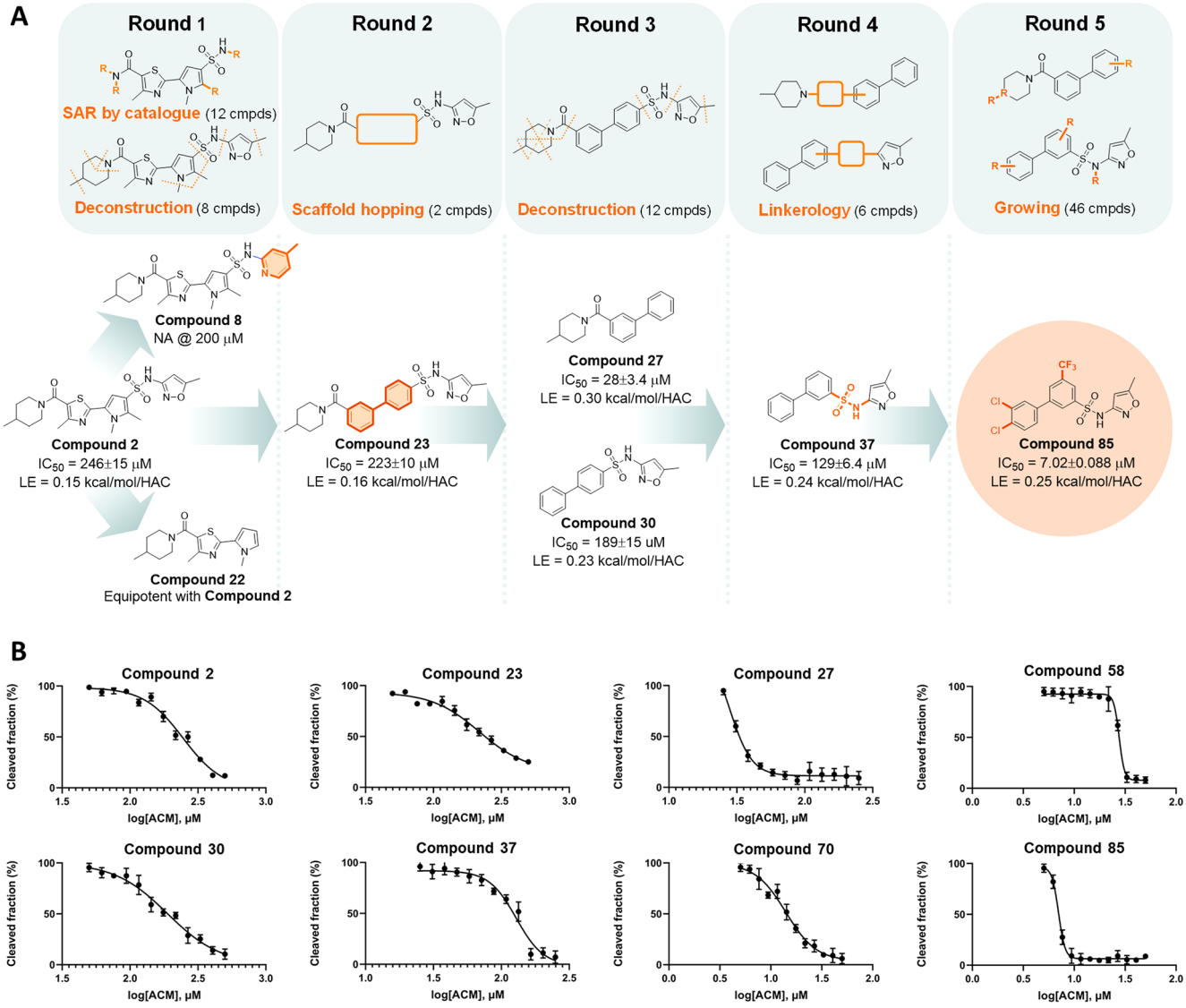

Figure 3. Overview of the **compound 2** SAR study. (A) We performed an extensive SAR study, which was divided into five rounds of optimization. The strategies and the number of compounds sampled are shown above in gray boxes, while key analogues from each round are shown together with their potency in the *in vitro* Cas9 cleavage assay. NA stands for no activity. (B) IC_{50} curve from *in vitro* Cas9 cleavage assay for selected ACM compounds. Cas9 cleavage assays were performed in triplicate. The IC_{50} values were determined with GraphPad Prism software. Error bars represent the standard deviation.

of optical density. Measuring fluorescence increase using a microplate reader allows for the detection of SpyCas9 inhibitory activity with our selection strain in a high-throughput fashion (Figure 1B).

Primary Screening and Hit Selection Criteria. We used our selection strain to isolate potential SpyCas9 inhibitors from a commercial library (ChemDiv Targeted Diversity Library, Figure 2A) of ∼50,000 drug-like molecules (Figure 1B). We incubated the compounds with our selection strain in a growth medium and measured fluorescence increase. Compounds inducing a more than 3-fold increase in fluorescence above the standard deviation of dimethyl sulfoxide (DMSO)-treated cells after 16 h incubation at 37 °C (Z-score > 3, Figure 2B) were selected as hits, but only if the fluorescence increase was not seen in a counter screen without the presence of the selection strain. To confirm the hits, a total of 128 primary hits were then further tested in dose−response experiments using the selection strain. From this, we obtained 53 promising hits reproducing a similar fluorescence increase (Z-score > 3), which were next subjected to *in vitro* activity evaluation (Figure 1C).

Small-Molecule Candidates Showed Inhibitory Activity against SpyCas9 *In Vitro*. We next tested the *in vitro* activity of the 53 hits in a Cas9 cleavage assay (Figure 2C). SpyCas9 was incubated with 500 μM of each compound, and Cas9 cleavage activity was determined by visualizing the target DNA bands in the agarose gel (Figure 2C). Triton X-100 (0.02%) was included in the assay buffer to avoid potential false-positives by aggregation.[28] From anti-CRISPR molecule (ACM) candidates, **compound 1** and **compound 2** showed inhibitory activity against SpyCas9 *in vitro*. However, **compound 1** includes a phenolic Mannich base—a PAINS motif that is well known to be able to cause artifacts in assays by chelating metal ions or covalently modifying proteins.[29−31] To probe whether our assay was sensitive toward these potential assay interferences, we tested an unrelated control

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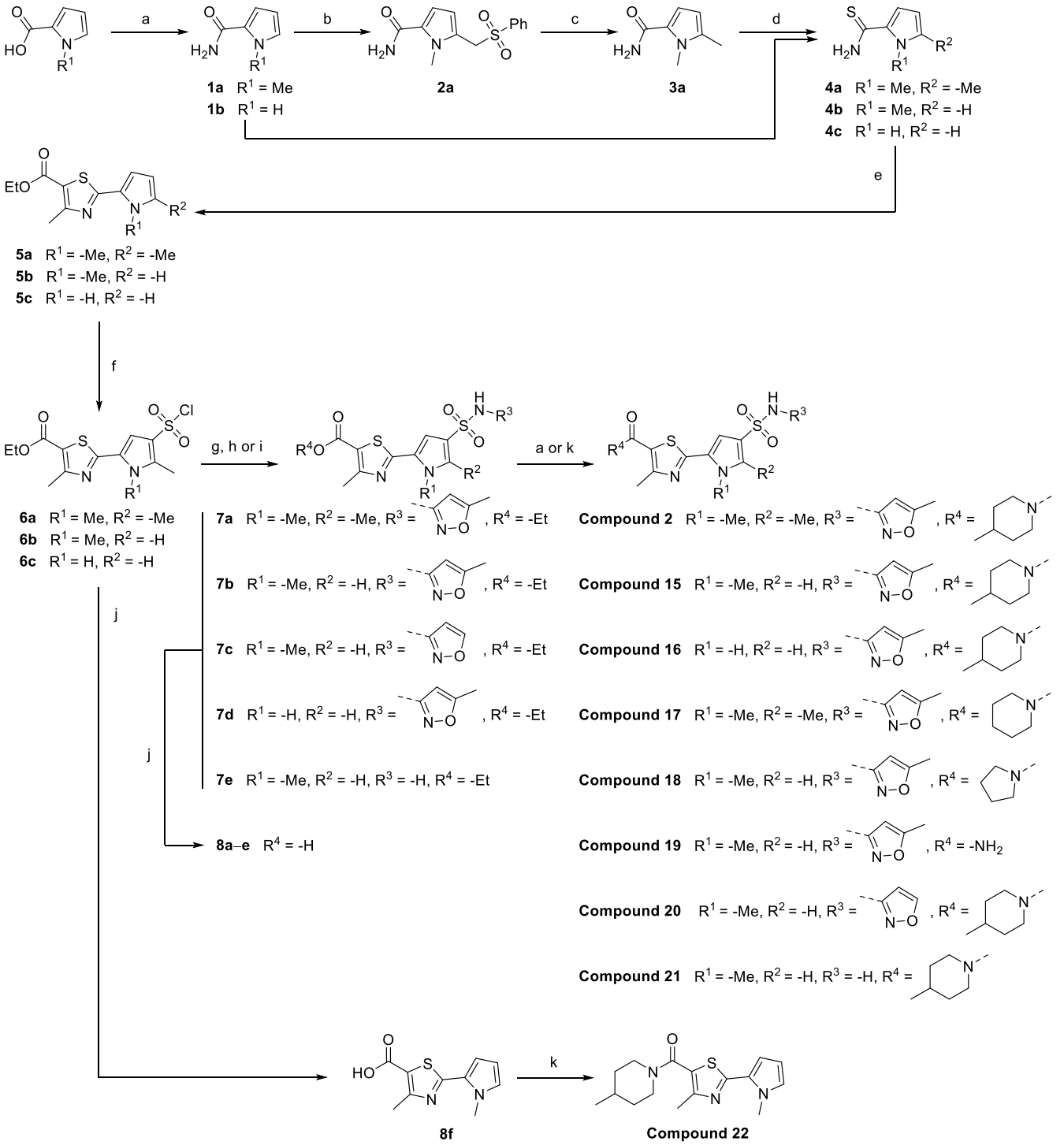
Scheme 1. Synthesis of Pyrrolylthiazole-Based Compounds[a]



[a]Reagents and conditions: (a) EDC·HCl, HOBt, DIPEA, DMF, 0 °C, and 0.5−1 h; then appropriate amine or NH_4Cl, rt, 5−47 h, and 70%-quantitative. (b) Baran PSMS reagent, TBHP, $PhCF_3$, H_2O, 0 °C−rt, 25 h, and quantitative. (c) SmI_2, THF, H_2O, rt, 0.5 h, and 88%. (d) Lawesson's reagent, THF, rt, 13−23 h, and 54%-quantitative. (e) Ethyl 2-chloroacetoacetate, pyridine, EtOH, reflux, 4−15 h, and 74%-quantitative. (f) $ClSO_3H$, MeCN, 0 °C−rt, 16−24 h, and 84%-quantitative. (g) Appropriate amine, pyridine, DCM, MW irradiation, 50 °C, 2 h, and 49%. (h) Appropriate amine, pyridine, DCM, reflux, 12−17 h, and 63−76%. (i) NH_4OH, 50 °C, 2.5 h, and quantitative. (j) aq. NaOH, EtOH, rt, 14−21 h, and 49%-quantitative. (k) HATU, DIPEA, DMF, 0 °C, and 30−45 min; and then appropriate amine, rt, 2.5−18 h, and 3−70%.

compound, **ZL006**,[32,33] which is structurally disparate from **compound 1** but carries the same phenolic Mannich base motif. We found that **ZL006** also showed strong inhibitory activity similar to **compound 1** (Figure 2D). The retainment of apparent activity despite the significant structural difference between the two molecules hints toward a non-specific mode of action attributable to the phenolic Mannich base. Thus, although we could not conclusively rule out genuine target engagement for **compound 1**, the known problems associated with the phenolic Mannich bases combined with the result of

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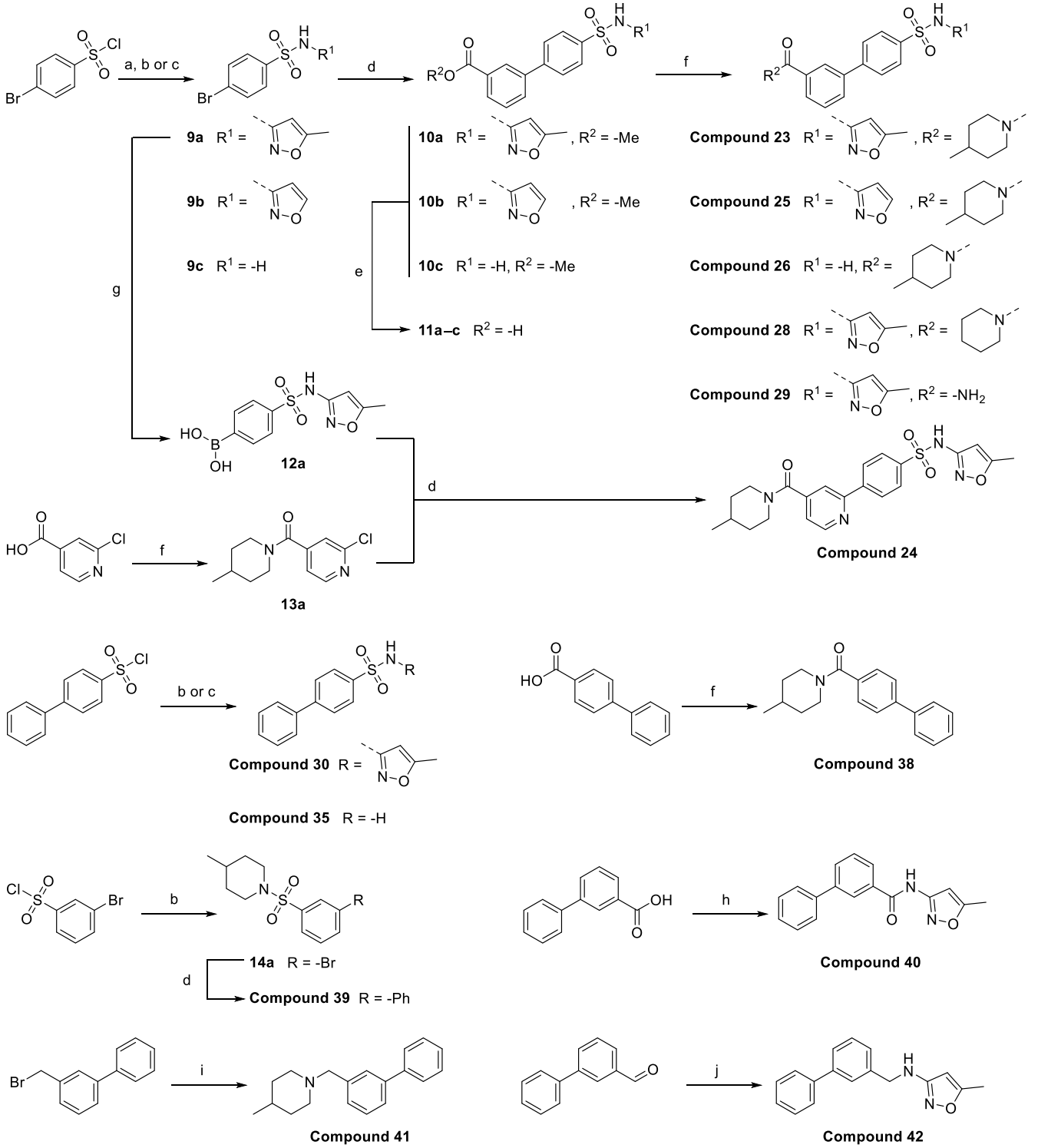
Scheme 2. Synthesis of Biphenyl-Based Compounds[a]



[a]Reagents and conditions: (a) 5-methylisoxazol-3-amine, pyridine, DCM, MW irradiation, 50 °C, 2 × 10 min, and 89%. (b) Appropriate amine, pyridine, DCM, 50 °C, 5−7 h, and 70−82%. (c) NH_4OH, 50 °C, 5−5.5 h, and 32−71%. (d) Appropriate boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3 or K_2CO_3, 1,4-dioxane, H_2O, 90−100 °C, 1−14 h, and 3−84%. (e) aq. NaOH, MeOH, rt, 16−24 h, and 93%-quantitative. (f) EDC·HCl, HOBt, DIPEA, DMF, 0 °C, and 10−60 min; then appropriate amine or NH_4Cl, rt, 12−23 h, and 21−82%. (g) $(Bpin)_2$, $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, reflux, 2 h, and yield ND. (h) $(COCl)_2$, DMF, DCM, 0 °C, and 2 h; then 5-methylisoxazol-3-amine, Et_3N, DCM, rt, 18 h, and 82%. (i) 4-Methylpiperidine, K_2CO_3, MeCN, 50 °C, 6.5 h, and 82%. (j) 5-Methylisoxazol-3-amine, EtOH, reflux, 2 h; then $NaBH_4$, MeOH, rt, 2 h, and 55%.

our control experiment made us decide to downprioritize this hit and focus on **compound 2**.

Compound 2 does not immediately feature any reactive or otherwise problematic chemical groups, and running the molecule through the property screening programs, FAF-

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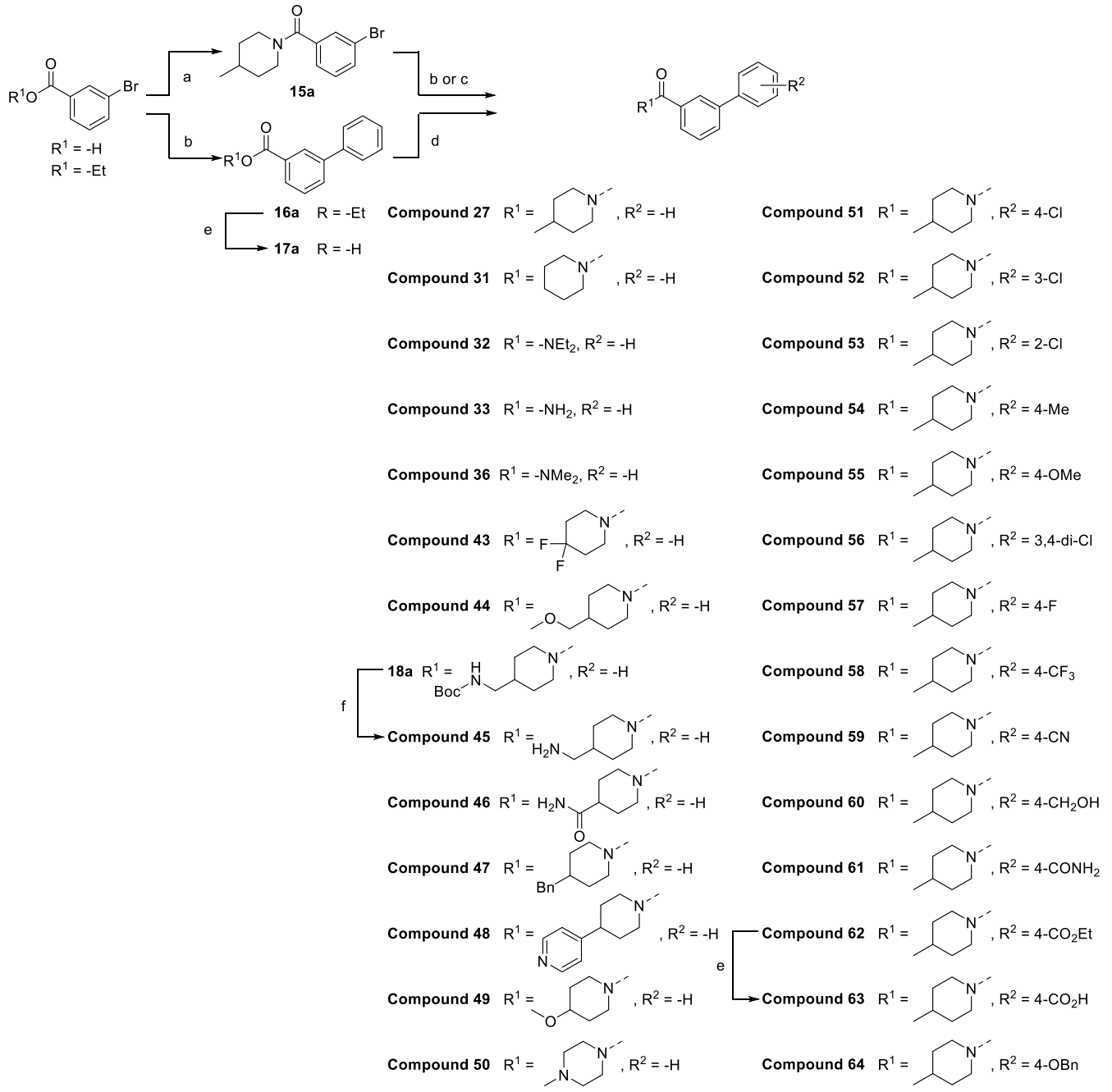
Scheme 3. Synthesis of Compound 27-Derived Compounds[a]



[a]Reagents and conditions: (a) HATU, DIPEA, DMF, 0 °C, and 30 min; then appropriate amine, rt, 1.5 h, and 82%. (b) Appropriate boronic acid, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, 90 °C, 1−14 h, and 42%-quantitative. (c) Appropriate boronic acid, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, MW irradiation, 90 °C, 10 min, and 46−91%. (d) EDC·HCl, HOBt, DIPEA, DMF, 0 °C, and 30 min; then appropriate amine or amine hydrochloride, rt, 18 h, and 37%-quantitative. (e) aq. NaOH, EtOH, rt, 13−22 h, and 82−95%. (f) TFA, DCM, 0 °C−rt, 16 h, and 62%.

Drugs4[34] and SwissADME,[35] resulted in no detected liabilities. In addition, to exclude undesired non-specific covalent or redox mode of action, **compound 2** was subjected to an LC−MS-based glutathione (GSH) assay. Gratifyingly, no adduct formation or redox chemistry was detected for **compound 2** in the incubation experiment (Figure S1). This supported that the activity of **compound 2** was at least not dependent on non-specific thiol reactivity.

SAR Study of Compound 2. In order to increase the potency of **compound 2** (Figure 3B, IC_{50} = 246 ± 15 μM), we performed extensive SAR studies guided by the *in vitro* Cas9 cleavage assay.

We commenced the studies by purchasing and testing a small library of commercially available analogues of the hit (Figure 3A, round 1, and Table S1). These analogues mainly sampled small changes to the peripheral isoxazole and piperidine rings. Surprisingly, we observed no improvement from the far majority of these analogues compared to **compound 2** in a preliminary test (Table S1). As an example, we observed no activity at 200 μM from the closely related pyridine analogue **compound 8**. These apparent activity cliffs

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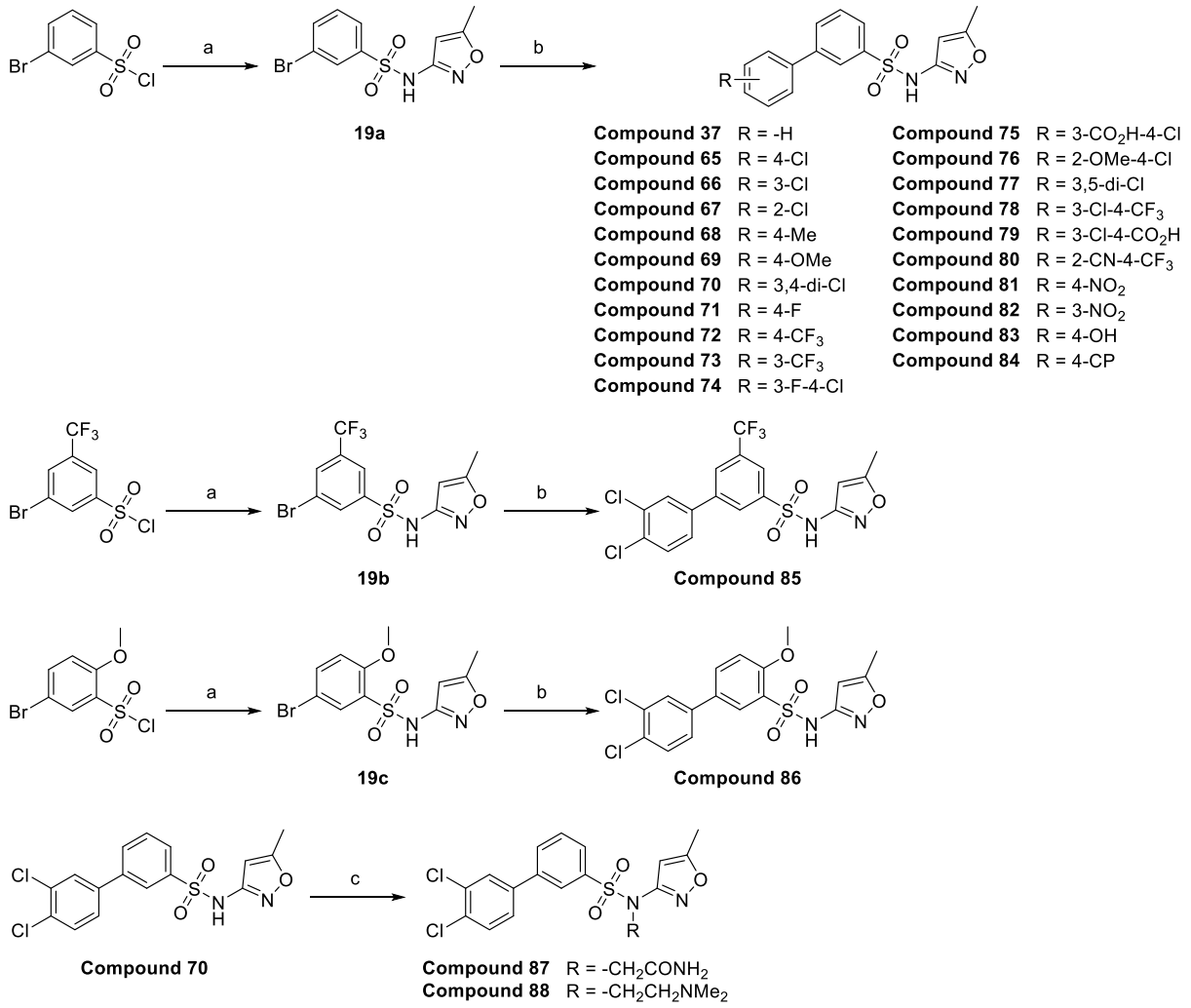
Scheme 4. Synthesis of Compound 37-Derived Compounds[a]



[a]Reagents and conditions: (a) 5-methylisoxazol-3-amine, pyridine, DCM, reflux, 4.5−5.5 h, and 60%-quantitative. (b) Appropriate boronic acid or ester, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, 90 °C, 1−2.5 h, and 15−91%. (c) Appropriate alkyl halide, K_2CO_3, DMF, 80 °C, 2.5−16 h, and 60−74%.

might suggest a tight ligand−protein complementarity but could also be a result of limited assay sensitivity not being able to detect small reductions in activity.

We next proceeded to synthesize analogues of **compound 2** (Schemes 1−4). We investigated if we could simplify the structure of **compound 2** by removing the multiple decorations on the pyrrolylthiazole core (Figure 3A, round 1, and Table S2). This revealed that all methyl groups are important and that retaining the piperidine and isoxazole rings is generally required for activity. Interestingly, removing both the isoxazole ring and the sulfonamide linker (**compound 22**) resulted in retained potency and thus in a significant increase in ligand efficiency.[36]

To facilitate further SAR studies, we next investigated scaffold hopping of the pyrrolylthiazole core into synthetically more accessible moieties (Figure 3A, round 2, and Table S3). Importantly, the biphenyl analogue **compound 23** retained potency (Figure 3B, IC_{50} = 223 ± 10 μM), and we thus proceeded with the SAR studies by focusing on this more synthetically feasible analogue.

Given the interesting result obtained by deconstructing **compound 2** into **compound 22**, we first investigated whether we could also simplify **compound 23** (Figure 3A, round 3, and Table S4). The results obtained from this were largely equivalent to those obtained for the pyrrolylthiazole core; that is, the decorating methyl groups were also important, and removing either the isoxazole or the piperidine ring while retaining the respective linkers (amide or sulfonamide) is generally not tolerable. Interestingly, removing both the isoxazole ring and the sulfonamide linker resulted in analogue **compound 27** with an 8-fold stronger activity (Figure 3B, IC_{50} = 28 ± 3.4 μM) and a significant increase in ligand efficiency[37] (LE = 0.29 kcal/mol/HAC compared with 0.16 kcal/mol/HAC for **compound 23**). The same phenomenon occurred when truncating the left-hand side of the molecule, that is, removing the piperidine ring and the amide linker to furnish analogue **compound 30**, which showed conserved potency (Figure 3B, IC_{50} = 189 ± 15 μM, LE = 0.23 kcal/mol/HAC). Further simplification of these two fragments, including making the unsubstituted biphenyl fragment **compound 34**, was not tolerated, which indicated that key pharmacophores had been isolated. It is unlikely that the two deconstructed fragments **compound 27** and **compound 30** retain the same binding mode as in the parent molecule, given that **compound**

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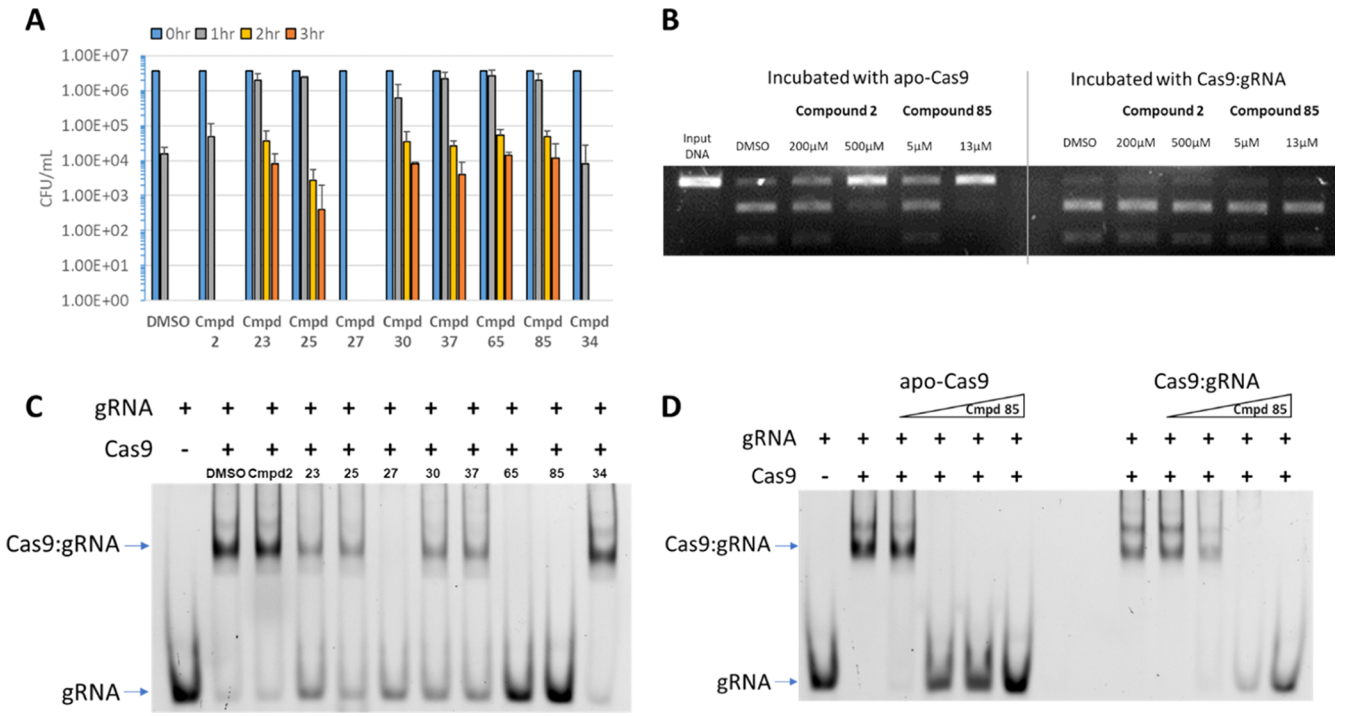

Figure 4. Validation of ACM compounds from the SAR study. (A) Selected ACM compounds from the SAR study helped the *E. coli* selection strain to survive SpyCas9-induced killing. Cell survival was generally correlated with the *in vitro* activity of ACM compounds. We also observed rapid cell death in samples containing **compound 27**, indicating cytotoxicity. Error bars represent the standard deviation derived from biological triplicates. (B) ACM compounds incubated with apo-Cas9 showed better inhibitory activity than with the Cas9:gRNA complex. Based on this result, we suspected that ACM compounds inhibit the assembly of the Cas9:gRNA complex. (C) RNA EMSA showed that ACM compounds (at 200 μM concentration) inhibit Cas9:gRNA complex formation. This result also generally correlated with activity from the previous *E. coli* survival assay (Figure 4A) and *in vitro* Cas9 cleavage assay (Figure 3). (D) RNA EMSA confirmed that **compound 85** (10, 25, 100, and 200 μM) can detach gRNA from preformed Cas9:gRNA complex while having weaker inhibitory activity. The same molar concentration (200 nM) for both apo-Cas9 and Cas9:gRNA complex was used.

23 does not benefit from merging these two fragments. It is more likely that the fragments more snuggly fit into place in subsites of the binding pocket and that combining them in the specific geometry provided in **compound 23** prohibits them from optimally occupying their subsites. Another possibility is that the two fragments occupy the same subsite given their structural similarity. We investigated this option by changing the regioisomery of the fragments and exchanging their linkers (Figure 3A, round 4, and Table S5). We here found the *meta*-regioisomery to be beneficial for **compound 30** as the resulting analogue **compound 37** featured a better potency (Figure 3B, IC_{50} = 129 ± 6.4 μM, LE = 0.24 kcal/mol/HAC).

We next turned to grow the identified fragments **compound 27** and **compound 37** into more potent compounds (Figure 3A, round 5). Growing efforts on **compound 27** focusing on extending or modifying the piperidine ring were generally unsuccessful with most of the analogues having reduced potency (Table S6). This suggested that the ring fitted tightly in a narrow subsite with limited space for further functionalization. Various substituents of different electronic and spatial properties were sampled on the distal phenyl ring. Generally, lipophilic substituents were tolerable with the trifluoromethyl analogue **compound 58** having a similar activity (Figure 3B, IC_{50} = 28 ± 0.34 μM) to **compound 27**. Polar functional groups on the other hand resulted in reduced activity. Growing efforts on **compound 37** were more successful, and a number of compounds displaying better potency were identified from sampling an exhaustive number of substituents on the distal phenyl ring (Table S7). Notably, the dichloro-substituted analogue **compound 70** (Figure 3B, IC_{50} = 14.0 ± 0.72 μM) had a 12-fold increased potency compared with **compound 37**. Further growing efforts, focusing on the core phenyl ring and the sulfonamide N−H vector, finally gave us the most potent analogue **compound 85** with single-digit micromolar potency (Figure 3B, IC_{50} = 7.02 ± 0.088 μM). This corresponded to an overall 35-fold improvement from the original hit **compound 2** and a dramatic improvement in ligand efficiency (0.15 kcal/mol for **compound 2** to 0.25 kcal/mol for **compound 85**).

In the absence of any available structural data, these medicinal chemistry efforts were exclusively ligand-based. Importantly, scaffold hopping from the initial pyrrolylthiazole core of **compound 2** to the equipotent but structurally simpler biphenyl core of **compound 23** was important to facilitate the rapid synthesis of follow-up analogues. Crucially, careful attention to the importance and redundancy of ligand motifs, partly guided by ligand efficiency, was instrumental in this study. Indeed, the sequential dissection of the initial structure allowed for the isolation of key pharmacophoric elements and removal of unproductive substituents, yielding fragments **compound 27**, **compound 30**, and **compound 37** with retained or even improved potencies. Followed by a systematic and exhaustive sampling of aryl substituents, this finally delivered our most potent **compound 85** showing significant improvement. It is a well-known limitation of HTS campaigns that poorly binding hits with low ligand efficiency (such as **compound 2** in this study) are often obtained.[38] We suggest that the deconstruction−reconstruction approach showcased

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in this study can serve as a generally applicable strategy toward optimizing HTS hits.

It is noticeable that **compound 85** is quite lipophilic (*clogP* = 5.65) and also features multiple hydrophobic motifs that are important for the activity of the compound—this could raise concerns on its specificity. However, surveying the *clogP* of all the analogues made across the optimization study shows that there is a poor correlation between lipophilicity and potency (Tables S1−S5). For instance, the most lipophilic analogue **compound 64** (*clogP* = 5.95) in the compound series shows only weak inhibitory activity (weaker than the parent **compound 27** with a *clogP* = 4.21). This suggests that the activity of **compound 85** is at least not only derived from its bulkiness and hydrophobicity.

Improved ACM Compounds from the SAR Study Validated in *E. coli*. We tested the activity of our improved compounds from the SAR study to validate their activity in the bacterial cell (Figure 4A). We incubated compounds with our selection strain and induced Cas9 activity to compare cell viability after Cas9 activation. Since other **compound 2** derivatives in this study showed activity to some extent, we also employed **compound 34** as a negative control, which was inactive in our *in vitro* cleavage assay (*vide supra*). The results hereof show that the SpyCas9-induced killing was more apparent in our negative controls. We observed that the activity of our selected compounds in *E. coli* survival assay (Figure 4A) generally correlated with the *in vitro* activity (Figure 3). Our strongest candidate from the SAR study, **compound 85**, also showed high cell viability after SpyCas9 induction. Interestingly, **compound 27** showed cytotoxicity (Figure 4A) while having relatively strong activity *in vitro* (Figure 3), suggesting non-specific activity toward cellular proteins. We observed no liable structural motifs within **compound 27** that could lead to toxicity via reactivity. Since we already ruled out aggregation by adding a surfactant (Triton X-100) in the assay buffer, we reason that the ligand—due to its fragment-like nature—is unspecific and can bind other targets inside the cells, resulting ultimately in cell death. Therefore, it suggests that careful assessment of cytotoxicity and *in vivo* validation are required for potential gene-editing applications with small molecules.

ACM Compounds Bind to Apo-Cas9. To further validate that the compounds bind directly to SpyCas9, we conducted a series of NMR-based protein−ligand interaction studies. Ligand-based NMR spectroscopy is a very powerful and information-rich analytical technology, and in the current study, both 1D proton (^{1}H)- and fluorine (^{19}F)-based experiments were used to evaluate the interactions.[39] For **compound 2**, **compound 23**, **compound 27**, **compound 37**, and **compound 65**, ^{1}H-based WaterLOGSY and saturation transfer difference experiments were performed, and for **compound 85**, both ^{1}H- and ^{19}F (CPMG)-based experiments were performed.[39] The NMR analyses confirmed the binding of all six compounds to apo-Cas9 (Figures S2−S7). By WaterLOGSY, ligand−Cas9 interactions are visible in the spectra in the form of signals with opposite phase (here negative) as opposed to non-binding ligands. We included alanine in the cocktail at the same concentration as the ligand to make sure that the spectra are phased correctly, hence verifying ligand binding. For **compound 85**, the ^{19}F CPMG experiments confirmed that it is a strong binder as the fluorine resonance was completely absent in the spectrum after the addition of SpyCas9 (Figure S8).

ACM Compounds Inhibit Cas9:gRNA Complex Formation. We have shown that our ACM compounds successfully inhibit the SpyCas9 activity *in vitro* and in *E. coli* survival assay (Figures 3 and 4A) and bind to apo-Cas9 (Figures S2−S8). Next, we conducted a series of experiments to further explore and elucidate their mechanism of action. First, in our *in vitro* Cas9 cleavage assay, ACM compounds showed stronger inhibition when preincubated with apo-Cas9 before adding gRNA compared to immediate incubation with the Cas9:gRNA complex (Figure 4B). This result suggests that our ACM compounds inhibit the assembly between gRNA and SpyCas9. To verify this hypothesis, we performed an electrophoretic mobility shift assay (EMSA) and thereby investigated if our compounds could disrupt Cas9:gRNA complex formation. We confirmed the inhibition of Cas9:gRNA interaction through RNA EMSA (Figure 4C). Furthermore, the activity from the *in vitro* Cas9 cleavage assay generally correlated with the gRNA binding inhibitory activity (Figures 3 and 4C). To investigate whether our compounds can detach gRNA from the preformed Cas9:gRNA complex, we incubated various concentrations of **compound 85** with a fixed amount of apo-Cas9 and Cas9:gRNA complex and compared them in the RNA EMSA (Figure 4D). **Compound 85** was able to detach gRNA from the preformed Cas9:gRNA complex while having weaker activity compared to apo-Cas9. This suggested that ACM compounds bind to apo-Cas9 to prevent Cas9:gRNA complex formation.

Based on these RNA EMSA studies together with observations from the *in vitro* cleavage assay in different incubation orders, we suggest that competitive inhibition of Cas9:gRNA complex formation is the likely major inhibition mechanism. We have yet to obtain structural data or mutagenesis studies to specify the binding site of our ACM compounds. Structural investigation by, for example, X-ray crystallography can demonstrate whether our ACM compounds interfere with the recognition (REC) lobe of SpyCas9, which is responsible for binding gRNA. Cas9−gRNA binding has previously been reported to be very tight (K_d in the picomolar range[40]) compared to the DNA binding affinity (nanomolar range[41]). This suggests that optimizing gRNA binding inhibitors can be more challenging, which is also supported by our observation in the first round of SAR where most of the **compound 2** derivatives displayed weaker potency (Tables S1 and S2).

Future studies should investigate the specificity of **compound 2** and its analogues (especially **compound 85**) since there were concerns about the role of hydrophobicity. Further optimization work should be directed toward the physicochemical properties of the inhibitors and should aim to bring them into a more drug-like space.

CONCLUSIONS

CRISPR/Cas9 and its applications bear great potentials; however, the non-specificity of Cas9 may lead to unwanted mutations. Therefore, precise control of Cas9 activity is an important target for drug activity. Small-molecule Cas9 inhibitors can be useful due to their permeability, proteolytic stability, and non-immunogenicity. In this study, we identified a new class of small-molecule SpyCas9 inhibitors using HTS with an *E. coli* selection strain. We further improved this scaffold (**compound 2**) via a SAR study. Multiple rounds of optimization finally delivered our most potent compound (**compound 85**) with significantly higher potency (35-fold

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improvement) and ligand efficiency. Further validation showed that inhibiting gRNA binding is likely the major inhibition mechanism. These compounds can potentially be applied to modulate and control Cas9 activity in various applications.

EXPERIMENTAL SECTION

Bacterial Strain and Growth Condition. We used a selection strain expressing GFP (bRU003) from our previous study.[27] For growth medium, synthetic M9 medium supplemented with 1% (w/v) glucose, 0.1% (w/v) casamino acids, 50 μg/mL spectinomycin, 50 μg/mL kanamycin, and 120 μg/mL chloramphenicol was used. 2 mM theophylline and 1% (w/v) arabinose were used to activate SpyCas9-induced killing.

High-Throughput Hit Selection from the Small-Molecule Library for Primary Screening. Primary screening was conducted at the ICCB-Longwood Screening Facility. We used our selection strain to isolate small molecules that can inhibit the SpyCas9 activity. The selection strain was streaked on a plate, and a single colony was inoculated for the primary screening. We diluted and dispersed the overnight culture of the selection strain in 384-well plates to make the selection plate. Compounds from ChemDiv small-molecule library (Targeted Diversity Library) were transferred to the selection plate [final 50 mg/L concentration in DMSO 1% (v/v)] and initial fluorescence was measured. After 16 h of incubation at 37 °C, the selection plate was measured again to determine the fluorescence change. Selection plates were briefly mixed by vortexing before every measurement. We calculated Z-score in each plate to isolate potential candidates which showed fluorescence increase larger than 3 standard deviations (Figure 2B). We also measured fluorescence in the counterselection plate (without selection strain) to rule out false-positive from autofluorescent molecules. Based on this, we selected 128 candidates [hit rate: 0.26% (128/49,128)] and confirmed them again in a dose−response test. 53 hits displaying reproducible fluorescence increase in three concentrations (5, 16.7, and 50 mg/L) compared to DMSO control (Z-score > 3) were selected for *in vitro* confirmation.

***In Vitro* Cas9 Cleavage Assay.** The DNA cleavage assay was carried out similar to our previous study with modification.[27] First, we incubated 5 nM SpyCas9 (New England Biolabs) with DMSO-dissolved compounds [final concentration: 5% (v/v)] for 15 min at 37 °C in a reaction buffer [PBS buffer + 10 mM $MgCl_2$ + 0.02% (v/v) Triton-X 100]. We added 6 nM gRNA [preformed Alt-R crRNA/tracrRNA duplex (Integrated DNA Technology)] and incubated for 5 min. Finally, 1 nM PCR-amplified DNA target was added and incubated for another 30 min for DNA cleavage. The reaction was quenched by proteinase K and visualized in 1% agarose gel. We tested 53 candidates from primary screening in relatively high concentrations (500 μM) so that we would not lose any weak inhibitors. The band intensity was quantified with ImageJ software, and the IC_{50} value was determined with the equation [Y = bottom + (top − bottom)/(1 + 10^((logIC_{50} − X) × HillSlope))] using the GraphPad Prism software.

GSH Assay. **Compound 2** was incubated at 500 μM with 1 mM GSH in an aqueous buffer (20 mM HEPES, 100 mM NaCl, 5 mM $MgCl_2$, and 0.1 mM EDTA) at 37 °C for 30 min. Subsequently, the assay mix was analyzed by LC−MS. The known cysteine-targeting covalent modifier sulforaphane was used as a positive control. Samples containing blank GSH and **compound 2** in the same aqueous buffer were used as negative controls.

***E. coli* Survival Assay for SpyCas9 Inhibitory Activity.** The selection strain was incubated with 200 μM of each ACM compound at 37 °C overnight in a growth medium supplemented with 0.1 mg/L polymyxin B to improve the permeability of compounds.[42] The respective culture was diluted in the same medium containing 200 μM compound and induced to compare the survivability after SpyCas9-induced killing. Each culture containing ACM compound was incubated at 37 °C in a 96-well plate. Colony-forming unit was measured every 1 h by counting colonies on LB-agar supplemented with 50 μg/mL spectinomycin, 50 μg/mL kanamycin, and 30 μg/mL chloramphenicol from serial-diluted cultures.

NMR-Based Protein−Ligand Interaction Studies. The NMR experiments were all performed using standard pulse sequences. Detail on the experiments is included in the Supporting Information.

Electrophoretic Mobility Shift Assay. The reaction was carried out in the same reaction buffer (PBS buffer + 10 mM $MgCl_2$ + 0.02% Triton-X 100). Fluorescently labeled gRNA was prepared by forming a duplex between Alt-R crRNA and Atto550-labeled tracrRNA (Integrated DNA Technology). For apo-Cas9, the ACM compound was incubated with 200 nM SpyCas9 (New England Biolabs) at 37 °C for 5 min. Then, 200 nM fluorescent-labeled gRNA was added and incubated for another 15 min. Lastly, the reaction was resolved and visualized on 6% TBE gel (Thermo Fisher Scientific). For Cas9:gRNA complex, 200 nM SpyCas9 and 200 nM fluorescent-labeled gRNA were incubated at 37 °C for 15 min to form a complex. Then, the ACM compound was incubated with the 200 nM Cas9:gRNA complex at 37 °C for 15 min and visualized on 6% TBE gel (Schemes 1−4).

Synthesis of ACM Compounds for SAR Study (Schemes 1−4). All chemicals and solvents were purchased from chemical vendors and used without prior purification. **Compound 2**, **compound 3** to **compound 14**, and **compound 34** were purchased from chemical vendors. However, to confirm the activity of the hit **compound 2**, the compound was also synthesized for retesting. All temperatures are given in degree Celsius (°C). Room temperature (rt) refers to temperatures of 20−25 °C. All reactions were conducted under anhydrous conditions in a nitrogen (N_2) atmosphere unless otherwise stated. Thin-layer chromatography (TLC) analysis was performed using TLC silica gel 60 F_{254} aluminum plates (Merck) and appropriate eluent systems. Visualization was performed using UV light (254 nm) and/or appropriate stains. ^{1}H NMR and ^{13}C NMR spectra were recorded using a 600 MHz Bruker Avance III HD instrument equipped with a cryogenically cooled 5 mm dual probe or a 400 MHz Bruker Avance III instrument equipped with a 5 mm broad-band probe. Samples were dissolved in DMSO-d_6 (VWR Chemicals, 99.80% D) or chloroform-d (Cambridge Isotope Laboratories, Inc., 99.8% D) and analyzed at 300 K. Chemical shifts (δ) are reported in ppm, referenced to DMSO-d_6 (^{1}H: 2.500 ppm and ^{13}C: 39.520 ppm) or chloroform-d (^{1}H: 7.260 ppm and ^{13}C: 77.160 ppm). Coupling constants (J) are reported in Hz. Abbreviations for multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; ddd, doublet of doublet of doublets; dt, doublet of triplets; td, triplet of doublets; and ttt, triplet of triplet of triplets. LC−MS analyses were carried out using either: (1) An Agilent 6410 Triple Quadrupole mass spectrometer instrument with electron spray ionization (ESI) coupled to an Agilent 1200 HPLC system, a C18 reverse-phase column (Zorbax Eclipse XBD-C18, 4.6 mm × 50 mm), an autosampler and a diode array detector, and a linear gradient of buffer A (Milli-Q H_2O/MeCN/formic acid, 95:5:0.1 v/v %) to buffer B (Milli-Q H_2O/MeCN/formic acid, 5:95:0.043 v/v %) with a flow rate of 1 mL/min. LC−MS was performed with positive (pos.) ion mode detection; (2) an Agilent 6130 mass spectrometer instrument using ESI coupled to an Agilent 1200 HPLC system with a C18 reverse-phase column (Zorbax Eclipse XBD-C18, 4.6 mm × 50 mm), an autosampler, and a diode array detector, using a linear gradient of the binary solvent system of buffer A (Milli-Q/H_2O/MeCN/formic acid, 95:5:0.1 v/v %) to buffer B (MeCN/formic acid, 100:0.1 v/v %) with a flow rate of 1 mL/min; and (3) a Waters Acquity H-class UPLC with a Sample Manager FTN and a TUV dual wavelength detector coupled to a QDa single quadrupole analyzer using ESI. UPLC separation was achieved with a C18 reversed-phase column (Acquity UPLC BEH C18, 2.1 mm × 50 mm, 1.7 μm) operated at 40 °C using a linear gradient of the binary solvent system of buffer A (Milli-Q H_2O/MeCN/formic acid, 95:5:0.1 v/v %) to buffer B (MeCN/formic acid, 100:0.1 v/v %) from 0 to 100% B in 3.5 min and then 1 min at 100% buffer B, maintaining a flow rate of 0.8 mL/min. Silica gel flash chromatography was carried out using prepacked RediSep Rf silica flash cartridges on a CombiFlash Rf + apparatus equipped with a detector with UV wavelengths at 254 and 280 nm.

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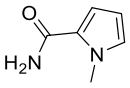
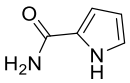
Heptane/EtOAc or dichloromethane (DCM)/MeOH were used as eluent systems. Reverse-phase preparative HPLC was performed using an Agilent 1200 series HPLC preparative system with an Agilent Zorbax 300-SB-C18 column (21.2 × 250 mm). A binary solvent system consisting of buffer A (Milli-Q H_2O/MeCN/TFA 95:5:0.1 v/v %) and buffer B (Milli-Q H_2O/MeCN/TFA 5:95:0.1 v/v %) was employed in various gradients. Microwave (MW)-assisted synthesis was carried out using a Biotage Initiator+ apparatus. All final compounds used for subsequent assaying had a purity of >95% as assessed by ^{1}H NMR and the LC−MS UV-trace.

*1-Methyl-1H-pyrrole-2-carboxamide (**1a**).*



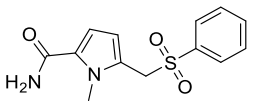
To a round-bottomed flask charged with a magnetic stirring bar was added a solution of 1-methyl-1*H*-pyrrole-2-carboxylic acid (0.626 g, 5.00 mmol, 1.00 equiv) in anhydrous dimethylformamide (DMF) (20.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.438 g, 7.50 mmol, 1.50 equiv), HOBt (1.013 g, 7.50 mmol, 1.50 equiv), and DIPEA (2.61 mL, 15.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, NH_4Cl (0.535 g, 10.0 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 14 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (100 mL). The mixture was extracted with EtOAc (4× 100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* (co-evaporating with toluene two times) to furnish a brown oil. The crude was purified by silica gel flash chromatography (DCM/MeOH, 0−10%) to afford the desired product **1a** as a white solid (0.34 g, 2.74 mmol, 55%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 (s, 1H), 6.86 (t, J = 2.2 Hz, 1H), 6.78 (dd, J = 3.9, 1.8 Hz, 1H), 5.98 (dd, J = 3.9, 2.5 Hz, 1H), 3.82 (s, 3H).

*1H-Pyrrole-2-carboxamide (**1b**).*



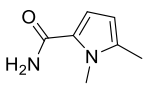
To a round-bottomed flask charged with a magnetic stirring bar was added a solution of 1*H*-pyrrole-2-carboxylic acid (1.11 g, 10.0 mmol, 1.00 equiv) in anhydrous DMF (20.0 mL). Under cooling at 0 °C were then added EDC·HCl (2.88 g, 15.0 mmol, 1.50 equiv), HOBt (2.03 g, 15.0 mmol, 1.50 equiv), and DIPEA (5.23 mL, 30.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 45 min. After preactivation, NH_4Cl (1.07 g, 20.0 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (20 mL) and concentrated *in vacuo*. The mixture was extracted with EtOAc (5× 20 mL) and 15% *i*-PrOH in EtOAc (3× 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* (co-evaporating with toluene two times). The crude was purified by silica gel flash chromatography (DCM/MeOH, 0−10%) to afford the desired product **1b** as a white solid (0.79 g, 7.15 mmol, 72%). ^{1}H NMR (400 MHz, DMSO-d_6 J = 2.7, 1.5 Hz, 1H), 6.75 (ddd, J = 3.9, 2.5, 1.5 Hz, 1H), 6.05 (dt, J = 3.6, 2.4 Hz, 1H).

*1-Methyl-5-((phenylsulfonyl)methyl)-1H-pyrrole-2-carboxamide (**2a**).*



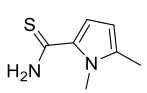
A previously reported protocol by Gui et al. was followed.[43] To a vial charged with a magnetic stirring bar were added 1-methyl-1*H*-pyrrole-2-carboxamide (**1a**; 0.124 g, 1.00 mmol, 1.00 equiv) and zinc bis[(phenylsulfonyl)methanesulfinate] (Baran PSMS reagent, synthesized according to previously reported protocol;[43] 0.756 g, 1.45 mmol, 1.45 equiv) in $PhCF_3$ (5.0 mL) and H_2O (2.0 mL). Under cooling at 0 °C was then added 70% aq. TBHP (0.684 mL, 5.00 mmol, 5.00 equiv). The mixture was stirred at 0 °C for 5 min and then at rt for 25 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (10 mL) and 5% aq. EDTA−2Na solution (10 mL). The mixture was extracted with DCM (25 mL) and EtOAc (3× 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **2** (0.31 g, ∼1.0 mmol, ∼quant.) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81−7.71 (m, 3H), 7.65−7.58 (m, 2H), 7.47 (s, 1H), 6.91 (s, 1H), 6.68 (d, J = 4.0 Hz, 1H), 5.77 (d, J = 3.9 Hz, 1H), 4.79 (s, 2H), 3.71 (s, 3H).

*1,5-Dimethyl-1H-pyrrole-2-carboxamide (**3a**).*



A previously reported protocol by Gui et al. was followed.[43] To a vial charged with a magnetic stirring bar was added a solution of 1-methyl-5-((phenylsulfonyl)methyl)-1*H*-pyrrole-2-carboxamide (**2**; 0.214 g, 0.77 mmol, 1.00 equiv) in tetrahydrofuran (THF) (15.0 mL) and H_2O (1.5 mL). The solution was degassed with N_2 for 20 min. Then 0.1 M SmI_2 in THF (46.1 mL, 4.61 mmol, 6.00 equiv) was added in one portion. The mixture was stirred at rt for 30 min. Upon reaction completion as determined by LC−MS, the reaction was quenched by opening the mixture to air, and the mixture was subsequently concentrated *in vacuo* to remove THF. The residue was added sat. aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (4× 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a brown oily solid. The crude was purified by silica gel flash chromatography (DCM/MeOH, 0−5%) to afford the desired product **3** as a light-yellow solid (0.094 g, 0.68 mmol, 88%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26 (s, 1H), 6.69 (d, J = 3.8 Hz, 1H), 5.79 (dd, J = 3.8, 0.9 Hz, 1H), 3.74 (s, 3H), 2.17 (s, 3H).

*1,5-Dimethyl-1-pyrrole-2-carbothioamide (**4a**).*



To a round-bottomed flask charged with a magnetic stirring bar was added a solution of 1,5-dimethyl-1*H*-pyrrole-2-carboxamide (**3**; 0.12 g, 0.85 mmol, 1.00 equiv) in anhydrous THF (10.0 mL). The solution was degassed with N_2 for 5 min. Then, at rt was added Lawesson's reagent (0.41 g, 1.02 mmol, 1.20 equiv). The mixture was stirred at rt for 15 h. Upon reaction completion as determined by LC−MS, the mixture

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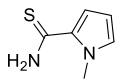
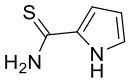
was concentrated *in vacuo* to remove THF. The crude was purified by silica gel flash chromatography (DCM) to afford the desired product **4a** as a light-yellow solid (0.070 g, 0.45 mmol, 54%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.90 (s, 1H), 8.73 (s, 1H), 6.59 (d, J = 3.8 Hz, 1H), 5.84 (dd, J = 3.9, 0.9 Hz, 1H), 3.84 (s, 3H), 2.19 (d, J = 0.7 Hz, 3H).

*1-Methyl-1H-pyrrole-2-carbothioamide (**4b**).*



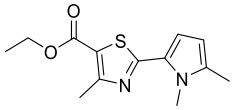
To a round-bottomed flask charged with a magnetic stirring bar was added a solution of 1-methyl-1*H*-pyrrole-2-carboxamide (**1a**; 0.248 g, 2.00 mmol, 1.00 equiv) in anhydrous THF (20.0 mL). The solution was degassed with N_2 for 10 min. Then, at rt was added Lawesson's reagent (0.971 g, 2.40 mmol, 1.20 equiv). The mixture was stirred at rt for 15 h. Upon reaction completion as determined by LC−MS, the mixture was concentrated *in vacuo* to remove THF. The crude was purified by silica gel flash chromatography (DCM/MeOH, 0−10%) to afford the desired product **4b** as a yellow oil (0.18 g, 1.27 mmol, 64%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.07−6.88 (m, 2H), 6.85 (t, J = 2.2 Hz, 1H), 6.62 (dd, J = 4.1, 1.7 Hz, 1H), 6.11 (dd, J = 4.0, 2.6 Hz, 1H), 4.08 (s, 3H).

*1H-Pyrrole-2-carbothioamide (**4c**).*



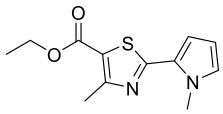
To a round-bottomed flask charged with a magnetic stirring bar was added a solution of 1*H*-pyrrole-2-carboxamide (**1b**; 0.220 g, 2.00 mmol, 1.00 equiv) in anhydrous THF (20.0 mL). The solution was degassed with N_2 for 10 min. Then, at rt was added Lawesson's reagent (0.971 g, 2.40 mmol, 1.20 equiv). The mixture was stirred at rt for 13 h. Upon reaction completion as determined by LC−MS, the mixture was concentrated *in vacuo* to remove THF. The crude was purified by silica gel flash chromatography (DCM/MeOH, 0−10%) to afford the desired product **4c** as a slightly green crystalline solid (0.25 g, 2.00 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6 10.90 (m, 1H), 9.01 (s, 1H), 8.89 (s, 1H), 6.95 (td, J = 2.7, 1.5 Hz, 1H), 6.89 (ddd, J = 3.9, 2.5, 1.5 Hz, 1H), 6.14 (dt, J = 3.8, 2.4 Hz, 1H).

*Ethyl 2-(1,5-Dimethyl-1H-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**5a**).*



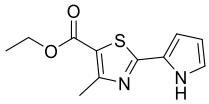
To a round-bottomed flask charged with a magnetic stirring bar was added a solution of 1,5-dimethyl-1-pyrrole-2-carbothioamide (**4a**; 0.070 g, 0.45 mmol, 1.00 equiv) in anhydrous EtOH (10.0 mL). Then, ethyl 2-chloroacetoacetate (0.062 mL, 0.45 mmol, 1.00 equiv) and pyridine (0.036 mL, 0.45 mmol, 1.00 equiv) were added. The mixture was stirred at reflux for 4 h. Upon reaction completion as determined by LC−MS, the mixture was concentrated *in vacuo* to remove EtOH. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−10%) to afford the desired product **5a** as a white crystalline solid (0.088 g, 0.33 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.75 (d, J = 3.9 Hz, 1H), 5.97 (dd, J = 3.9, 0.9 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 2.63 (s, 3H), 2.25 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H).

*Ethyl 4-Methyl-2-(1-methyl-1H-pyrrol-2-yl)thiazole-5-carboxylate (**5b**).*



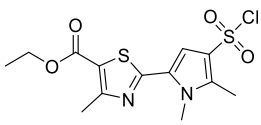
To a round-bottomed flask charged with a magnetic stirring bar was added a solution of 1-methyl-1*H*-pyrrole-2-carbothioamide (**4b**; 0.52 g, 3.71 mmol, 1.00 equiv) in anhydrous EtOH (50.0 mL). Then, ethyl 2-chloroacetoacetate (0.513 mL, 3.71 mmol, 1.00 equiv) and pyridine (0.300 mL, 3.71 mmol, 1.00 equiv) were added. The mixture was stirred at reflux for 5 h. Upon reaction completion as determined by TLC, the mixture was concentrated *in vacuo* to remove EtOH. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−20%) to afford the desired product **5b** as a yellowish solid (0.79 g, 3.16 mmol, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.07 (t, J = 2.2 Hz, 1H), 6.83 (dd, J = 4.0, 1.7 Hz, 1H), 6.14 (dd, J = 4.0, 2.6 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 2.64 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H).

*Ethyl 4-Methyl-2-(1H-pyrrol-2-yl)thiazole-5-carboxylate (**5c**).*



To a round-bottomed flask charged with a magnetic stirring bar was added a solution of 1-methyl-1*H*-pyrrole-2-carbothioamide (**4c**; 0.25 g, 2.00 mmol, 1.00 equiv) in anhydrous EtOH (20.0 mL). Then, ethyl 2-chloroacetoacetate (0.28 mL, 2.00 mmol, 1.00 equiv) and pyridine (0.16 mL, 2.00 mmol, 1.00 equiv) were added. The mixture was stirred at reflux for 15 h. Upon reaction completion as determined by LC−MS, the mixture was concentrated *in vacuo* to remove EtOH. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−50%) to afford the desired product **5c** as a white solid (0.47 g, 2.00 mmol, quantitative). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.96 (s, 1H), 7.00 (td, J = 2.7, 1.4 Hz, 1H), 6.83 (ddd, J = 3.8, 2.5, 1.5 Hz, 1H), 6.20 (dt, J = 3.7, 2.3 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.63 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 161.98, 161.59, 160.00, 125.22, 123.34, 117.54, 111.95, 110.29, 60.83, 17.08, 14.16.

*Ethyl 2-(4-(Chlorosulfonyl)-1,5-dimethyl-1H-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**6a**).*



To a vial charged with a magnetic stirring bar was added ethyl 2-(1,5-dimethyl-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**5a**; 0.088 g, 0.33 mmol, 1.00 equiv) in anhydrous MeCN (2.0 mL). Under cooling at 0 °C was then added $ClSO_3H$ (0.110 mL, 1.65 mmol, 5.00 equiv). The mixture was stirred at 0 °C and allowed to slowly reach rt over 16 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of ice-cold water (5 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **6a** as a light-yellow solid (0.11 g, 0.31 mmol, 94%) used without further purification. ^{1}H NMR (400

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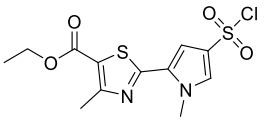
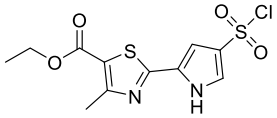
MHz, DMSO-d_6): δ 6.74 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 2.63 (s, 3H), 2.37 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.15, 161.52, 159.70, 133.92, 129.53, 121.92, 117.49, 112.93, 60.92, 32.60, 17.31, 14.18, 10.60.

*Ethyl 2-(4-(Chlorosulfonyl)-1-methyl-1H-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**6b**).*



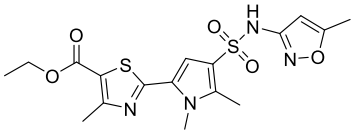
To a vial charged with a magnetic stirring bar was added ethyl 4-methyl-2-(1-methyl-1*H*-pyrrol-2-yl)thiazole-5-carboxylate (**5b**; 0.50 g, 2.00 mmol, 1.00 equiv) in anhydrous MeCN (10.0 mL). Under cooling at 0 °C was then added $ClSO_3H$ (0.66 mL, 10.0 mmol, 5.00 equiv). The mixture was stirred at 0 °C for 5 min and then stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of ice-cold water (20 mL). The mixture was extracted with EtOAc (3× 30 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **6b** as a light-yellow solid (0.82 g, ∼2.0 mmol, ∼quant.) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.16 (d, J = 1.8 Hz, 1H), 6.75 (d, J = 1.9 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 2.64 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H).

*Ethyl 2-(4-(Chlorosulfonyl)-1H-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**6c**).*



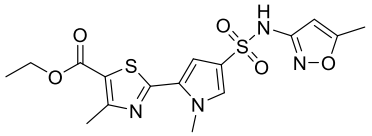
To a vial charged with a magnetic stirring bar was added ethyl 4-methyl-2-(1*H*-pyrrol-2-yl)thiazole-5-carboxylate (**5c**; 0.236 g, 1.00 mmol, 1.00 equiv) in anhydrous MeCN (6.0 mL). Under cooling at 0 °C was then added $ClSO_3H$ (0.332 mL, 5.00 mmol, 5.00 equiv). The mixture was stirred at 0 °C and slowly allowed to reach rt over 24 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of ice-cold water (15 mL). The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **6c** as a yellow solid (0.28 g, 0.83 mmol, 84%) used without further purification. ^{1}H NMR (400 MHz, chloroform-*d*): δ 10.68 (s, 1H), 7.64 (d, J = 1.6 Hz, 1H), 7.15 (d, J = 1.5 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.71 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H).

*Ethyl 2-(1,5-Dimethyl-4-(N-(5-methylisoxazol-3-yl)sulfamoyl)-1H-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**7a**).*



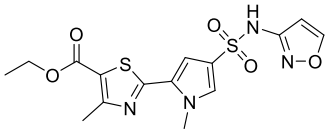
To a pressure vial charged with a magnetic stirring bar were added ethyl 2-(4-(chlorosulfonyl)-1,5-dimethyl-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**6a**; 0.11 g, 0.31 mmol, 1.00 equiv), 5-methylisoxazol-3-amine (0.185 g, 1.89 mmol, 6.08 equiv), pyridine (0.20 mL, 2.48 mmol, 8.00 equiv), and DCM (2.0 mL). The vial was capped, and the mixture was subjected to MW irradiation at 50 °C for 2 h. Upon reaction completion as determined by TLC, the reaction was quenched by the addition of 1 M aq. HCl (5 mL). The mixture was extracted with DCM (3× 10 mL), and the combined organic layers were washed with 1 M aq. HCl (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness in vacuo to afford a yellow oil. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−50%) to afford the desired product **7a** as a white powder (0.065 g, 0.15 mmol, 49%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.19 (s, 1H), 7.05 (s, 1H), 6.14 (q, J = 0.8 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 2.65 (s, 3H), 2.46 (s, 3H), 2.29 (d, J = 0.9 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.00, 161.29, 160.53, 159.71, 157.67, 137.55, 124.42, 119.54, 119.33, 113.32, 95.25, 61.16, 33.12, 17.22, 14.12, 12.03, 10.63.

*Ethyl 4-Methyl-2-(1-methyl-4-(N-(5-methylisoxazol-3-yl)-sulfamoyl)-1H-pyrrol-2-yl)thiazole-5-carboxylate (**7b**).*



To a pressure vial charged with a magnetic stirring bar were added ethyl 2-(4-(chlorosulfonyl)-1-methyl-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**6b**; 0.52 g, 1.50 mmol, 1.00 equiv), 5-methylisoxazol-3-amine (0.88 g, 9.00 mmol, 6.00 equiv), pyridine (0.97 mL, 12.00 mmol, 8.00 equiv), and DCM (15.0 mL). The vial was capped, and the mixture was stirred at 50 °C for 14 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (10 mL). The mixture was extracted with DCM (2× 10 mL), and the combined organic layers were washed with 1 M aq. HCl (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a brown oil. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−60%) to afford the desired product **7b** as a white solid (0.45 g, 1.09 mmol, 72%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.15 (s, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.05 (d, J = 1.9 Hz, 1H), 6.17 (d, J = 1.0 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 2.65 (s, 3H), 2.32 (d, J = 0.9 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H).

*Ethyl 2-(4-(N-(Isoxazol-3-yl)sulfamoyl)-1-methyl-1H-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**7c**).*



To a pressure vial charged with a magnetic stirring bar were added ethyl 2-(4-(chlorosulfonyl)-1-methyl-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**6b**; 0.105 g, 0.30 mmol, 1.00 equiv), isoxazol-3-amine (0.133 mL, 1.80 mmol, 6.00 equiv), pyridine (0.194 mL, 2.40 mmol, 8.00 equiv), and DCM (3.0 mL). The vial was capped, and the mixture was stirred at 50 °C for 12 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (5 mL). The mixture was extracted with DCM (4× 5 mL), and the combined organic layers were washed with 1 M aq. HCl (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a slightly yellow viscous oil. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−60%) to afford the

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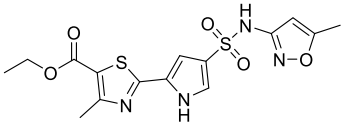
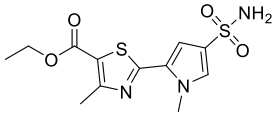
desired product **7c** as a white powder (0.076 g, 0.19 mmol, 63%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1H), 8.74 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.48 (d, J = 1.8 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 2.65 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.25, 160.67, 159.82, 159.76, 157.19, 130.54, 126.82, 122.03, 119.92, 111.68, 98.18, 61.22, 37.18, 17.19, 14.11.

*Ethyl 2-(4-(N-(Isoxazol-3-yl)sulfamoyl)-1H-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**7d**).*



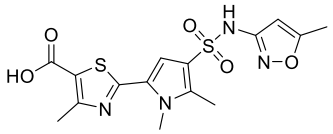
To a pressure vial charged with a magnetic stirring bar were added ethyl 2-(4-(chlorosulfonyl)-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**6c**; 0.28 g, 0.83 mmol, 1.00 equiv), 5-methylisoxazol-3-amine (0.49 g, 4.98 mmol, 6.00 equiv), pyridine (0.537 mL, 6.64 mmol, 8.00 equiv), and DCM (6.0 mL). The vial was capped, and the mixture was stirred at 50 °C for 17 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (10 mL). The mixture was extracted with DCM (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a light brown solid. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−80%) to afford the desired product **7d** as an off-white solid (0.25 g, 0.64 mmol, 76%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (s, 1H), 11.12 (s, 1H), 7.52 (dd, J = 3.2, 1.7 Hz, 1H), 7.06 (dd, J = 2.5, 1.6 Hz, 1H), 6.20 (d, J = 1.1 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.65 (s, 3H), 2.31 (d, J = 0.9 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H).

*Ethyl 4-Methyl-2-(1-methyl-4-sulfamoyl-1H-pyrrol-2-yl)thiazole-5-carboxylate (**7e**).*



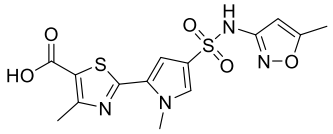
To a pressure vial charged with a magnetic stirring bar were added ethyl 2-(4-(chlorosulfonyl)-1-methyl-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**6b**; 0.13 g, 0.37 mmol, 1.00 equiv) and 25% NH_4OH (5.8 mL, 37.0 mmol, 100.0 equiv). The vial was capped, and the mixture was stirred at 50 °C for 2.5 h. Upon reaction completion as determined by UPLC−MS, the reaction was quenched by the addition of 1 M aq. HCl (10 mL). The mixture was extracted with EtOAc (2× 15 mL). The aqueous layer was acidified with 2 M HCl until pH 1−2 and further extracted with EtOAc (15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **7e** as an off-white solid (0.12 g, 0.37 mmol, quantitative) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.57 (d, J = 1.9 Hz, 1H), 7.13 (s, 2H), 7.04 (d, J = 1.9 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 2.67 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H).

*2-(1,5-Dimethyl-4-(N-(5-methylisoxazol-3-yl)sulfamoyl)-1H-pyrrol-2-yl)-4-methylthiazole-5-carboxylic Acid (**8a**).*



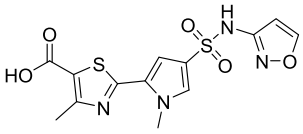
To a vial charged with a magnetic stirring bar was added a solution of ethyl 2-(1,5-dimethyl-4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**7a**; 0.065 g, 0.15 mmol, 1.00 equiv) in abs. EtOH (1.5 mL). This solution was then treated with 1 M aq. NaOH (0.60 mL, 0.60 mmol, 4.00 equiv). The mixture was stirred at rt for 14 h. Upon reaction completion as determined by LC−MS, the mixture was pH-adjusted to 1−2 with 1 M aq. HCl. The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **8a** as a white solid (0.060 g, ∼0.15 mmol, ∼quant.) used without further purification. LC−MS (ESI, pos. mode) m/z: 397.0 $[M + 1]^+$, t_R = 2.01 min.

*4-Methyl-2-(1-methyl-4-(N-(5-methylisoxazol-3-yl)sulfamoyl)-1H-pyrrol-2-yl)thiazole-5-carboxylic Acid (**8b**).*



To a vial charged with a magnetic stirring bar was added a solution of ethyl 4-methyl-2-(1-methyl-4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)-1*H*-pyrrol-2-yl)thiazole-5-carboxylate (**7b**; 0.45 g, 1.09 mmol, 1.00 equiv) in abs. EtOH (10.0 mL). This solution was then treated with 1 M aq. NaOH (4.37 mL, 4.37 mmol, 4.00 equiv). The mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the mixture was pH-adjusted to 1−2 with 2 M aq. HCl. The mixture was extracted with EtOAc (3× 15 mL) and 15% *i*-PrOH in EtOAc (2× 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **8b** as a white solid (0.41 g, 1.08 mmol, 98%) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.14 (s, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.01 (d, J = 1.9 Hz, 1H), 6.17 (d, J = 1.0 Hz, 1H), 3.97 (s, 3H), 2.63 (s, 3H), 2.32 (d, J = 0.9 Hz, 3H).

*2-(4-(N-(Isoxazol-3-yl)sulfamoyl)-1-methyl-1H-pyrrol-2-yl)-4-methylthiazole-5-carboxylic Acid (**8c**).*



To a vial charged with a magnetic stirring bar was added a solution of ethyl 2-(4-(*N*-(isoxazol-3-yl)sulfamoyl)-1-methyl-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**7c**; 0.075 g, 0.19 mmol, 1.00 equiv) in abs. EtOH (3.0 mL). This solution was then treated with 1 M aq. NaOH (0.76 mL, 0.76 mmol, 4.00 equiv). The mixture was stirred at rt for 16 h. Upon reaction completion as determined by LC−MS, the mixture was pH-adjusted to 1−2 with 1 M aq. HCl. The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and

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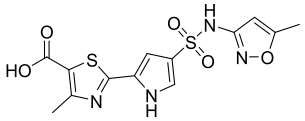
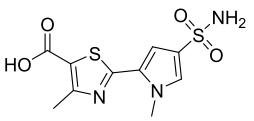
evaporated to dryness *in vacuo* to afford the desired crude product **8c** as a white solid (0.070 g, 0.19 mmol, quant.) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.31 (s, 1H), 11.29 (s, 1H), 8.74 (d, J = 1.8 Hz, 1H), 7.76 (d, J = 1.9 Hz, 1H), 7.01 (d, J = 1.9 Hz, 1H), 6.47 (d, J = 1.8 Hz, 1H), 3.97 (s, 3H), 2.63 (s, 3H).

*4-Methyl-2-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)-1H-pyrrol-2-yl)thiazole-5-carboxylic Acid (**8d**).*



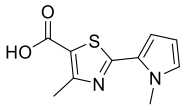
To a vial charged with a magnetic stirring bar was added a solution of ethyl 2-(4-(*N*-(isoxazol-3-yl)sulfamoyl)-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylate (**7d**; 0.25 g, 0.64 mmol, 1.00 equiv) in abs. EtOH (6.0 mL). This solution was then treated with 1 M aq. NaOH (2.56 mL, 2.56 mmol, 4.00 equiv). The mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the mixture was pH-adjusted to 1−2 with 2 M aq. HCl. The resulting precipitate was isolated by suction filtration, washed thoroughly with water, and oven-dried to afford the desired crude product **8d** as a white solid (0.12 g, 0.32 mmol, 49%) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.82 (t, J = 3.0 Hz, 1H), 11.11 (s, 1H), 7.51 (dd, J = 3.2, 1.6 Hz, 1H), 7.02 (t, J = 2.1 Hz, 1H), 6.19 (d, J = 1.0 Hz, 1H), 2.63 (s, 3H), 2.31 (s, 3H).

*4-Methyl-2-(1-methyl-4-sulfamoyl-1H-pyrrol-2-yl)thiazole-5-carboxylic Acid (**8e**).*



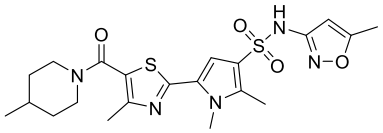
To a vial charged with a magnetic stirring bar was added a solution of ethyl 4-methyl-2-(1-methyl-4-sulfamoyl-1*H*-pyrrol-2-yl)thiazole-5-carboxylate (**7e**; 0.12 g, 0.37 mmol, 1.00 equiv) in abs. EtOH (4.0 mL). This solution was then treated with 1 M aq. NaOH (1.48 mL, 1.48 mmol, 4.00 equiv). The mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the mixture was pH-adjusted to 1−2 with 1 M aq. HCl. The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **8e** as an off-white solid (0.11 g, 0.37 mmol, quantitative) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.55 (d, J = 1.9 Hz, 1H), 7.12 (s, 2H), 7.00 (d, J = 1.9 Hz, 1H), 3.98 (s, 3H), 2.64 (s, 3H).

*4-Methyl-2-(1-methyl-1H-pyrrol-2-yl)thiazole-5-carboxylic Acid (**8f**).*



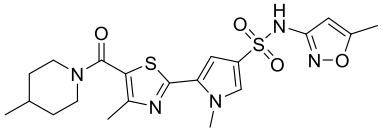
To a vial charged with a magnetic stirring bar was added a solution of ethyl 4-methyl-2-(1-methyl-1*H*-pyrrol-2-yl)-thiazole-5-carboxylate (**5b**; 0.15 g, 0.60 mmol, 1.00 equiv) in abs. EtOH (6.0 mL). This solution was then treated with 1 M aq. NaOH (2.40 mL, 2.40 mmol, 4.00 equiv). The mixture was stirred at rt for 17 h. Upon reaction completion as determined by LC−MS, the mixture was pH-adjusted to 1−2 with 1 M HCl. The mixture was extracted with EtOAc (2× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **8f** as a brown solid (0.078 g, 0.35 mmol, 60%) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.13 (s, 1H), 7.06 (t, J = 2.1 Hz, 1H), 6.80 (dd, J = 3.9, 1.7 Hz, 1H), 6.14 (dd, J = 3.9, 2.6 Hz, 1H), 3.97 (s, 3H), 2.63 (s, 3H).

*1,2-Dimethyl-5-(4-methyl-5-(4-methylpiperidine-1-carbonyl)-thiazol-2-yl)-N-(5-methylisoxazol-3-yl)-1H-pyrrole-3-sulfonamide (**Compound 2**).*



To a vial charged with a magnetic stirring bar was added a solution of 2-(1,5-dimethyl-4-(*N*-(5-methylisoxazol-3-yl)-sulfamoyl)-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylic acid (**8a**; 0.030 g, 0.076 mmol, 1.00 equiv) in DMF (2.0 mL). Under cooling at 0 °C were then added HATU (0.058 g, 0.152 mmol, 2.00 equiv) and DIPEA (0.040 mL, 0.228 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, 4-methylpiperidine (0.018 mL, 0.152 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the mixture was directly purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 2** as a yellowish solid (0.022 g, 0.047 mmol, 62%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.14 (s, 1H), 6.89 (s, 1H), 6.12 (d, J = 1.1 Hz, 1H), 3.87 (s, 3H), 2.96 (s, 2H), 2.45 (s, 3H), 2.35 (s, 3H), 2.29 (d, J = 0.9 Hz, 3H), 1.72−1.58 (m, 3H), 1.12−1.00 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.97, 160.76, 157.71, 157.62, 150.87, 136.75, 124.47, 123.57, 119.02, 112.03, 95.25, 33.83, 32.87, 30.27, 21.45, 16.16, 12.03, 10.58. LC−MS (ESI, pos. mode) m/z: 478.2 $[M+1]^+$, t_R = 2.42 min.

*1-Methyl-5-(4-methyl-5-(4-methylpiperidine-1-carbonyl)thiazol-2-yl)-N-(5-methylisoxazol-3-yl)-1H-pyrrole-3-sulfonamide (**Compound 15**).*



To a vial charged with a magnetic stirring bar was added a solution of 4-methyl-2-(1-methyl-4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)-1*H*-pyrrol-2-yl)thiazole-5-carboxylic acid (**8b**; 0.024 g, 0.063 mmol, 1.00 equiv) in DMF (2.0 mL). Under cooling at 0 °C were then added EDC·HCl (0.024 g, 0.127 mmol, 2.00 equiv), HOBt (0.017 g, 0.127 mmol, 2.00 equiv), and DIPEA (0.044 mL, 0.252 mmol, 4.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, 4-methylpiperidine (0.030 mL, 0.252 mmol, 4.00 equiv) was added, and the mixture was stirred at rt for 47 h. Upon reaction completion as determined by LC−MS, the mixture was directly purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−80%, 40 min) to afford the desired product **compound 15** as a white solid (0.020 g, 0.044 mmol, 70%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.11 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.16 (d, J = 1.1 Hz, 1H), 3.95 (s, 3H), 2.95 (s, 2H), 2.35 (s, 3H), 2.32 (d, J = 0.9 Hz, 3H), 1.71−1.57 (m, 3H), 1.05 (p, J = 9.5, 7.6 Hz, 2H), 0.92

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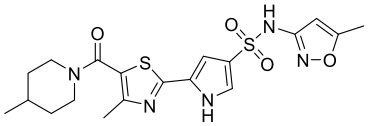
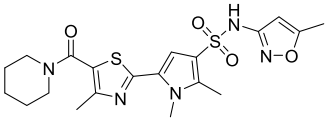
(d, J = 6.2 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.01, 160.70, 157.76, 156.98, 150.96, 129.73, 126.80, 124.03, 121.86, 110.53, 95.32, 40.06, 39.92, 39.17, 36.93, 33.85, 30.27, 21.45, 16.12, 12.08. LC−MS (ESI, pos. mode) m/z: 464.2 $[M + 1]^+$, 927.3 $[2M + 1]^+$, t_R = 4.26 min.

*5-(4-Methyl-5-(4-methylpiperidine-1-carbonyl)thiazol-2-yl)-N-(5-methylisoxazol-3-yl)-1H-pyrrole-3-sulfonamide (**Compound 16**).*



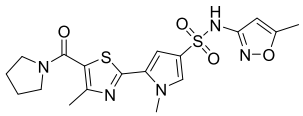
To a vial charged with a magnetic stirring bar was added a solution of 4-methyl-2-(4-(*N*-(5-methylisoxazol-3-yl)-sulfamoyl)-1*H*-pyrrol-2-yl)thiazole-5-carboxylic acid (**8d**; 0.12 g, 0.32 mmol, 1.00 equiv) in DMF (5.0 mL). Under cooling at 0 °C were then added HATU (0.24 g, 0.64 mmol, 2.00 equiv) and DIPEA (0.167 mL, 0.96 mmol, 3.00 equiv). The solution was stirred at 0 °C for 40 min. After preactivation, 4-methylpiperidine (0.076 mL, 0.64 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 6 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (15 mL). The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were washed with sat. brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 30 min) to afford the desired product **compound 16** as a light-brown solid (0.030 g, 0.067 mmol, 22%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.75 (t, J = 2.9 Hz, 1H), 11.08 (s, 1H), 7.47 (dd, J = 3.2, 1.7 Hz, 1H), 6.92 (dd, J = 2.6, 1.7 Hz, 1H), 6.19 (d, J = 1.1 Hz, 1H), 2.95 (s, 2H), 2.34 (s, 3H), 2.31 (d, J = 0.9 Hz, 3H), 1.70−1.58 (m, 3H), 1.10−1.00 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.01, 160.81, 157.86, 157.22, 150.88, 126.82, 124.90, 123.73, 108.07, 95.32, 33.86, 30.27, 21.45, 15.99, 12.06. LC−MS (ESI, pos. mode) m/z: 450.1 $[M + 1]^+$, t_R = 2.19 min.

*1,2-Dimethyl-5-(4-methyl-5-(piperidine-1-carbonyl)thiazol-2-yl)-N-(5-methylisoxazol-3-yl)-1H-pyrrole-3-sulfonamide (**Compound 17**).*



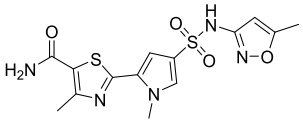
To a vial charged with a magnetic stirring bar was added a solution of 2-(1,5-dimethyl-4-(*N*-(5-methylisoxazol-3-yl)-sulfamoyl)-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylic acid (**8a**; 0.030 g, 0.076 mmol, 1.00 equiv) in DMF (2.0 mL). Under cooling at 0 °C were then added HATU (0.058 g, 0.152 mmol, 2.00 equiv) and DIPEA (0.040 mL, 0.228 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, piperidine (0.015 mL, 0.152 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the mixture was directly purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 17** as a yellowish solid (0.026 g, 0.055 mmol, 73%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.14 (s, 1H), 6.89 (s, 1H), 6.12 (d, J = 1.0 Hz, 1H), 3.87 (s, 3H), 3.48 (s, 4H), 2.45 (s, 3H), 2.35 (s, 3H), 2.29 (d, J = 0.9 Hz, 3H), 1.62 (d, J = 5.7 Hz, 2H), 1.52 (d, J = 6.1 Hz, 4H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.97, 160.75, 157.70, 157.60, 150.84, 136.74, 124.47, 123.52, 119.01, 112.02, 95.26, 32.87, 25.70, 23.85, 16.14, 12.03, 10.58. LC−MS (ESI, pos. mode) m/z: 464.2 $[M + 1]^+$, 927.4 $[2M + 1]^+$, t_R = 3.24 min.

*1-Methyl-5-(4-methyl-5-(pyrrolidine-1-carbonyl)thiazol-2-yl)-N-(5-methylisoxazol-3-yl)-1H-pyrrole-3-sulfonamide (**Compound 18**).*



To a vial charged with a magnetic stirring bar was added a solution of 4-methyl-2-(1-methyl-4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)-1*H*-pyrrol-2-yl)thiazole-5-carboxylic acid (**8b**; 0.076 g, 0.20 mmol, 1.00 equiv) in DMF (5.0 mL). Under cooling at 0 °C were then added HATU (0.152 g, 0.40 mmol, 2.00 equiv) and DIPEA (0.105 mL, 0.60 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, pyrrolidine (0.033 mL, 0.40 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 15 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (15 mL). The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 18** as a white to slightly yellow solid (0.031 g, 0.071 mmol, 36%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.12 (s, 1H), 7.71 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.16 (d, J = 1.0 Hz, 1H), 3.96 (s, 3H), 3.45 (s, 4H), 2.43 (s, 3H), 2.32 (d, J = 0.9 Hz, 3H), 1.91−1.83 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.02, 160.39, 157.75, 156.76, 153.01, 129.78, 126.79, 124.20, 121.88, 110.51, 95.32, 48.38, 46.18, 36.94, 25.75, 23.87, 16.62, 12.08. LC−MS (ESI, pos. mode) m/z: 436.2 $[M + 1]^+$, 871.3 $[2M + 1]^+$, t_R = 2.90 min.

*4-Methyl-2-(1-methyl-4-(N-(5-methylisoxazol-3-yl)sulfamoyl)-1H-pyrrol-2-yl)thiazole-5-carboxamide (**Compound 19**).*



To a vial charged with a magnetic stirring bar was added a solution of 4-methyl-2-(1-methyl-4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)-1*H*-pyrrol-2-yl)thiazole-5-carboxylic acid (**8b**; 0.076 g, 0.20 mmol, 1.00 equiv) in DMF (5.0 mL). Under cooling at 0 °C were then added HATU (0.152 g, 0.40 mmol, 2.00 equiv) and DIPEA (0.105 mL, 0.60 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, NH_4Cl (0.021 g, 0.40 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 15 h. Upon reaction completion as determined by LC−MS, the mixture was diluted with 1 M HCl (15 mL) and extracted with EtOAc (3× 15 mL). The combined organic layers were washed with sat. brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 19** as a white solid (0.046 g, 0.12 mmol, 61%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.12 (s, 1H), 7.71 (d, J = 1.9 Hz, 1H), 7.62 (s, 2H), 6.89 (d,

https://doi.org/10.1021/acs.jmedchem.1c01834
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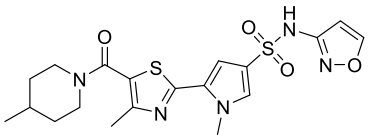
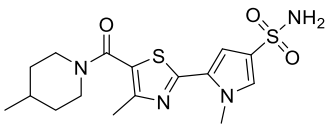
J = 2.0 Hz, 1H), 6.17 (d, J = 1.0 Hz, 1H), 3.96 (s, 3H), 2.58 (s, 3H), 2.32 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.04, 162.42, 157.76, 156.98, 154.75, 129.85, 126.96, 125.37, 121.95, 110.60, 95.33, 37.00, 17.06, 12.09. LC−MS (ESI, pos. mode) m/z: 382.2 $[M + 1]^+$, 763.2 $[2M + 1]^+$, t_R = 2.48 min.

*N-(Isoxazol-3-yl)-1-methyl-5-(4-methyl-5-(4-methylpiperidine-1-carbonyl)thiazol-2-yl)-1H-pyrrole-3-sulfonamide (**Compound 20**).*



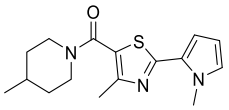
To a vial charged with a magnetic stirring bar was added a solution of 2-(4-(*N*-(isoxazol-3-yl)sulfamoyl)-1-methyl-1*H*-pyrrol-2-yl)-4-methylthiazole-5-carboxylic acid (**8c**; 0.070 g, 0.19 mmol, 1.00 equiv) in DMF (5.0 mL). Under cooling at 0 °C were then added HATU (0.144 g, 0.38 mmol, 2.00 equiv) and DIPEA (0.099 mL, 0.57 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, 4-methylpiperidine (0.045 mL, 0.38 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (20 mL). The mixture was extracted with EtOAc (4× 20 mL), and the combined organic layers were washed with sat. brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a golden-brown oil. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 20** as a white to slightly yellow solid (0.041 g, 0.091 mmol, 48%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.30 (s, 1H), 8.74 (d, J = 1.8 Hz, 1H), 7.75 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.47 (d, J = 1.8 Hz, 1H), 3.95 (s, 3H), 3.14−2.82 (m, 4H), 2.34 (s, 3H), 1.72−1.55 (m, 3H), 1.05 (q, J = 11.5 Hz, 2H), 0.91 (d, J = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 160.69, 160.67, 157.25, 156.95, 150.96, 129.86, 126.87, 124.04, 121.66, 110.53, 110.51, 98.21, 98.17, 36.98, 36.90, 33.85, 30.27, 21.45, 16.12. LC−MS (ESI, pos. mode) m/z: 450.2 $[M + 1]^+$, t_R = 2.27 min.

*1-Methyl-5-(4-methyl-5-(4-methylpiperidine-1-carbonyl)thiazol-2-yl)-1H-pyrrole-3-sulfonamide (**Compound 21**).*



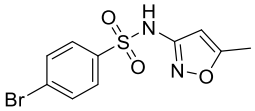
To a vial charged with a magnetic stirring bar was added a solution of 4-methyl-2-(1-methyl-4-sulfamoyl-1*H*-pyrrol-2-yl)-thiazole-5-carboxylic acid (**8e**; 0.11 g, 0.37 mmol, 1.00 equiv) in DMF (5.0 mL). Under cooling at 0 °C were then added HATU (0.28 g, 0.74 mmol, 2.00 equiv) and DIPEA (0.19 mL, 1.11 mmol, 3.00 equiv). The solution was stirred at 0 °C for 45 min. After preactivation, 4-methylpiperidine (0.088 mL, 0.74 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 4 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (20 mL). The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were washed with sat. brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 21** as a white solid (0.0040 g, 0.010 mmol, 3%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.51 (d, J = 1.9 Hz, 1H), 7.10 (s, 2H), 6.91 (d, J = 2.0 Hz, 1H), 3.97 (s, 3H), 2.96 (s, 2H), 2.36 (s, 3H), 1.73−1.56 (m, 3H), 1.15−0.98 (m, 2H), 0.93 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 160.79, 157.60, 150.96, 127.66, 127.40, 125.98, 123.54, 110.27, 36.67, 33.86, 30.27, 21.45, 16.17. LC−MS (ESI, pos. mode) m/z: 383.2 $[M + 1]^+$, t_R = 2.04 min.

*(4-Methyl-2-(1-methyl-1H-pyrrol-2-yl)thiazol-5-yl)(4-methylpiperidin-1-yl)methanone (**Compound 22**).*



To a vial charged with a magnetic stirring bar was added a solution of 4-methyl-2-(1-methyl-1*H*-pyrrol-2-yl)thiazole-5-carboxylic acid (**8f**; 0.078 g, 0.35 mmol, 1.00 equiv) in DMF (5.0 mL). Under cooling at 0 °C were then added HATU (0.267 g, 0.70 mmol, 2.00 equiv) and DIPEA (0.183 mL, 1.05 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, 4-methylpiperidine (0.083 mL, 0.70 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 2.5 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (20 mL). The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were washed with sat. brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a brown oil. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 22** as a white to light-brown solid (0.077 g, 0.25 mmol, 70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.01 (t, J = 2.2 Hz, 1H), 6.67 (dd, J = 3.9, 1.7 Hz, 1H), 6.11 (dd, J = 3.9, 2.6 Hz, 1H), 3.94 (s, 3H), 3.51 (s, 2H), 2.95 (s, 2H), 2.33 (s, 3H), 1.73−1.55 (m, 3H), 1.13−0.97 (m, 2H), 0.92 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.19, 159.14, 150.71, 127.95, 125.11, 122.05, 112.96, 108.37, 39.19, 36.26, 33.88, 30.30, 21.46, 16.24. LC−MS (ESI, pos. mode) m/z: 450.2 $[M + 1]^+$, t_R = 2.27 min.

*4-Bromo-N-(5-methylisoxazol-3-yl)benzenesulfonamide (**9a**).*



To a pressure vial charged with a magnetic stirring bar were added 5-methylisoxazol-3-amine (0.491 g, 5.00 mmol, 1.00 equiv), pyridine (0.809 mL, 10.0 mmol, 2.00 equiv), and DCM (10.0 mL). The solution was then treated with 4-bromobenzenesulfonyl chloride (1.278 g, 5.00 mmol, 1.00 equiv). The vial was capped, and the mixture was subjected to MW irradiation at 50 °C for 20 min. Upon reaction completion as determined by TLC, the reaction was quenched by the addition of 1 M aq. HCl (20 mL). The mixture was extracted with DCM (2× 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **9a** as a light-brown solid (1.42 g, 4.48 mmol, 89%) used without further purification. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.75−7.66 (m, 2H), 7.65−7.58 (m, 2H), 6.22 (d, J = 1.0 Hz, 1H), 2.38 (d, J = 0.9 Hz, 3H).

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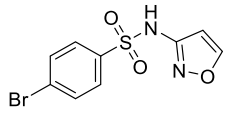
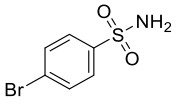
*4-Bromo-N-(isoxazol-3-yl)benzenesulfonamide (**9b**).*



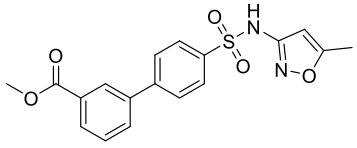
To a pressure vial charged with a magnetic stirring bar were added isoxazol-3-amine (0.44 mL, 6.00 mmol, 6.00 equiv), pyridine (0.65 mL, 8.00 mmol, 8.00 equiv), and DCM (5.0 mL). The solution was then treated with 4-bromobenzenesulfonyl chloride (0.26 g, 1.00 mmol, 1.00 equiv). The vial was capped, and the mixture was stirred at reflux (50 °C) for 5 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (5 mL). The mixture was extracted with DCM (2× 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified using silica gel flash chromatography (heptane/EtOAc, 0−70%) to afford the desired product **9b** as a white solid (0.25 g, 0.82 mmol, 82%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.31 (s, 1H), 8.27 (d, J = 1.7 Hz, 1H), 7.74−7.67 (m, 2H), 7.66−7.60 (m, 2H), 6.60 (d, J = 1.7 Hz, 1H).

*4-Bromobenzenesulfonamide (**9c**).*



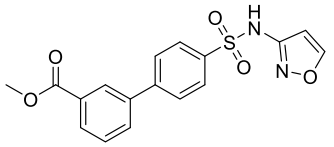
To a pressure vial charged with a magnetic stirring bar were added 4-bromobenzenesulfonyl chloride (0.26 g, 1.00 mmol, 1.00 equiv) and 25% NH_4OH (7.8 mL, 50.0 mmol, 50.0 equiv). The vial was capped, and the mixture was stirred at 50 °C for 5 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 2 M aq. HCl (20 mL). The resulting precipitate was isolated by suction filtration, washed with water (2× 10 mL), and oven-dried overnight. The filtrate was further extracted with EtOAc (2× 25 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The two solids were pooled to afford the desired crude product **9c** as a white solid (0.17 g, 0.71 mmol, 71%) used with further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84−7.77 (m, 2H), 7.77−7.70 (m, 2H), 7.45 (s, 2H).

*Methyl 4′-(N-(5-Methylisoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylate (**10a**).*



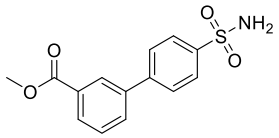
To a pressure vial charged with a magnetic stirring bar were added 4-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**9a**; 0.317 g, 1.00 mmol, 1.00 equiv), (3-(methoxycarbonyl)-phenyl)boronic acid (0.270 g, 1.50 mmol, 1.50 equiv), Cs_2CO_3 (0.977 g, 3.00 mmol, 3.00 equiv), 1,4-dioxane (8.0 mL), and H_2O (2.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.116 g, 0.10 mmol, 0.10 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by TLC, the reaction was quenched by the addition of H_2O (20 mL). The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a golden-brown oil. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−50%) to afford the desired product **10a** as a yellowish powder (0.14 g, 0.38 mmol, 38%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.52 (s, 1H), 8.24 (d, J = 2.5 Hz, 2H), 8.08−7.92 (m, 6H), 7.67 (t, J = 7.8 Hz, 1H), 6.18 (d, J = 1.0 Hz, 1H), 3.89 (s, 3H), 2.30 (s, 3H).

*Methyl 4′-(N-(Isoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylate (**10b**).*



To a pressure vial charged with a magnetic stirring bar were added 4-bromo-*N*-(isoxazol-3-yl)benzenesulfonamide (**9b**; 0.30 g, 1.00 mmol, 1.00 equiv), (3-(methoxycarbonyl)phenyl)-boronic acid (0.270 g, 1.50 mmol, 1.50 equiv), K_2CO_3 (0.415 g, 3.00 mmol, 3.00 equiv), 1,4-dioxane (8.0 mL), and H_2O (2.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.116 g, 0.10 mmol, 0.10 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by TLC, the reaction was quenched by the addition of H_2O (15 mL), and the mixture was extracted with EtOAc (3× 15 mL). The aq. phase was acidified to pH 1−2 with 1 M aq. HCl and further extracted with EtOAc (2× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a golden-brown oil. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−75%) to afford the desired product **10b** as a white sticky solid (0.30 g, 0.84 mmol, 84%). ^{1}H NMR (600 MHz, chloroform-*d*): δ 8.27 (d, J = 1.8 Hz, 1H), 8.24 (t, J = 1.8 Hz, 1H), 8.08 (dt, J = 7.7, 1.4 Hz, 1H), 7.96−7.90 (m, 2H), 7.75 (ddd, J = 7.8, 2.0, 1.1 Hz, 1H), 7.73−7.70 (m, 2H), 7.55 (t, J = 7.8 Hz, 1H), 6.65 (d, J = 1.8 Hz, 1H), 3.95 (s, 3H).

*Methyl 4′-Sulfamoyl-[1,1′-biphenyl]-3-carboxylate (**10c**).*



To a round-bottomed flask charged with a magnetic stirring bar were added 4-bromobenzenesulfonamide (**9c**; 0.17 g, 0.71 mmol, 1.00 equiv), (3-(methoxycarbonyl)phenyl)boronic acid (0.19 g, 1.07 mmol, 1.50 equiv), K_2CO_3 (0.29 g, 2.13 mmol, 3.00 equiv), 1,4-dioxane (8.0 mL), and H_2O (2.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.082 g, 0.071 mmol, 0.10 equiv) against a positive flow of N_2. The flask was capped, and the mixture was stirred at 90 °C for 14 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (15 mL), and the mixture was extracted with EtOAc (3× 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a dark-brown oil. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−80%) to afford the desired product **10c** as a yellowish solid (0.21 g, 0.32 mmol, 45%). ^{1}H NMR (600 MHz, chloroform-*d*): δ 8.28 (d, J = 1.8 Hz, 1H), 8.09 (dd, J =

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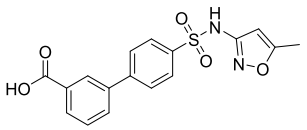
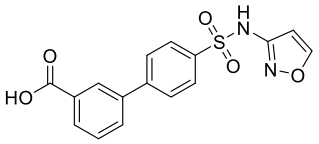
7.8, 1.4 Hz, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.79 (ddd, J = 7.7, 2.1, 1.1 Hz, 1H), 7.76 (d, J = 8.3 Hz, 2H), 7.56 (t, J = 7.7 Hz, 1H), 4.91 (s, 2H), 3.96 (s, 3H).

*4′-(N-(5-Methylisoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylic Acid (**11a**).*



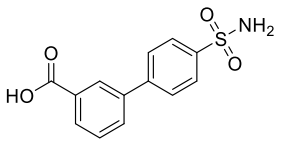
To a vial charged with a magnetic stirring bar was added a solution of methyl 4′-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylate (**10a**; 0.17 g, 0.46 mmol, 1.00 equiv) in MeOH (5.0 mL). This solution was then treated with 1 M aq. NaOH (1.83 mL, 1.83 mmol, 4.00 equiv). The mixture was stirred at rt for 14 h. Upon reaction completion as determined by LC−MS, the mixture was pH-adjusted to 1−2 with 1 M aq. HCl. The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **11a** as a light-brown solid (0.13 g, 0.37 mmol, 83%) used without further purification. ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.09 (s, 1H), 11.52 (s, 1H), 8.23 (t, J = 1.8 Hz, 1H), 8.02−7.98 (m, 2H), 7.96−7.94 (m, 4H), 7.65 (t, J = 7.7 Hz, 1H), 6.18 (d, J = 1.0 Hz, 1H), 2.31 (d, J = 0.9 Hz, 3H).

*4′-(N-(Isoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylic Acid (**11b**).*



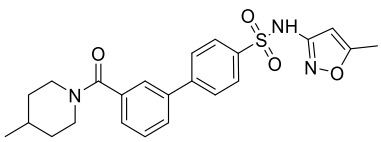
To a vial charged with a magnetic stirring bar was added a solution of methyl 4′-(*N*-(isoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylate (**10b**; 0.30 g, 0.84 mmol, 1.00 equiv) in MeOH (8.0 mL). This solution was then treated with 1 M aq. NaOH (3.36 mL, 3.36 mmol, 4.00 equiv). The mixture was stirred at rt for 16 h. Upon reaction completion as determined by LC−MS, the mixture was pH-adjusted to 1−2 with 1 M aq. HCl. The mixture was extracted with EtOAc (3× 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **11b** as a white solid (0.35 g, ∼1.00 mmol, ∼quant.) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.67 (s, 1H), 8.74 (d, J = 1.8 Hz, 1H), 8.23 (t, J = 1.8 Hz, 1H), 8.07−7.88 (m, 6H), 7.64 (t, J = 7.8 Hz, 1H), 6.47 (d, J = 1.8 Hz, 1H).

*4′-Sulfamoyl-[1,1′-biphenyl]-3-carboxylic Acid (**11c**).*



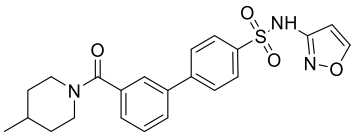
To a vial charged with a magnetic stirring bar was added a solution of methyl 4′-sulfamoyl-[1,1′-biphenyl]-3-carboxylate (**10c**; 0.094 g, 0.32 mmol, 1.00 equiv) in MeOH (3.0 mL). This solution was then treated with 1 M aq. NaOH (1.29 mL, 1.29 mmol, 4.00 equiv). The mixture was stirred at rt for 24 h. Upon reaction completion as determined by LC−MS, the mixture was pH-adjusted to 1−2 with 1 M aq. HCl. The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **11c** as a white solid (0.11 g, ∼0.32 mmol, ∼quant.) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.10 (s, 1H), 8.24 (d, J = 1.8 Hz, 1H), 8.00 (dt, J = 7.9, 1.8 Hz, 2H), 7.92 (s, 4H), 7.65 (t, J = 7.8 Hz, 1H), 7.42 (s, 2H).

*N-(5-Methylisoxazol-3-yl)-3′-(4-methylpiperidine-1-carbonyl)-[1,1′-biphenyl]-4-sulfonamide (**Compound 23**).*



To a vial charged with a magnetic stirring bar was added a solution of 4′-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylic acid (**11a**; 0.13 g, 0.36 mmol, 1.00 equiv) in DMF (2.0 mL). Under cooling at 0 °C were then added EDC·HCl (0.10 g, 0.54 mmol, 1.50 equiv), HOBt (0.073 g, 0.54 mmol, 1.50 equiv), and DIPEA (0.188 mL, 1.08 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, 4-methylpiperidine (0.085 mL, 0.72 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 17 h. Upon reaction completion as determined by LC−MS, the mixture was concentrated *in vacuo* to remove DMF. The residue was added H_2O (5 mL) and extracted with EtOAc (3× 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* (co-evaporating with toluene two times) to afford a golden-brown oil. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−90%, 40 min) to afford the desired product **compound 23** as a white powder (0.059 g, 0.13 mmol, 37%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.51 (s, 1H), 7.96−7.91 (m, 4H), 7.80 (dt, J = 8.0, 1.4 Hz, 1H), 7.69 (t, J = 1.8 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.42 (dt, J = 7.5, 1.3 Hz, 1H), 6.18 (d, J = 1.0 Hz, 1H), 4.46 (s, 1H), 3.55 (s, 1H), 3.04 (s, 1H), 2.77 (s, 1H), 2.30 (d, J = 0.8 Hz, 3H), 1.78−1.46 (m, 3H), 1.09 (s, 2H), 0.92 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.41, 168.35, 157.44, 143.97, 138.49, 138.35, 137.50, 129.28, 127.88, 127.74, 127.39, 126.74, 125.14, 95.42, 47.35, 41.66, 34.03, 33.37, 30.43, 21.54, 12.05. LC−MS (ESI, pos. mode) m/z: 440.2 $[M + 1]^+$, t_R = 2.49 min.

*N-(Isoxazol-3-yl)-3′-(4-methylpiperidine-1-carbonyl)-[1,1′-biphenyl]-4-sulfonamide (**Compound 25**).*



To a vial charged with a magnetic stirring bar was added a solution of 4′-(*N*-(isoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylic acid (**11b**; 0.35 g, 0.84 mmol, 1.00 equiv) in DMF (5.0 mL). Under cooling at 0 °C were then added EDC·HCl (0.242 g, 1.26 mmol, 1.50 equiv), HOBt (0.170 g, 1.26 mmol, 1.50 equiv), and DIPEA (0.439 mL, 2.52 mmol, 3.00 equiv). The solution was stirred at 0 °C for 40 min. After preactivation, 4-methylpiperidine (0.199 mL, 1.68 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 22 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (20

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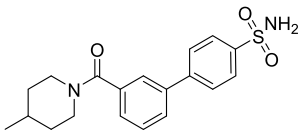
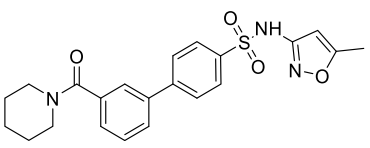
mL). The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (DCM/MeOH, 0−10%) to afford the desired product **compound 25** as a white solid (0.20 g, 0.46 mmol, 54%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.66 (s, 1H), 8.75 (d, J = 1.8 Hz, 1H), 7.96−7.89 (m, 4H), 7.80 (ddd, J = 7.9, 2.0, 1.1 Hz, 1H), 7.69 (t, J = 1.8 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.42 (dt, J = 7.6, 1.3 Hz, 1H), 6.47 (d, J = 1.8 Hz, 1H), 4.46 (s, 1H), 3.55 (s, 1H), 3.03 (s, 1H), 2.76 (s, 1H), 1.70 (s, 1H), 1.61 (ttt, J = 10.6, 6.8, 3.9 Hz, 1H), 1.54 (s, 1H), 1.09 (s, 2H), 0.92 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.35, 160.99, 156.93, 144.05, 138.33, 137.50, 129.27, 127.89, 127.75, 127.44, 126.76, 125.13, 98.35, 47.35, 41.66, 34.03, 33.37, 30.43, 21.54. LC−MS (ESI, pos. mode) m/z: 426.2 $[M + 1]^+$, t_R = 2.39 min.

*3′-(4-Methylpiperidine-1-carbonyl)-[1,1′-biphenyl]-4-sulfonamide (**Compound 26**).*



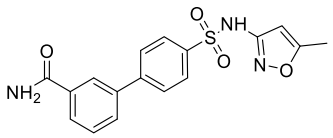
To a vial charged with a magnetic stirring bar was added a solution of 4′-sulfamoyl-[1,1′-biphenyl]-3-carboxylic acid (**11c**; 0.11 g, 0.32 mmol, 1.00 equiv) in DMF (2.0 mL). Under cooling at 0 °C were then added EDC·HCl (0.092 g, 0.48 mmol, 1.50 equiv), HOBt (0.065 g, 0.48 mmol, 1.50 equiv), and DIPEA (0.167 mL, 0.96 mmol, 3.00 equiv). The solution was stirred at 0 °C for 1 h. After preactivation, 4-methylpiperidine (0.076 mL, 0.64 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 20 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of water (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 26** as a white solid (0.035 g, 0.097 mmol, 32%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.90 (s, 4H), 7.80 (ddd, J = 7.9, 2.0, 1.1 Hz, 1H), 7.69 (t, J = 1.8 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.44−7.38 (m, 3H), 4.47 (s, 1H), 3.58 (s, 1H), 3.05 (s, 1H), 2.77 (s, 1H), 1.71 (s, 1H), 1.63 (dtq, J = 10.7, 7.2, 3.8 Hz, 1H), 1.56 (s, 1H), 1.10 (s, 2H), 0.93 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.43, 143.23, 142.53, 138.82, 137.46, 129.22, 127.78, 127.30, 126.42, 126.30, 125.06, 47.37, 41.67, 34.06, 33.39, 30.44, 21.56. LC−MS (ESI, pos. mode) m/z: 359.2 $[M + 1]^+$, t_R = 2.16 min.

*N-(5-Methylisoxazol-3-yl)-3′-(piperidine-1-carbonyl)-[1,1′-biphenyl]-4-sulfonamide (**Compound 28**).*



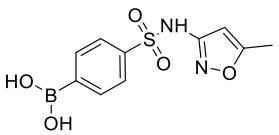
To a vial charged with a magnetic stirring bar was added a solution of 4′-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylic acid (**11a**; 0.072 g, 0.20 mmol, 1.00 equiv) in DMF (1.0 mL). Under cooling at 0 °C were then added EDC·HCl (0.058 g, 0.30 mmol, 1.50 equiv), HOBt (0.041 g, 0.30 mmol, 1.50 equiv), and DIPEA (0.105 mL, 0.60 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, piperidine (0.040 mL, 0.40 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 23 h. Upon reaction completion as determined by LC−MS, the mixture was concentrated *in vacuo* to remove DMF. The residue was added H_2O (5 mL) and extracted with EtOAc (3× 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* (co-evaporating with toluene two times). The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 28** as a white solid (0.018 g, 0.042 mmol, 21%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.51 (s, 1H), 7.97−7.89 (m, 4H), 7.80 (ddd, J = 7.8, 2.0, 1.1 Hz, 1H), 7.69 (t, J = 1.8 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.42 (dt, J = 7.6, 1.3 Hz, 1H), 6.18 (d, J = 1.0 Hz, 1H), 3.60 (s, 2H), 3.29 (s, 2H), 2.30 (d, J = 0.9 Hz, 3H), 1.61 (q, J = 6.4 Hz, 2H), 1.57 (s, 2H), 1.46 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.42, 168.35, 157.44, 143.96, 138.49, 138.34, 137.49, 129.28, 127.86, 127.73, 127.39, 126.73, 125.12, 95.42, 48.07, 42.32, 25.91, 25.19, 24.02, 12.05. LC−MS (ESI, pos. mode) m/z: 426.2 $[M + 1]^+$, t_R = 2.31 min.

*4′-(N-(5-Methylisoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxamide (**Compound 29**).*



To a vial charged with a magnetic stirring bar was added a solution of 4′-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylic acid (**11a**; 0.072 g, 0.20 mmol, 1.00 equiv) in DMF (1.0 mL). Under cooling at 0 °C were then added EDC·HCl (0.058 g, 0.30 mmol, 1.50 equiv), HOBt (0.041 g, 0.30 mmol, 1.50 equiv), and DIPEA (0.105 mL, 0.60 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, NH_4Cl (0.021 g, 0.40 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 23 h. Upon reaction completion as determined by LC−MS, the mixture was concentrated *in vacuo* to remove DMF. The residue was added H_2O (5 mL) and extracted with EtOAc (3× 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* (co-evaporating with toluene two times). The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−60%, 40 min) to afford the desired product **compound 29** as a white solid (0.024 g, 0.067 mmol, 34%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.50 (s, 1H), 8.21 (t, J = 1.8 Hz, 1H), 8.10 (s, 1H), 7.99−7.94 (m, 4H), 7.93 (dt, J = 7.8, 1.4 Hz, 1H), 7.89 (ddd, J = 7.8, 2.0, 1.2 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.46 (s, 1H), 6.19 (d, J = 1.0 Hz, 1H), 2.31 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.42, 167.45, 157.45, 144.21, 138.44, 138.23, 135.09, 129.80, 129.15, 127.75, 127.73, 127.39, 126.10, 95.43, 40.06, 39.92, 39.15, 12.05. LC−MS (ESI, pos. mode) m/z: 358.1 $[M + 1]^+$, t_R = 1.86 min.

*(4-(N-(5-Methylisoxazol-3-yl)sulfamoyl)phenyl)boronic Acid (**12a**).*



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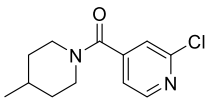
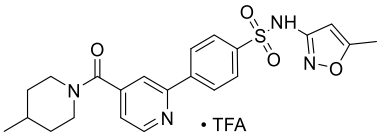
To a round-bottomed flask charged with a magnetic stirring bar were added 4-bromo-*N*-(5-methylisoxazol-3-yl)-benzenesulfonamide (**9a**; 0.317 g, 1.00 mmol, 1.00 equiv), bis(pinacolato)diboron (0.330, 1.30 mmol, 1.30 equiv), anhydrous KOAc (0.294 g, 3.00 mmol, 3.00 equiv), and anhydrous 1,4-dioxane (5.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(dppf)Cl_2$·DCM (0.082 g, 0.10 mmol, 0.10 equiv) against a positive flow of N_2. The flask was charged with a condenser, and the mixture was stirred at reflux for 2 h. Upon reaction completion as determined by LC−MS, the mixture was concentrated *in vacuo* to remove 1,4-dioxane. The residue was partitioned between EtOAc (25 mL) and H_2O (25 mL), and the aqueous layer was further extracted with EtOAc (2× 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **12** as a dark-brown oil (yield ND) used without further purification. LC−MS (ESI, pos. mode) m/z: 283.0 $[M + 1]^+$, t_R = 1.55 min.

*(2-Chloropyridin-4-yl)(4-methylpiperidin-1-yl)methanone (**13a**).*



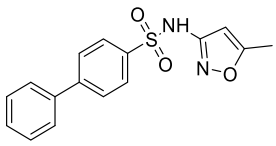
To a round-bottomed flask charged with a magnetic stirring bar was added a solution of 2-chloroisonicotinic acid (0.315 g, 2.00 mmol, 1.00 equiv) in DMF (5.0 mL). Under cooling at 0 °C were then added EDC·HCl (0.575 g, 3.00 mmol, 1.50 equiv), HOBt (0.405 g, 3.00 mmol, 1.50 equiv), and DIPEA (1.05 mL, 6.00 mmol, 3.00 equiv). The solution was stirred at 0 °C for 1 h. After preactivation, 4-methylpiperidine (0.473 mL, 4.00 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 16 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (25 mL). The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* (co-evaporating with toluene two times) to afford a golden-brown oil. The crude was purified by silica gel flash chromatography (DCM) to afford the desired product **13** as a golden-brown oil (0.25 g, 1.04 mmol, 52%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48 (d, J = 5.0 Hz, 1H), 7.53 (t, J = 1.0 Hz, 1H), 7.40 (dd, J = 5.0, 1.3 Hz, 1H), 4.49−4.27 (m, 1H), 3.35 (d, J = 13.7 Hz, 1H), 3.02 (td, J = 13.6, 13.0, 2.9 Hz, 1H), 2.89 (s, 1H), 2.78 (dd, J = 12.7, 2.9 Hz, 1H), 1.76−1.47 (m, 3H), 1.17−0.99 (m, 2H), 0.92 (d, J = 6.4 Hz, 3H).

*N-(5-Methylisoxazol-3-yl)-4-(4-(4-methylpiperidine-1-carbonyl)-pyridin-2-yl)benzenesulfonamide Trifluoroacetate (**Compound 24**).*



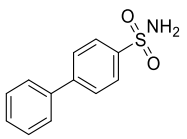
To a pressure vial charged with a magnetic stirring bar were added (2-chloropyridin-4-yl)(4-methylpiperidin-1-yl)-methanone (**13**; 0.239 g, 1.00 mmol, 1.00 equiv), (4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)boronic acid (**12**; 0.80 g, 1.00 mmol, 1.00 equiv), Cs_2CO_3 (0.977 g, 3.00 mmol, 3.00 equiv), 1,4-dioxane (8.0 mL), and H_2O (2.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.116 g, 0.10 mmol, 0.10 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 100 °C for 2 h and at rt for 14 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (20 mL), and the mixture was extracted with EtOAc (3× 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a dark-brown oil. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 24** as a yellow solid (0.017 g, 0.031 mmol, 3%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.82 (s, 1H), 8.80−8.75 (m, 1H), 8.31−8.24 (m, 2H), 8.01 (t, J = 1.2 Hz, 1H), 7.98−7.93 (m, 2H), 7.39 (dd, J = 4.9, 1.4 Hz, 1H), 6.89 (q, J = 1.5 Hz, 1H), 4.47 (d, J = 12.9 Hz, 1H), 3.43 (d, J = 13.4 Hz, 1H), 3.11−2.97 (m, 1H), 2.79 (td, J = 12.8, 2.9 Hz, 1H), 2.12 (d, J = 1.5 Hz, 3H), 1.76−1.67 (m, 1H), 1.64 (qt, J = 6.9, 3.7 Hz, 1H), 1.54 (d, J = 13.0 Hz, 1H), 1.13 (dtd, J = 28.1, 11.8, 10.4, 3.9 Hz, 2H), 0.93 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 166.41, 158.38, 158.13, 155.83, 155.00, 150.11, 145.61, 143.62, 141.55, 140.97, 127.14, 126.46, 120.38, 118.01, 110.46, 47.12, 41.49, 40.06, 39.92, 33.88, 33.24, 30.34, 21.50, 10.40. LC−MS (ESI, pos. mode) m/z: 441.2 $[M + 1]^+$, t_R = 2.06 min.

*N-(5-Methylisoxazol-3-yl)-[1,1′-biphenyl]-4-sulfonamide (**Compound 30**).*



To a pressure vial charged with a magnetic stirring bar were added 5-methylisoxazol-3-amine (0.59 g, 6.00 mmol, 6.00 equiv), pyridine (0.65 mL, 8.00 mmol, 8.00 equiv), and DCM (7.0 mL). The solution was then treated with [1,1′-biphenyl]-4-sulfonyl chloride (0.25 g, 1.00 mmol, 1.00 equiv). The vial was capped, and the mixture was stirred at reflux (50 °C) for 7 h. Upon reaction completion as determined by LC−MS, the mixture was diluted with DCM (5 mL) and washed with 1 M aq. HCl. The aq. phase was re-extracted with DCM (10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a yellowish oily solid. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−70%) to afford the desired product **compound 30** as a white crystalline solid (0.22 g, 0.70 mmol, 70%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.90 (s, 1H), 7.96−7.87 (m, 2H), 7.70−7.62 (m, 2H), 7.58−7.51 (m, 2H), 7.49−7.37 (m, 3H), 6.29 (d, J = 1.0 Hz, 1H), 2.38 (d, J = 0.8 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*): δ 171.23, 157.73, 146.61, 139.16, 137.66, 129.20, 128.78, 128.03, 127.72, 127.46, 95.72, 12.90. LC−MS (ESI, pos. mode) m/z: 315.0 $[M + 1]^+$, t_R = 2.42 min.

*[1,1′-Biphenyl]-4-sulfonamide (**Compound 35**).*



To a pressure vial charged with a magnetic stirring bar were added [1,1′-biphenyl]-4-sulfonyl chloride (0.25 g, 1.00 mmol, 1.00 equiv) and 25% NH_4OH (7.8 mL, 50.0 mmol, 50.0 equiv). The vial was capped, and the mixture was stirred at 50 °C for 5.5 h. Upon reaction completion as determined by

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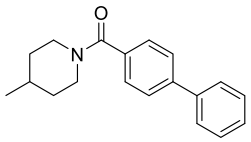
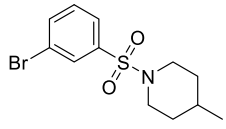
TLC, the reaction was quenched by the addition of 2 M HCl (20 mL). The resulting precipitate was isolated by suction filtration, washed with water (2× 10 mL), and air-dried overnight. The filtrate was further extracted with EtOAc (2× 25 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The two solids were pooled. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−100%) to afford the desired product **compound 35** as a white solid (0.074 g, 0.32 mmol, 32%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.92−7.88 (m, 2H), 7.88−7.84 (m, 2H), 7.75−7.72 (m, 2H), 7.51 (dd, J = 8.4, 7.0 Hz, 2H), 7.46−7.42 (m, 1H), 7.39 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 143.34, 142.92, 138.69, 129.07, 128.33, 127.13, 127.00, 126.26.

*[1,1′-Biphenyl]-4-yl(4-methylpiperidin-1-yl)methanone (**Compound 38**).*



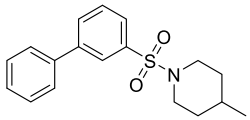
To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-4-carboxylic acid (0.198 g, 1.00 mmol, 1.00 equiv) in DMF (2.0 mL). Under cooling at 0 °C were then added EDC·HCl (0.288 g, 1.50 mmol, 1.50 equiv), HOBt (0.203 g, 1.50 mmol, 1.50 equiv), and DIPEA (0.523 mL, 3.00 mmol, 3.00 equiv). The solution was stirred at 0 °C for 10 min. After preactivation, 4-methylpiperidine (0.237 mL, 2.00 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 12 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M HCl (10 mL). The mixture was extracted with EtOAc (4× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−50%) to afford the desired product **compound 35** as a white solid (0.28 g, 0.82 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75−7.67 (m, 4H), 7.53−7.43 (m, 4H), 7.43−7.36 (m, 1H), 4.45 (s, 1H), 3.62 (s, 1H), 3.03 (s, 1H), 2.78 (s, 1H), 1.81−1.36 (m, 3H), 1.09 (d, J = 12.5 Hz, 2H), 0.93 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.59, 140.95, 139.35, 135.41, 128.98, 127.80, 127.35, 126.74, 126.60, 30.44, 21.57. LC−MS (ESI, pos. mode) m/z: 280.0 $[M + 1]^+$, t_R = 2.78 min.

*1-((3-Bromophenyl)sulfonyl)-4-methylpiperidine (**14a**).*



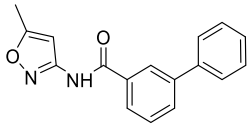
To a pressure vial charged with a magnetic stirring bar were added 4-methylpiperidine (0.237 mL, 2.00 mmol, 2.00 equiv), pyridine (0.234 mL, 3.00 mmol, 3.00 equiv), and DCM (5.0 mL). The solution was then treated with 3-bromobenzenesulfonyl chloride (0.256 g, 1.00 mmol, 1.00 equiv). The vial was capped, and the mixture was stirred at 50 °C for 6.5 h. Upon reaction completion as determined by TLC, the reaction was quenched by the addition of H_2O (20 mL). The mixture was extracted with DCM (2× 10 mL), and the combined organic layers were washed with 1 M HCl (2× 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **14** as a yellow crystalline solid (0.23 g, 0.73 mmol, 73%) used without further purification. ^{1}H NMR (600 MHz, chloroform-d): δ 7.90 (t, J = 1.8 Hz, 1H), 7.71 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.69 (dt, J = 7.9, 1.3 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H), 3.80−3.72 (m, 2H), 2.29 (td, J = 11.5, 2.5 Hz, 2H), 1.68 (dt, J = 12.9, 2.6 Hz, 2H), 1.30 (hd, J = 11.3, 9.8, 3.5 Hz, 3H), 0.92 (d, J = 5.7 Hz, 3H).

*1-([1,1′-Biphenyl]-3-ylsulfonyl)-4-methylpiperidine (**Compound 39**).*



To a pressure vial charged with a magnetic stirring bar were added 1-((3-bromophenyl)sulfonyl)-4-methylpiperidine (**14**; 0.232 g, 0.73 mmol, 1.00 equiv), phenylboronic acid (0.134 g, 1.10 mmol, 1.50 equiv), K_2CO_3 (0.303 g, 2.19 mmol, 3.00 equiv), 1,4-dioxane (8.0 mL), and H_2O (2.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.085 g, 0.07 mmol, 0.10 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 3 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (15 mL). The mixture was extracted with EtOAc (3× 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a dark red-brown oil. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−30%) to afford the desired product **compound 39** as a sticky colorless oil (0.19 g, 0.61 mmol, 84%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (dt, J = 6.5, 2.2 Hz, 1H), 7.89 (q, J = 1.4 Hz, 1H), 7.73 (ddd, J = 5.5, 3.8, 1.3 Hz, 4H), 7.52 (dd, J = 8.3, 6.7 Hz, 2H), 7.47−7.41 (m, 1H), 3.66 (dt, J = 11.4, 2.5 Hz, 2H), 2.24 (td, J = 12.0, 2.5 Hz, 2H), 1.70−1.59 (m, 2H), 1.30 (qdd, J = 10.1, 6.7, 3.8 Hz, 1H), 1.20−1.06 (m, 2H), 0.84 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 141.25, 138.43, 136.41, 131.23, 130.09, 129.16, 128.32, 126.99, 126.24, 125.01, 46.09, 32.84, 29.21, 21.30. LC−MS (ESI, pos. mode) m/z: 316.1 $[M + 1]^+$, t_R = 2.92 min.

*N-(5-Methylisoxazol-3-yl)-[1,1′-biphenyl]-3-carboxamide (**Compound 40**).*



To a round-bottomed flask charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (0.099 g, 0.50 mmol, 1.00 equiv) in DCM (5.0 mL). Under cooling at 0 °C were then added $(COCl)_2$ (0.254 mL, 3.00 mmol, 6.00 equiv) and DMF (3 drops, catalytic). The solution was stirred at 0 °C for 2 h. Upon reaction completion, the mixture was concentrated *in vacuo*. The prepared acyl chloride was redissolved in DCM (5.0 mL) and then added 5-methylisoxazol-3-amine (0.147 g, 1.50 mmol, 3.00 equiv) and Et_3N (0.139 mL, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M HCl (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a light-yellow solid. The crude was purified by silica gel flash chromatography (DCM/MeOH, 0−5%) to afford the

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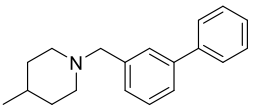
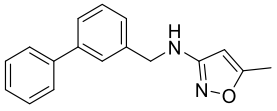
desired product **compound 40** as a white solid (0.11 g, 0.41 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 8.34 (t, J = 1.8 Hz, 1H), 7.98 (dt, J = 7.8, 1.4 Hz, 1H), 7.92 (dt, J = 7.8, 1.4 Hz, 1H), 7.83−7.77 (m, 2H), 7.62 (t, J = 7.8 Hz, 1H), 7.51 (dd, J = 8.4, 6.9 Hz, 2H), 7.46−7.38 (m, 1H), 6.79 (d, J = 1.1 Hz, 1H), 2.43 (d, J = 0.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.42, 165.07, 158.65, 140.28, 139.26, 133.73, 130.37, 129.21, 128.94, 127.86, 127.22, 126.91, 126.04, 96.95, 12.13. LC−MS (ESI, pos. mode) m/z: 279.0 $[M + 1]^+$, t_R = 2.42 min.

*1-([1,1′-Biphenyl]-3-ylmethyl)-4-methylpiperidine (**Compound 41**).*



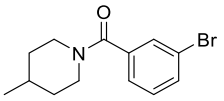
To a vial charged with a magnetic stirring bar were added 3-(bromomethyl)-1,1′-biphenyl (0.247 g, 1.00 mmol, 1.00 equiv), 4-methylpiperidine (0.237 mL, 2.00 mmol, 2.00 equiv), K_2CO_3 (0.415 g, 3.00 mmol, 3.00 equiv), and MeCN (5.0 mL). The vial was capped, and the mixture was stirred at 50 °C for 6.5 h. Upon reaction completion as determined by TLC, the mixture was cooled and filtered, and the filter cake was washed with EtOAc (5× 5 mL). The combined filtrates were evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (DCM/MeOH, 0−10%) to afford the desired product **compound 41** as a colorless oil (0.27 g, 0.82 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67−7.61 (m, 2H), 7.56−7.49 (m, 2H), 7.46 (dd, J = 8.3, 6.9 Hz, 2H), 7.43−7.32 (m, 2H), 7.28 (dt, J = 7.6, 1.3 Hz, 1H), 3.50 (s, 2H), 2.79 (dt, J = 11.7, 3.3 Hz, 2H), 1.92 (td, J = 11.6, 2.4 Hz, 2H), 1.60−1.51 (m, 2H), 1.31 (dtt, J = 10.3, 7.0, 3.9 Hz, 1H), 1.13 (qd, J = 11.9, 3.8 Hz, 2H), 0.87 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 140.22, 140.00, 139.39, 128.86, 128.68, 127.81, 127.32, 126.97, 126.65, 125.16, 62.41, 53.27, 33.96, 30.28, 21.79. LC−MS (ESI, pos. mode) m/z: 266.1 $[M + 1]^+$, t_R = 1.91 min.

*N-([1,1′-Biphenyl]-3-ylmethyl)-5-methylisoxazol-3-amine (**Compound 42**).*



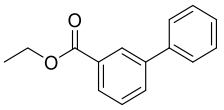
To a round-bottomed flask charged with a magnetic stirring bar were added [1,1′-biphenyl]-3-carbaldehyde (0.163 mL, 1.00 mmol, 1.00 equiv), 5-methylisoxazol-3-amine (0.196 g, 2.00 mmol, 2.00 equiv), and abs. EtOH (10.0 mL). The flask was attached a condenser, and the mixture was stirred at reflux for 2 h. Upon reaction completion as determined by TLC, the mixture was evaporated to dryness *in vacuo*. The prepared imine was redissolved in MeOH (10.0 mL) and then carefully treated with $NaBH_4$ at rt (0.076 g, 2.00 mmol, 2.00 equiv). The mixture was stirred at rt for 2 h. Upon reaction completion as determined by LC−MS, the reaction was quenched with ice-cold water (20 mL) and extracted with EtOAc (3× 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 42** as a colorless oil (0.14 g, 0.55 mmol, 55%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.63 (ddt, J = 8.0, 4.9, 1.6 Hz, 3H), 7.53 (dt, J = 7.7, 1.5 Hz, 1H), 7.47 (dd, J = 8.4, 7.1 Hz, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.38−7.35 (m, 1H), 7.32 (dt, J = 7.7, 1.3 Hz, 1H), 6.55 (s, 1H), 5.68 (d, J = 1.0 Hz, 1H), 4.29 (s, 2H), 2.20 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 167.47, 164.36, 140.61, 140.22, 140.09, 128.90, 128.79, 127.40, 126.64, 126.51, 125.78, 125.09, 93.57, 46.54, 11.99. LC−MS (ESI, pos. mode) m/z: 265.1 $[M + 1]^+$, t_R = 2.42 min.

*(3-Bromophenyl)(4-methylpiperidin-1-yl)methanone (**15a**).*



To a vial charged with a magnetic stirring bar was added a solution of 3-bromobenzoic acid (0.20 g, 1.00 mmol, 1.00 equiv) in DMF (5.0 mL). Under cooling at 0 °C were then added HATU (0.76 g, 2.00 mmol, 2.00 equiv) and DIPEA (0.523 mL, 3.00 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, 4-methylpiperidine (0.237 mL, 2.00 mmol, 2.00 equiv) was added, and the mixture was stirred at rt for 1.5 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O. The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were washed with sat. brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−40%) to afford the desired product **15** as a colorless oil (0.23 g, 0.82 mmol, 82%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.59−7.45 (m, 2H), 7.35−7.22 (m, 2H), 4.64 (s, 1H), 3.66 (s, 1H), 2.99 (s, 1H), 2.77 (s, 1H), 1.86−1.50 (m, 3H), 1.36−1.02 (m, 2H), 0.98 (d, J = 6.4 Hz, 3H).

*Ethyl [1,1′-Biphenyl]-3-carboxylate (**16a**).*



To a round-bottomed flask charged with a magnetic stirring bar were added ethyl 3-bromobenzoate (1.60 mL, 10.0 mmol, 1.00 equiv), phenylboronic acid (1.83 g, 15.0 mmol, 1.50 equiv), K_2CO_3 (4.15 g, 30.0 mmol, 3.00 equiv), 1,4-dioxane (40.0 mL), and H_2O (10.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.58 g, 0.50 mmol, 0.05 equiv) against a positive flow of N_2. The flask was equipped with a reflux condenser and capped, and the entire system was purged with N_2. The mixture was stirred at 90 °C for 4 h. Upon reaction completion as determined by TLC, the reaction mixture was concentrated *in vacuo* to remove 1,4-dioxane. The residue was added H_2O (20 mL) and extracted with EtOAc (3× 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a dark-red oily crystalline solid. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−30%) to afford the desired product **5** as a colorless to slightly yellow-green oil (1.58 g, 6.98 mmol, 70%). ^{1}H NMR (600 MHz, chloroform-*d*): δ 8.29 (t, J = 1.8 Hz, 1H), 8.04 (dt, J = 7.7, 1.4 Hz, 1H), 7.78 (dt, J = 7.8, 1.2 Hz, 1H), 7.63 (dd, J = 8.1, 1.4 Hz, 2H), 7.52 (t, J = 7.7 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.41−7.36 (m, 1H), 4.42 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H).

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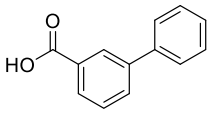
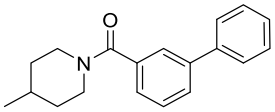
*[1,1′-Biphenyl]-3-carboxylic Acid (**17a**).*



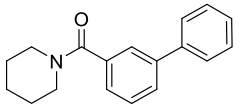
To a round-bottomed flask charged with a magnetic stirring bar was added a solution of ethyl [1,1′-biphenyl]-3-carboxylate (**16**; 1.58 g, 6.98 mmol, 1.00 equiv) in abs. EtOH (70.0 mL). This solution was then treated with 1 M aq. NaOH (28 mL, 27.92 mmol, 4.00 equiv). The mixture was stirred at rt for 22 h. Upon reaction completion as determined by TLC, the mixture was pH-adjusted to 1−2 with conc. aq. HCl. The mixture was extracted with EtOAc (3× 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **17** as a white solid (1.38 g, 6.60 mmol, 95%) used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.07 (s, 1H), 8.18 (t, J = 1.8 Hz, 1H), 7.97−7.89 (m, 2H), 7.73−7.67 (m, 2H), 7.60 (t, J = 7.7 Hz, 1H), 7.50 (dd, J = 8.3, 6.9 Hz, 2H), 7.44−7.37 (m, 1H). NMR data matches those previously reported.[44]

*[1,1′-Biphenyl]-3-yl(4-methylpiperidin-1-yl)methanone (**Compound 27**).*



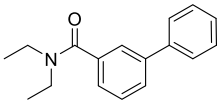
To a round-bottomed flask charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)-methanone (**15**; 0.23 g, 0.82 mmol, 1.00 equiv), phenylboronic acid (0.15 g, 1.23 mmol, 1.50 equiv), K_2CO_3 (0.34 g, 2.46 mmol, 3.00 equiv), 1,4-dioxane (8.0 mL), and H_2O (2.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.095 g, 0.082 mmol, 0.10 equiv) against a positive flow of N_2. The flask was equipped with a reflux condenser and capped, and the entire system was purged with N_2. The mixture was stirred at 90 °C for 14 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (15 mL). The mixture was extracted with EtOAc (3× 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a dark-brown oil. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−60%) to afford the desired product **compound 27** as a dark-green oil (0.23 g, 0.64 mmol, 77%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73 (dt, J = 7.9, 1.4 Hz, 1H), 7.71−7.66 (m, 2H), 7.61 (t, J = 1.8 Hz, 1H), 7.57−7.44 (m, 3H), 7.43−7.32 (m, 2H), 4.47 (s, 1H), 3.59 (s, 1H), 3.04 (s, 1H), 2.77 (s, 1H), 1.81−1.47 (m, 3H), 1.09 (s, 2H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.63, 140.23, 139.38, 137.28, 129.06, 128.99, 127.75, 127.46, 126.76, 125.57, 124.66, 47.32, 41.66, 39.21, 34.08, 33.41, 30.45, 21.55. LC−MS (ESI, pos. mode) m/z: 280.1 $[M + 1]^+$, t_R = 2.72 min.

*[1,1′-Biphenyl]-3-yl(piperidin-1-yl)methanone (**Compound 31**).*



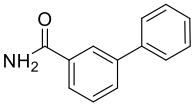
To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.694 g, 3.50 mmol, 1.00 equiv) in DMF (7.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.006 g, 5.25 mmol, 1.50 equiv), HOBt (0.709 g, 5.25 mmol, 1.50 equiv), and DIPEA (1.828 mL, 10.50 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/7 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with piperidine (0.099 mL, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−70%) to afford the desired product **compound 31** as a colorless oil (0.095 g, 0.36 mmol, 72%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.73 (ddd, J = 7.9, 2.0, 1.2 Hz, 1H), 7.71−7.67 (m, 2H), 7.61 (t, J = 1.8 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.50−7.45 (m, 1H), 7.42−7.37 (m, 1H), 7.35 (dt, J = 7.6, 1.4 Hz, 1H), 3.60 (s, 2H), 3.31 (s, 2H), 1.62 (td, J = 6.9, 4.3 Hz, 2H), 1.57 (s, 2H), 1.47 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.63, 140.22, 139.38, 137.27, 129.07, 129.00, 127.76, 127.44, 126.76, 125.56, 124.66, 48.05, 42.29, 25.94, 25.22, 24.04. LC−MS (ESI, pos. mode) m/z: 266.0 $[M + 1]^+$, t_R = 2.57 min.

*N,N-Diethyl-[1,1′-biphenyl]-3-carboxamide (**Compound 32**).*



To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.694 g, 3.50 mmol, 1.00 equiv) in DMF (7.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.006 g, 5.25 mmol, 1.50 equiv), HOBt (0.709 g, 5.25 mmol, 1.50 equiv), and DIPEA (1.828 mL, 10.50 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/7 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with diethylammonium chloride (0.110 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−50%) to afford the desired product **compound 32** as a colorless oil (0.096 g, 0.38 mmol, 76%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.73 (ddd, J = 7.8, 2.0, 1.1 Hz, 1H), 7.71−7.67 (m, 2H), 7.58 (t, J = 1.8 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.48 (dd, J = 8.3, 7.1 Hz, 2H), 7.41−7.37 (m, 1H), 7.33 (dt, J = 7.6, 1.3 Hz, 1H), 3.45 (s, 2H), 3.22 (s, 2H), 1.16 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.70, 140.21, 139.39, 138.03, 129.08, 129.00, 127.75, 127.20, 126.75, 125.07, 124.13, 42.84, 38.65, 14.07, 12.83. LC−MS (ESI, pos. mode) m/z: 254.0 $[M + 1]^+$, t_R = 2.51 min.

*[1,1′-Biphenyl]-3-carboxamide (**Compound 33**).*



https://doi.org/10.1021/acs.jmedchem.1c01834
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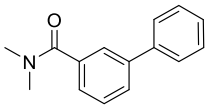
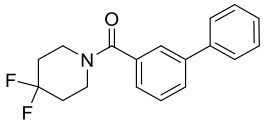
To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.694 g, 3.50 mmol, 1.00 equiv) in DMF (7.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.006 g, 5.25 mmol, 1.50 equiv), HOBt (0.709 g, 5.25 mmol, 1.50 equiv), and DIPEA (1.828 mL, 10.50 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/7 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with ammonium chloride (0.053 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 33** as a white solid (0.062 g, 0.31 mmol, 62%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.16 (t, J = 1.8 Hz, 1H), 8.10 (s, 1H), 7.87 (dt, J = 7.7, 1.4 Hz, 1H), 7.82 (dt, J = 7.7, 1.4 Hz, 1H), 7.77−7.69 (m, 2H), 7.55 (t, J = 7.7 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.45−7.36 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 167.75, 140.11, 139.57, 134.93, 129.37, 128.96, 128.91, 127.71, 126.82, 126.58, 125.65. LC−MS (ESI, pos. mode) m/z: 198.0 $[M + 1]^+$, t_R = 2.03 min.

*N,N-Dimethyl-[1,1′-biphenyl]-3-carboxamide (**Compound 36**).*



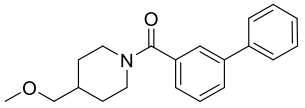
To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.694 g, 3.50 mmol, 1.00 equiv) in DMF (7.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.006 g, 5.25 mmol, 1.50 equiv), HOBt (0.709 g, 5.25 mmol, 1.50 equiv), and DIPEA (1.828 mL, 10.50 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/7 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with dimethylammonium chloride (0.082 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 18 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M aq. HCl (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (heptane/EtOAc, 0−50%) to afford the desired product **compound 36** as a colorless oil (0.042 g, 0.19 mmol, 37%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.74 (ddd, J = 7.8, 2.0, 1.1 Hz, 1H), 7.71−7.68 (m, 2H), 7.65 (t, J = 1.8 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.48 (dd, J = 8.4, 7.0 Hz, 2H), 7.39 (ddt, J = 9.1, 7.6, 1.3 Hz, 2H), 3.01 (s, 3H), 2.95 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.90, 140.12, 139.41, 137.24, 128.98, 128.95, 127.74, 127.52, 126.77, 125.88, 125.01, 34.71. LC−MS (ESI, pos. mode) m/z: 226.0 $[M + 1]^+$, t_R = 2.21 min.

*[1,1′-Biphenyl]-3-yl(4,4-difluoropiperidin-1-yl)methanone (**Compound 43**).*



To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.991 g, 5.00 mmol, 1.00 equiv) in DMF (10.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.438 g, 7.50 mmol, 1.50 equiv), HOBt (1.013 g, 7.50 mmol, 1.50 equiv), and DIPEA (2.61 mL, 15.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/10 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with 4,4-difluoropiperidine hydrochloride (0.157 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were washed with 1 M NaOH (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (DCM/MeOH, 0−5%) to afford the desired product **compound 43** as a colorless oil (0.056 g, 0.19 mmol, 37%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77 (dt, J = 7.8, 1.5 Hz, 1H), 7.74−7.68 (m, 3H), 7.55 (t, J = 7.7 Hz, 1H), 7.49 (dd, J = 8.4, 6.9 Hz, 2H), 7.45−7.37 (m, 2H), 3.89−3.31 (m, 4H), 2.08 (d, J = 18.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.02, 140.28, 139.28, 136.42, 129.13, 128.98, 127.80, 126.80, 125.73, 124.86. LC−MS (ESI, pos. mode) m/z: 302.4 $[M + 1]^+$, t_R = 3.62 min.

*[1,1′-Biphenyl]-3-yl(4-(methoxymethyl)piperidin-1-yl)-methanone (**Compound 44**).*



To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.991 g, 5.00 mmol, 1.00 equiv) in DMF (10.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.438 g, 7.50 mmol, 1.50 equiv), HOBt (1.013 g, 7.50 mmol, 1.50 equiv), and DIPEA (2.61 mL, 15.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/10 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with 4-(methoxymethyl)piperidine (0.129 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were washed with 1 M NaOH (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (hep/EtOAc, 0−100%) to afford the desired product **compound 44** as a colorless oil (0.11 g, 0.36 mmol, 72%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.73 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.71−7.67 (m, 2H), 7.61 (t, J = 1.8 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.51−7.46 (m, 2H), 7.42−7.37 (m, 1H), 7.35 (dt, J = 7.5, 1.3 Hz, 1H), 4.49 (s, 1H), 3.62 (s, 1H), 3.23 (s, 3H), 3.20 (d, J = 6.4 Hz, 2H), 3.05 (s, 1H), 2.77 (s, 1H), 1.83 (th, J = 13.9, 3.4 Hz, 1H), 1.74 (s, 1H), 1.61 (s, 1H), 1.17 (d, J = 22.3 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.67, 140.26, 139.39, 137.22, 129.08, 129.00, 127.77, 127.51, 126.78, 125.60, 124.69, 76.51, 58.13, 47.03, 41.32, 35.72, 29.00, 28.35. LC−MS (ESI, pos. mode) m/z: 310.2 $[M + 1]^+$, t_R = 4.44 min.

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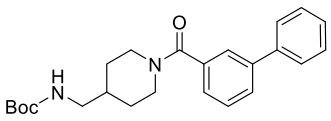
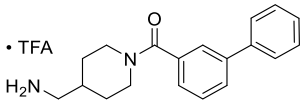
*tert-Butyl ((1-([1,1′-Biphenyl]-3-carbonyl)piperidin-4-yl)methyl)-carbamate (**18a**).*



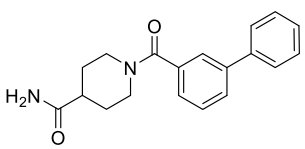
To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.991 g, 5.00 mmol, 1.00 equiv) in DMF (10.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.438 g, 7.50 mmol, 1.50 equiv), HOBt (1.013 g, 7.50 mmol, 1.50 equiv), and DIPEA (2.61 mL, 15.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/10 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with *tert*-butyl (piperidin-4-ylmethyl)carbamate (0.214 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were washed with 1 M NaOH (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **18** as a yellowish oily solid (0.21 g, ∼0.50 mmol, ∼quantitative) used without further purification. LC−MS (ESI, pos. mode) *m*/*z*: 395.3 $[M + 1]^+$, t_R = 2.62 min.

*[1,1′-Biphenyl]-3-yl(4-(aminomethyl)piperidin-1-yl)methanone (**Compound 45**).*



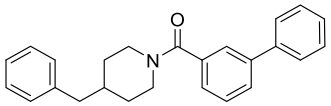
To a vial charged with a magnetic stirring bar was added a solution of *tert*-Butyl ((1-([1,1′-biphenyl]-3-carbonyl)-piperidin-4-yl)methyl)carbamate (**18**; 0.21 g, 0.50 mmol, 1.00 equiv) in DCM (5.0 mL). Under cooling at 0 °C were then added TFA (5.0 mL, 65.0 mmol, 130 equiv). The mixture was stirred and slowly allowed to reach rt over 16 h. Upon reaction completion as determined by LC−MS, the volatiles were removed under a jet of N_2. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 45** as a yellowish oily solid (0.14 g, 0.31 mmol, 62%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (s, 3H), 7.75 (dt, J = 7.8, 1.5 Hz, 1H), 7.71−7.66 (m, 2H), 7.62 (d, J = 1.8 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.49 (dd, J = 8.4, 6.9 Hz, 2H), 7.43−7.33 (m, 2H), 4.50 (s, 1H), 3.63 (s, 1H), 3.06 (s, 1H), 2.76 (p, J = 5.9 Hz, 2H), 1.95−1.55 (m, 3H), 1.22 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.71, 158.33 (TFA), 157.99 (TFA), 140.28, 139.37, 137.05, 129.14, 129.01, 127.81, 127.62, 126.78, 125.61, 124.65, 46.65, 43.49, 40.96, 33.96, 28.99. LC−MS (ESI, pos. mode) *m*/*z*: 295.2 $[M + 1]^+$, t_R = 2.99 min.

*1-([1,1′-Biphenyl]-3-carbonyl)piperidine-4-carboxamide (**Compound 46**).*



To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.991 g, 5.00 mmol, 1.00 equiv) in DMF (10.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.438 g, 7.50 mmol, 1.50 equiv), HOBt (1.013 g, 7.50 mmol, 1.50 equiv), and DIPEA (2.61 mL, 15.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/10 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with piperidine-4-carboxamide (0.128 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were washed with 1 M NaOH (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 46** as a white solid (0.11 g, 0.35 mmol, 70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (dt, J = 7.9, 1.5 Hz, 1H), 7.72−7.66 (m, 2H), 7.62 (t, J = 1.8 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.48 (dd, J = 8.4, 6.9 Hz, 2H), 7.43−7.38 (m, 1H), 7.36 (dt, J = 7.6, 1.4 Hz, 1H), 7.28 (s, 1H), 6.80 (s, 1H), 4.46 (s, 1H), 3.64 (s, 1H), 3.07 (s, 1H), 2.84 (s, 1H), 2.37 (tq, J = 11.9, 3.9 Hz, 1H), 1.79 (s, 1H), 1.68 (s, 1H), 1.52 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 175.80, 168.73, 140.26, 139.37, 137.06, 129.12, 129.00, 127.77, 127.56, 126.77, 125.63, 124.70, 46.61, 41.51, 41.03, 28.55. LC−MS (ESI, pos. mode) *m*/*z*: 309.2 $[M + 1]^+$, t_R = 3.58 min.

*[1,1′-Biphenyl]-3-yl(4-benzylpiperidin-1-yl)methanone (**Compound 47**).*



To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.991 g, 5.00 mmol, 1.00 equiv) in DMF (10.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.438 g, 7.50 mmol, 1.50 equiv), HOBt (1.013 g, 7.50 mmol, 1.50 equiv), and DIPEA (2.61 mL, 15.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/10 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with 4-benzylpiperidine (0.175 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were washed with 1 M NaOH (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (hep/EtOAc, 0−40%) to afford the desired product **compound 47** as a colorless sticky oil (0.15 g, 0.43 mmol, 87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73 (dt, J = 8.0, 1.4 Hz, 1H), 7.71−7.66 (m, 2H), 7.60 (t, J = 1.8 Hz, 1H), 7.55−7.45 (m, 3H), 7.43−7.36 (m, 1H), 7.34 (dt, J = 7.5, 1.4 Hz, 1H), 7.31−7.24 (m, 2H), 7.21−7.13 (m, 3H), 4.47 (s, 1H), 3.60 (s, 1H), 3.00 (s, 1H), 2.73 (s, 1H), 2.54 (d, J = 7.2 Hz, 2H), 1.79 (ddp, J = 11.0, 7.3, 3.7 Hz, 1H), 1.65 (s, 2H), 1.53 (s, 1H), 1.20 (d, J = 23.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.64, 140.24, 139.99, 139.38, 137.21, 129.04, 128.99, 128.96, 128.13, 127.75, 127.49, 126.76, 125.79, 125.57, 124.70, 47.30, 42.01, 37.47, 31.97. LC−MS (ESI, pos. mode) *m*/*z*: 356.2 $[M + 1]^+$, t_R = 5.27 min.

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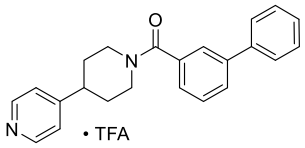
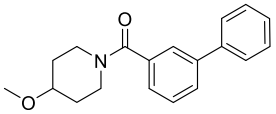
*[1,1′-Biphenyl]-3-yl(4-(pyridin-4-yl)piperidin-1-yl)methanone (**Compound 48**).*



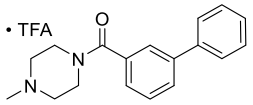
To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.991 g, 5.00 mmol, 1.00 equiv) in DMF (10.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.438 g, 7.50 mmol, 1.50 equiv), HOBt (1.013 g, 7.50 mmol, 1.50 equiv), and DIPEA (2.61 mL, 15.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/10 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with 4-(piperidin-4-yl)pyridine (0.162 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were washed with 1 M NaOH (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 48** as a yellow oil (0.17 g, 0.38 mmol, 76%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87−8.80 (m, 2H), 8.02−7.94 (m, 2H), 7.76 (dt, J = 7.8, 1.5 Hz, 1H), 7.70 (dt, J = 5.4, 1.3 Hz, 3H), 7.56 (t, J = 7.7 Hz, 1H), 7.49 (dd, J = 8.4, 6.9 Hz, 2H), 7.46−7.35 (m, 2H), 4.70 (s, 1H), 3.77 (s, 1H), 3.18 (td, J = 11.6, 5.7 Hz, 2H), 2.91 (s, 1H), 1.94 (s, 1H), 1.75 (ddd, J = 16.6, 12.2, 6.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.79, 163.94, 142.75, 140.31, 139.39, 137.01, 129.11, 129.01, 127.80, 127.64, 126.80, 125.71, 125.22, 124.80, 41.70, 31.20. LC−MS (ESI, pos. mode) m/z: 343.2 $[M + 1]^+$, t_R = 3.21 min.

*[1,1′-Biphenyl]-3-yl(4-methoxypiperidin-1-yl)methanone (**Compound 49**).*



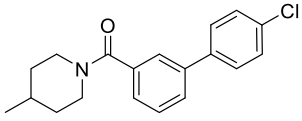
To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.991 g, 5.00 mmol, 1.00 equiv) in DMF (10.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.438 g, 7.50 mmol, 1.50 equiv), HOBt (1.013 g, 7.50 mmol, 1.50 equiv), and DIPEA (2.61 mL, 15.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/10 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with 4-methoxypiperidine (0.115 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were washed with 1 M NaOH (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (hep/EtOAc, 0−75%) to afford the desired product **compound 49** as a colorless oil (0.12 g, 0.39 mmol, 78%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (dt, J = 8.0, 1.4 Hz, 1H), 7.72−7.67 (m, 2H), 7.63 (t, J = 1.8 Hz, 1H), 7.56−7.45 (m, 3H), 7.42−7.34 (m, 2H), 3.94 (s, 1H), 3.45 (td, J = 7.8, 3.9 Hz, 2H), 3.31 (s, 1H), 3.26 (s, 3H), 3.20 (s, 1H), 1.85 (d, J = 29.1 Hz, 2H), 1.46 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.21, 140.71, 139.84, 137.53, 129.56, 129.47, 128.25, 128.02, 127.26, 126.09, 125.20, 75.45, 55.51, 44.93, 40.34, 31.20. LC−MS (ESI, pos. mode) m/z: 296.1 $[M + 1]^+$, t_R = 4.39 min.

*[1,1′-Biphenyl]-3-yl(4-methylpiperazin-1-yl)methanone (**Compound 50**).*



To a vial charged with a magnetic stirring bar was added a solution of [1,1′-biphenyl]-3-carboxylic acid (**17**; 0.991 g, 5.00 mmol, 1.00 equiv) in DMF (10.0 mL). Under cooling at 0 °C were then added EDC·HCl (1.438 g, 7.50 mmol, 1.50 equiv), HOBt (1.013 g, 7.50 mmol, 1.50 equiv), and DIPEA (2.61 mL, 15.0 mmol, 3.00 equiv). The solution was stirred at 0 °C for 30 min. After preactivation, ∼1/10 of the reaction mixture was transferred to a vial charged with a magnetic stirring bar and treated with 1-methylpiperazine (0.100 g, 1.00 mmol, 2.00 equiv), and the mixture was stirred at rt for 21 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of water (5 mL). The mixture was extracted with EtOAc (4× 5 mL), and the combined organic layers were washed with 1 M NaOH (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 50** as a yellow oil (0.14 g, 0.35 mmol, 70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 7.80 (dt, J = 7.8, 1.5 Hz, 1H), 7.73−7.67 (m, 3H), 7.58 (t, J = 7.7 Hz, 1H), 7.50 (dd, J = 8.4, 6.9 Hz, 2H), 7.46−7.37 (m, 2H), 4.54 (s, 1H), 3.84 (s, 1H), 3.28 (d, J = 124.4 Hz, 6H), 2.83 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.01, 158.28 (q, J = 35.4 Hz, TFA), 140.41, 139.25, 135.49, 129.28, 129.01, 128.24, 127.88, 126.83, 126.08, 125.12, 52.15, 42.29. LC−MS (ESI, pos. mode) m/z: 281.1 $[M + 1]^+$, t_R = 2.90 min.

*(4′-Chloro-[1,1′-biphenyl]-3-yl)(4-methylpiperidin-1-yl)-methanone (**Compound 51**).*



To a round-bottomed flask charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)-methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (4-chlorophenyl)boronic acid (0.117 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The mixture was stirred under nitrogen at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were washed with 1 M HCl (10 mL), 1 M NaOH (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 51** as a

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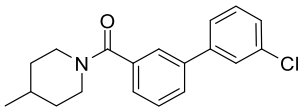
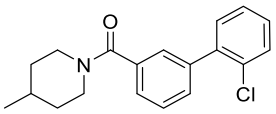
golden-brown oil (0.13 g, 0.41 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77−7.70 (m, 3H), 7.62 (t, J = 1.8 Hz, 1H), 7.57−7.49 (m, 3H), 7.36 (dt, J = 7.6, 1.3 Hz, 1H), 4.46 (s, 1H), 3.57 (s, 1H), 3.03 (s, 1H), 2.77 (s, 1H), 1.62 (tdq, J = 10.4, 7.0, 3.6 Hz, 3H), 1.09 (s, 2H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.51, 138.91, 138.18, 137.39, 132.67, 129.14, 128.92, 128.57, 127.39, 125.90, 124.64, 47.35, 41.60, 34.03, 33.43, 30.44, 21.54. LC−MS (ESI, pos. mode) m/z: 314.2 $[M + 1]^+$, t_R = 3.81 min.

*(3′-Chloro-[1,1′-biphenyl]-3-yl)(4-methylpiperidin-1-yl)-methanone (**Compound 52**).*



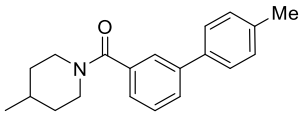
To a round-bottomed flask charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)-methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (3-chlorophenyl)boronic acid (0.117 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The mixture was stirred under nitrogen at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 52** as a colorless oil (0.11 g, 0.34 mmol, 69%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.78−7.75 (m, 2H), 7.69−7.64 (m, 2H), 7.52 (dt, J = 18.1, 7.7 Hz, 2H), 7.45 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.38 (dt, J = 7.6, 1.4 Hz, 1H), 4.46 (s, 1H), 3.56 (s, 1H), 3.04 (s, 1H), 2.76 (s, 1H), 1.76−1.45 (m, 3H), 1.09 (s, 2H), 0.92 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.46, 141.54, 138.69, 137.42, 133.79, 130.80, 129.16, 127.61, 126.56, 126.20, 125.52, 124.86, 47.34, 41.65, 34.04, 33.37, 30.44, 21.55. LC−MS (ESI, pos. mode) m/z: 314.2 $[M + 1]^+$, t_R = 5.16 min.

*(2′-Chloro-[1,1′-biphenyl]-3-yl)(4-methylpiperidin-1-yl)-methanone (**Compound 53**).*



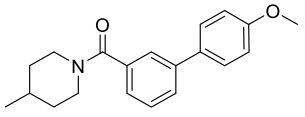
To a round-bottomed flask charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)-methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (2-chlorophenyl)boronic acid (0.0.50 g, 0.32 mmol, 0.64 equiv—used sub-stoichiometric due to shortage of chemical), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The mixture was stirred under nitrogen at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 53** as a yellowish oil (0.042 g, 0.14 mmol, 42%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.58 (dt, J = 6.7, 1.3 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.49 (dt, J = 7.7, 1.6 Hz, 1H), 7.47−7.37 (m, 5H), 4.44 (s, 1H), 3.71−3.55 (m, 1H), 3.04 (s, 1H), 2.75 (s, 1H), 1.76−1.49 (m, 3H), 1.10 (s, 2H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.38, 139.02, 138.55, 136.37, 131.49, 131.23, 130.02, 129.87, 129.48, 128.55, 127.61, 127.22, 126.16, 47.33, 41.70, 40.06, 39.92, 39.57, 34.10, 33.40, 30.44, 21.54. LC−MS (ESI, pos. mode) m/z: 314.2 $[M + 1]^+$, t_R = 5.06 min.

*(4′-Methyl-[1,1′-biphenyl]-3-yl)(4-methylpiperidin-1-yl)-methanone (**Compound 54**).*



To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), *p*-tolylboronic acid (0.102 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (hep/EtOAc, 0−40%) to afford the desired product **compound 54** as a yellowish solid (0.15 g, 0.50 mmol, quantitative). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.70 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.60−7.56 (m, 3H), 7.50 (t, J = 7.7 Hz, 1H), 7.31 (dt, J = 7.6, 1.4 Hz, 1H), 7.28 (d, J = 7.9 Hz, 2H), 4.46 (s, 1H), 3.58 (s, 1H), 3.03 (s, 1H), 2.76 (s, 1H), 2.35 (s, 3H), 1.78−1.46 (m, 3H), 1.18−0.99 (m, 2H), 0.92 (d, J = 6.5 Hz, 3H). ^{13}C NMR (ktt.191122.a600_13, 151 MHz, DMSO-d_6): δ 168.68, 140.15, 137.23, 137.11, 136.49, 129.58, 128.99, 127.17, 126.57, 125.24, 124.41, 47.33, 41.64, 34.08, 33.40, 30.45, 21.55, 20.64. LC−MS (ESI, pos. mode) m/z: 294.1 $[M + 1]^+$, t_R = 5.13 min.

*(4′-Methoxy-[1,1′-biphenyl]-3-yl)(4-methylpiperidin-1-yl)-methanone (**Compound 55**).*



To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (4-methoxyphenyl)-boronic acid (0.114 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic

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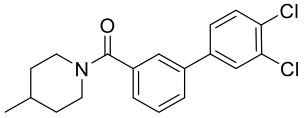
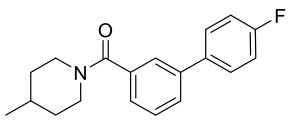
layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (hep/EtOAc, 0−40%) to afford the desired product **compound 55** as a brown oil (0.13 g, 0.43 mmol, 87%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.68 (ddd, J = 7.8, 2.0, 1.1 Hz, 1H), 7.65−7.61 (m, 2H), 7.56 (t, J = 1.8 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.28 (dt, J = 7.5, 1.3 Hz, 1H), 7.06−6.99 (m, 2H), 4.46 (s, 1H), 3.80 (s, 3H), 3.59 (s, 1H), 3.03 (s, 1H), 2.76 (s, 1H), 1.76−1.47 (m, 3H), 1.17−0.97 (m, 2H), 0.92 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.73, 159.12, 139.87, 137.21, 131.69, 128.96, 127.86, 126.90, 124.82, 124.12, 114.42, 55.18, 47.33, 41.63, 40.06, 39.92, 34.08, 33.41, 30.46, 21.56. LC−MS (ESI, pos. mode) m/z: 310.2 $[M + 1]^+$, t_R = 4.85 min.

*(3′,4′-Dichloro-[1,1′-biphenyl]-3-yl)(4-methylpiperidin-1-yl)-methanone (**Compound 56**).*



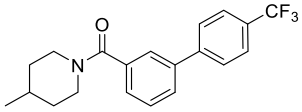
To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (3,4-dichlorophenyl)-boronic acid (0.143 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was subjected to MW irradiation at 90 °C for 10 min. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (hep/EtOAc, 0−50%) to afford the desired product **compound 56** as a yellowish oil (0.16 g, 0.45 mmol, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (d, J = 1.4 Hz, 1H), 7.79 (dt, J = 8.0, 1.4 Hz, 1H), 7.72 (d, J = 1.6 Hz, 2H), 7.69 (t, J = 1.8 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.39 (dt, J = 7.7, 1.3 Hz, 1H), 4.46 (s, 1H), 3.55 (s, 1H), 3.04 (s, 1H), 2.77 (s, 1H), 1.78−1.45 (m, 3H), 1.09 (s, 2H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.37, 139.98, 137.62, 137.48, 131.76, 131.00, 130.52, 129.19, 128.64, 127.55, 127.03, 126.41, 124.84, 47.24, 41.66, 33.96, 30.42, 21.54. LC−MS (ESI, pos. mode) m/z: 348.1 $[M + 1]^+$, t_R = 5.38 min.

*(4′-Fluoro-[1,1′-biphenyl]-3-yl)(4-methylpiperidin-1-yl)-methanone (**Compound 57**).*



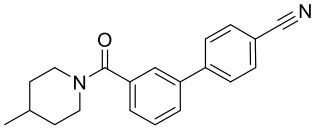
To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (4-fluorophenyl)boronic acid (0.105 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was subjected to MW irradiation at 90 °C for 10 min. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (hep/EtOAc, 0−60%) to afford the desired product **compound 57** as a golden-brown oil (0.13 g, 0.42 mmol, 85%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.77−7.70 (m, 3H), 7.60 (t, J = 1.8 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.34 (dt, J = 7.6, 1.4 Hz, 1H), 7.32−7.27 (m, 2H), 4.46 (s, 1H), 3.57 (s, 1H), 3.03 (s, 1H), 2.76 (s, 1H), 1.80−1.45 (m, 3H), 1.09 (s, 2H), 0.92 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.57, 162.03 (d, J = 244.8 Hz), 139.20, 137.32, 135.84 (d, J = 3.2 Hz), 129.08, 128.82 (d, J = 8.2 Hz), 127.40, 125.54, 124.62, 115.77 (d, J = 21.0 Hz), 47.34, 41.65, 40.06, 39.92, 39.43, 39.29, 39.14, 34.06, 33.39, 30.45, 21.55. LC−MS (ESI, pos. mode) m/z: 298.2 $[M + 1]^+$, t_R = 4.92 min.

*(4-Methylpiperidin-1-yl)(4′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)methanone (**Compound 58**).*



To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (4-(trifluoromethyl)-phenyl)boronic acid (0.142 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was subjected to MW irradiation at 90 °C for 10 min. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (hep/EtOAc, 0−40%) to afford the desired product **compound 58** as a golden-brown oil (0.11 g, 0.31 mmol, 62%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.93 (d, J = 8.1 Hz, 2H), 7.85−7.78 (m, 3H), 7.70 (t, J = 1.8 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.42 (dt, J = 7.6, 1.3 Hz, 1H), 4.47 (s, 1H), 3.57 (s, 1H), 3.04 (s, 1H), 2.77 (s, 1H), 1.79−1.44 (m, 3H), 1.10 (s, 2H), 0.92 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.40, 143.38, 138.69, 137.49, 129.26, 128.11 (q, J = 31.8 Hz), 127.82, 127.64, 126.55, 125.80 (q, J = 3.7 Hz), 125.07, 124.78 (q, J = 272.8 Hz), 47.35, 41.67, 39.57, 34.05, 33.38, 30.44, 21.54. LC−MS (ESI, pos. mode) m/z: 348.2 $[M + 1]^+$, t_R = 5.17 min.

*3′-(4-Methylpiperidine-1-carbonyl)-[1,1′-biphenyl]-4-carbonitrile (**Compound 59**).*



To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (4-cyanophenyl)boronic acid (0.110 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50

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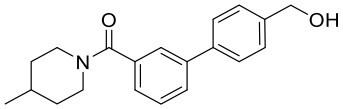
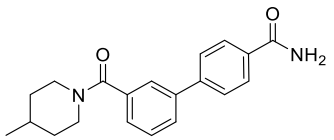
mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was subjected to MW irradiation at 90 °C for 10 min. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were washed with 1 M HCl (10 mL) and 1 M NaOH (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−65%, 40 min) to afford the desired product **compound 59** as a yellow oil (0.13 g, 0.43 mmol, 86%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96−7.88 (m, 4H), 7.85−7.79 (m, 1H), 7.71 (t, J = 1.8 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.43 (dt, J = 7.6, 1.3 Hz, 1H), 4.46 (s, 1H), 3.56 (s, 1H), 3.04 (s, 1H), 2.77 (s, 1H), 1.62 (dtt, J = 10.8, 7.3, 3.7 Hz, 3H), 1.09 (s, 2H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.33, 143.83, 138.36, 137.54, 132.87, 129.31, 127.83, 127.72, 126.83, 125.08, 118.75, 110.36, 47.34, 41.67, 38.99, 34.00, 33.39, 30.43, 21.54. LC−MS (ESI, pos. mode) m/z: 305.2 $[M + 1]^+$, t_R = 4.64 min.

*(4′-(Hydroxymethyl)-[1,1′-biphenyl]-3-yl)(4-methylpiperidin-1-yl)methanone (**Compound 60**).*



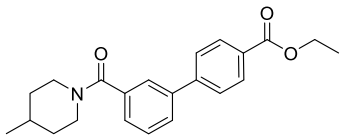
To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (4-(hydroxymethyl) phenyl)boronic acid (0.114 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was subjected to MW irradiation at 90 °C for 10 min. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were washed with 1 M HCl (10 mL) and 1 M NaOH (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−60%, 40 min) to afford the desired product **compound 60** as a light-yellow oil (0.070 g, 0.23 mmol, 46%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (dt, J = 7.9, 1.4 Hz, 1H), 7.68−7.63 (m, 2H), 7.61−7.59 (m, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.33 (dt, J = 7.6, 1.3 Hz, 1H), 5.19 (s, 1H), 4.55 (s, 2H), 4.46 (s, 1H), 3.59 (s, 1H), 3.03 (s, 1H), 2.77 (s, 1H), 1.63 (tdt, J = 10.9, 7.1, 3.9 Hz, 1H), 1.09 (s, 2H), 0.93 (d, J = 6.4 Hz, 3H).^{13}C NMR (ktt.191202.a400_43, 101 MHz, DMSO-d_6): δ 168.67, 142.18, 140.16, 137.73, 137.25, 129.01, 127.30, 127.04, 126.45, 125.36, 124.54, 62.54, 30.45, 21.55. LC−MS (ESI, pos. mode) m/z: 310.2 $[M + 1]^+$, t_R = 4.15 min.

*3′-(4-Methylpiperidine-1-carbonyl)-[1,1′-biphenyl]-4-carboxamide (**Compound 61**).*



To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (4-carbamoylphenyl)-boronic acid (0.124 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was subjected to MW irradiation at 90 °C for 10 min. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were washed with 1 M HCl (10 mL) and 1 M NaOH (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 61** as a white solid (0.078 g, 0.24 mmol, 49%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (s, 1H), 8.01−7.94 (m, 2H), 7.83−7.75 (m, 3H), 7.68 (t, J = 1.8 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.38 (dt, J = 7.4, 1.3 Hz, 2H), 4.47 (s, 1H), 3.58 (s, 1H), 3.04 (s, 1H), 2.77 (s, 1H), 1.63 (dtt, J = 10.6, 7.1, 3.8 Hz, 3H), 1.10 (s, 2H), 0.93 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.52, 167.42, 141.91, 139.31, 137.38, 133.38, 129.13, 128.18, 127.62, 126.55, 126.09, 124.86, 30.44, 21.55. LC−MS (ESI, pos. mode) m/z: 323.2 $[M + 1]^+$, t_R = 3.82 min.

*Ethyl 3′-(4-Methylpiperidine-1-carbonyl)-[1,1′-biphenyl]-4-carboxylate (**Compound 62**).*



To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (4-(ethoxycarbonyl)-phenyl)boronic acid (0.145 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was subjected to MW irradiation at 90 °C for 10 min. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were washed with 1 M HCl (10 mL) and 1 M NaOH (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 62** as a golden-brown oil (0.13 g, 0.36 mmol, 71%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07−8.01 (m, 2H), 7.89−7.83 (m, 2H), 7.81 (dt, J = 7.9, 1.4 Hz, 1H), 7.69 (t, J = 1.7 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.41 (dt, J = 7.6, 1.3 Hz, 1H), 4.47 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.57 (s, 1H), 3.04

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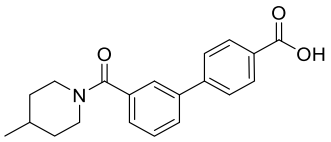
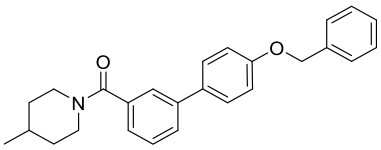
(s, 1H), 2.77 (s, 1H), 2.07 (s, 0H), 1.62 (dtt, J = 10.8, 7.3, 3.7 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.09 (s, 2H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.44, 165.46, 143.79, 138.97, 137.46, 129.78, 129.21, 129.01, 127.73, 127.05, 126.45, 125.00, 60.76, 47.34, 41.59, 34.03, 33.41, 30.43, 21.54, 14.15. LC−MS (ESI, pos. mode) m/z: 352.3 $[M + 1]^+$, t_R = 5.06 min.

*3′-(4-Methylpiperidine-1-carbonyl)-[1,1′-biphenyl]-4-carboxylic Acid (**Compound 63**).*



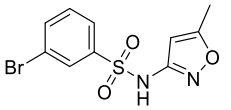
To a vial charged with a magnetic stirring bar was added a solution of ethyl 3′-(4-methylpiperidine-1-carbonyl)-[1,1′-biphenyl]-4-carboxylate (**compound 62**; 0.050 g, 0.14 mmol, 1.00 equiv) in abs. EtOH (1.4 mL). This solution was then treated with 1 M aq. NaOH (0.57 mL, 0.57 mmol, 4.00 equiv), and the mixture was stirred at rt for 13 h. Upon reaction completion as determined by LC−MS, the pH was adjusted to 1−2 with 1 M HCl, and the mixture was extracted with EtOAc (3× 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 63** as a white solid (0.037 g, 0.11 mmol, 82%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.99 (s, 1H), 8.06−8.00 (m, 2H), 7.85−7.82 (m, 2H), 7.80 (ddd, J = 7.8, 2.0, 1.1 Hz, 1H), 7.69 (t, J = 1.8 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.40 (dt, J = 7.5, 1.3 Hz, 1H), 4.47 (s, 1H), 3.57 (s, 1H), 3.05 (s, 1H), 2.77 (s, 1H), 1.77−1.45 (m, 3H), 1.10 (s, 2H), 0.93 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 168.47, 167.04, 143.47, 139.12, 137.44, 129.97, 129.90, 129.21, 127.71, 126.94, 126.36, 124.97, 47.36, 41.66, 34.06, 33.38, 30.44, 21.55. LC−MS (ESI, pos. mode) m/z: 324.4 $[M + 1]^+$, t_R = 2.32 min.

*(4′-(Benzyloxy)-[1,1′-biphenyl]-3-yl)(4-methylpiperidin-1-yl)-methanone (**Compound 64**).*



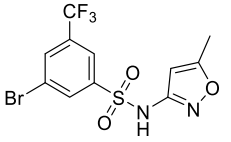
To a pressure vial charged with a magnetic stirring bar were added (3-bromophenyl)(4-methylpiperidin-1-yl)methanone (**15**; 0.141 g, 0.50 mmol, 1.00 equiv), (4-(benzyloxy)phenyl)-boronic acid (0.171 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were washed with 1 M HCl (10 mL) and 1 M NaOH (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by silica gel flash chromatography (hep/EtOAc, 0−55%) to afford the desired product **compound 64** as a yellowish solid (0.14 g, 0.36 mmol, 73%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (dt, J = 8.0, 1.3 Hz, 1H), 7.65−7.60 (m, 2H), 7.56 (t, J = 1.8 Hz, 1H), 7.48 (t, J = 7.5 Hz, 3H), 7.43−7.37 (m, 2H), 7.36−7.30 (m, 1H), 7.28 (dt, J = 7.5, 1.3 Hz, 1H), 7.14−7.08 (m, 2H), 5.16 (s, 2H), 4.46 (s, 1H), 3.58 (s, 1H), 3.02 (s, 1H), 2.76 (s, 1H), 1.80−1.44 (m, 2H), 1.09 (s, 2H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.72, 158.20, 139.81, 137.21, 137.00, 131.91, 128.96, 128.42, 127.87, 127.81, 127.62, 126.91, 124.86, 124.12, 115.31, 69.24, 30.45, 21.55. LC−MS (ESI, pos. mode) m/z: 386.3 $[M + 1]^+$, t_R = 5.34 min.

*3-Bromo-N-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**).*



To a round-bottomed flask charged with a magnetic stirring bar were added 5-methylisoxazol-3-amine (1.96 g, 20.0 mmol, 2.55 equiv), pyridine (4.04 mL, 50.0 mmol, 6.39 equiv), and DCM (50.0 mL). The solution was then treated with 3-bromobenzenesulfonyl chloride (2.00 g, 7.83 mmol, 1.00 equiv). The flask was equipped with a reflux condenser, and the mixture was stirred at reflux for 6 h. Upon reaction completion as determined by TLC, the reaction mixture was washed with 2 M aq. HCl (2× 30 mL) and sat. brine (30 mL), and the organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **19a** as a light-yellow solid (3.17 g, 4.60 mmol, 59%) used without further purification. ^{1}H NMR (600 MHz, chloroform-*d*): δ 9.61 (s, 1H), 7.97 (t, J = 1.9 Hz, 1H), 7.75 (ddd, J = 8.0, 1.8, 1.0 Hz, 1H), 7.67 (ddd, J = 8.0, 1.9, 1.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 6.25 (d, J = 1.0 Hz, 1H), 2.40 (d, J = 0.9 Hz, 3H).

*3-Bromo-N-(5-methylisoxazol-3-yl)-5-(trifluoromethyl)-benzenesulfonamide (**19b**).*



To a round-bottomed flask charged with a magnetic stirring bar were added 5-methylisoxazol-3-amine (0.20 g, 2.00 mmol, 2.00 equiv), pyridine (0.40 mL, 5.00 mmol, 5.00 equiv), and DCM (5.0 mL). The solution was then treated with 3-bromo-5-(trifluoromethyl)benzenesulfonyl chloride (0.32 g, 1.00 mmol, 1.00 equiv). The flask was equipped with a reflux condenser, and the mixture was stirred at reflux for 4.5 h. Upon reaction completion as determined by TLC, the reaction mixture was evaporated to dryness *in vacuo*. The residue was redissolved in EtOAc (15 mL) and washed with 1 M aq. HCl (2× 10 mL) and sat. brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **19b** as a red solid (0.47 g, ∼1.00 mmol, ∼quantitative) used without further purification. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.15 (d, J = 1.7 Hz, 1H), 8.03 (s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 6.27 (d, J = 1.0 Hz, 1H), 2.45−2.38 (m, 3H).

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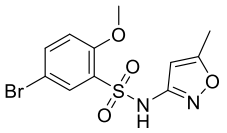
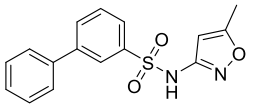
*5-Bromo-2-methoxy-N-(5-methylisoxazol-3-yl)-benzenesulfonamide (**19c**).*



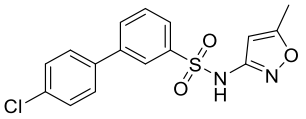
To a round-bottomed flask charged with a magnetic stirring bar were added 5-methylisoxazol-3-amine (0.20 g, 2.00 mmol, 2.00 equiv), pyridine (0.40 mL, 5.00 mmol, 5.00 equiv), and DCM (5.0 mL). The solution was then treated with 3-bromo-2-methoxybenzenesulfonyl chloride (0.29 g, 1.00 mmol, 1.00 equiv). The flask was equipped with a reflux condenser, and the mixture was stirred at reflux for 16 h. Upon reaction completion as determined by TLC, the reaction mixture was evaporated to dryness *in vacuo*. The residue was redissolved in EtOAc (15 mL) and washed with 1 M aq. HCl (2× 10 mL) and sat. brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the desired crude product **19c** (0.291 g, 0.84 mmol, 84%) used without further purification. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.98 (d, J = 2.5 Hz, 1H), 7.63 (dd, J = 8.9, 2.5 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.19−6.13 (m, 1H), 3.95 (s, 3H), 2.33 (s, 3H).

*N-(5-Methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 37**).*



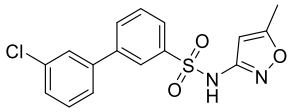
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.19 g, 0.60 mmol, 1.00 equiv), phenylboronic acid (0.11 g, 0.90 mmol, 1.50 equiv), K_2CO_3 (0.25 g, 1.80 mmol, 3.00 equiv), 1,4-dioxane (4.8 mL), and H_2O (1.2 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.069 g, 0.060 mmol, 0.10 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 2 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford a yellow-green oil. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 37** as a white solid (0.035 g, 0.11 mmol, 18%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.47 (s, 1H), 8.09 (t, J = 1.9 Hz, 1H), 7.98 (dt, J = 7.8, 1.5 Hz, 1H), 7.84 (dt, J = 7.9, 1.4 Hz, 1H), 7.78−7.64 (m, 3H), 7.58−7.49 (m, 2H), 7.49−7.41 (m, 1H), 6.20 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.48, 157.46, 141.17, 140.14, 138.27, 131.53, 130.15, 129.23, 128.42, 126.81, 125.44, 124.55, 95.47, 12.02. LC−MS (ESI, pos. mode) m/z: 315.0 $[M + 1]^+$, t_R = 2.42 min.

*4′-Chloro-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 65**).*



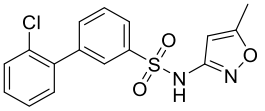
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (4-chlorophenyl)-boronic acid (0.117 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 65** as a white solid (0.044 g, 0.13 mmol, 25%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.48 (s, 1H), 8.09 (t, J = 1.9 Hz, 1H), 7.99 (dt, J = 7.8, 1.4 Hz, 1H), 7.86 (dt, J = 8.0, 1.3 Hz, 1H), 7.75−7.68 (m, 3H), 7.62−7.56 (m, 2H), 6.19 (d, J = 1.0 Hz, 1H), 2.29 (d, J = 0.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.50, 157.43, 140.23, 139.86, 137.07, 133.37, 131.52, 130.26, 129.20, 128.63, 125.78, 124.50, 95.47, 12.02. LC−MS (ESI, pos. mode) m/z: 349.1 $[M + 1]^+$, t_R = 4.61 min.

*3′-Chloro-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 66**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (3-chlorophenyl)-boronic acid (0.117 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 2 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 66** as a white solid (0.050 g, 0.14 mmol, 28%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.11 (t, J = 1.9 Hz, 1H), 8.02 (dt, J = 7.8, 1.4 Hz, 1H), 7.87 (dt, J = 8.0, 1.3 Hz, 1H), 7.76−7.68 (m, 2H), 7.66 (dt, J = 7.5, 1.6 Hz, 1H), 7.62−7.49 (m, 2H), 6.21 (d, J = 1.0 Hz, 1H), 2.30 (d, J = 0.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.52, 157.45, 140.39, 140.20, 139.62, 133.96, 131.77, 131.07, 130.27, 128.27, 126.62, 126.06, 125.59, 124.74, 95.51, 12.02. LC−MS (ESI, pos. mode) m/z: 349.1 $[M + 1]^+$, t_R = 4.59 min.

*2′-Chloro-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 67**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (2-chlorophenyl)-

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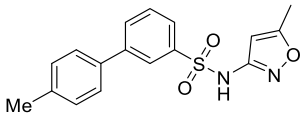
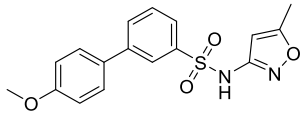
boronic acid (0.117 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by TLC, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 67** as a white solid (0.027 g, 0.077 mmol, 15%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.50 (s, 1H), 7.90 (dd, J = 7.3, 1.6 Hz, 2H), 7.77−7.70 (m, 2H), 7.63−7.59 (m, 1H), 7.50−7.42 (m, 3H), 6.18 (d, J = 1.0 Hz, 1H), 2.30 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.44, 157.41, 139.44, 139.38, 137.85, 134.12, 131.44, 131.12, 130.06, 130.01, 129.65, 127.81, 127.31, 125.96, 95.52, 12.03. LC−MS (ESI, pos. mode) m/z: 349.1 $[M + 1]^+$, t_R = 4.49 min.

*4′-Methyl-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 68**).*



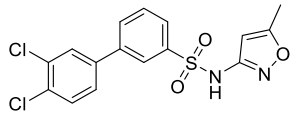
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), *p*-tolylboronic acid (0.102 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by TLC, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 68** as a white solid (0.16 g, 0.15 mmol, 30%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.07 (t, J = 1.9 Hz, 1H), 7.95 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.81 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.60−7.55 (m, 2H), 7.36−7.31 (m, 2H), 6.19 (d, J = 1.0 Hz, 1H), 2.36 (s, 3H), 2.29 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.49, 157.50, 141.09, 140.12, 137.95, 135.37, 131.24, 130.10, 129.82, 126.63, 125.14, 124.23, 95.47, 20.67, 12.02. LC−MS (ESI, pos. mode) m/z: 329.1 $[M + 1]^+$, t_R = 4.60 min.

*4′-Methoxy-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 69**).*



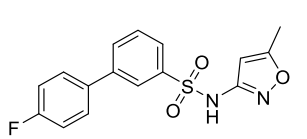
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (4-methoxyphenyl)-boronic acid (0.114 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by TLC, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 69** as a white solid (0.054 g, 0.16 mmol, 31%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 8.05 (t, J = 1.9 Hz, 1H), 7.96−7.87 (m, 1H), 7.77 (dt, J = 7.9, 1.3 Hz, 1H), 7.70−7.57 (m, 3H), 7.12−7.04 (m, 2H), 6.19 (d, J = 1.0 Hz, 1H), 3.82 (s, 3H), 2.30 (d, J = 0.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.45, 159.60, 157.49, 140.84, 140.09, 130.92, 130.51, 130.03, 127.98, 124.66, 123.91, 114.66, 95.46, 55.26, 12.02. LC−MS (ESI, pos. mode) m/z: 345.1 $[M + 1]^+$, t_R = 4.35 min.

*3′,4′-Dichloro-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 70**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (3,4-dichlorophenyl)-boronic acid (0.143 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−65%, 40 min) to afford the desired product **compound 70** as a white solid (0.10 g, 0.27 mmol, 55%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.48 (s, 1H), 8.13 (t, J = 1.9 Hz, 1H), 8.04 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.88 (ddd, J = 7.9, 1.9, 1.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.9 Hz, 1H), 7.69 (dd, J = 8.4, 2.2 Hz, 1H), 6.21 (d, J = 1.0 Hz, 1H), 2.29 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.52, 157.43, 140.26, 138.85, 138.59, 131.98, 131.78, 131.30, 131.26, 130.32, 128.76, 127.10, 126.29, 124.72, 95.50, 12.03. LC−MS (ESI, pos. mode) m/z: 383.1 $[M + 1]^+$, t_R = 4.88 min.

*4′-Fluoro-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 71**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide

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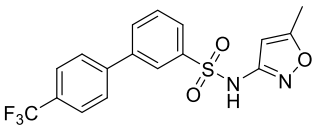
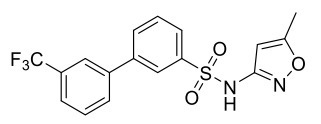
(**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (4-fluorophenyl)-boronic acid (0.105 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−70%, 40 min) to afford the desired product **compound 71** as a white solid (0.17 g, 0.23 mmol, 46%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.47 (s, 1H), 8.07 (t, J = 1.9 Hz, 1H), 7.96 (dt, J = 7.8, 1.4 Hz, 1H), 7.84 (dt, J = 8.0, 1.3 Hz, 1H), 7.75−7.67 (m, 3H), 7.40−7.31 (m, 2H), 6.19 (d, J = 1.0 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.49, 162.37 (d, J = 245.7 Hz), 157.45, 140.16 (d, J = 1.7 Hz), 134.77 (d, J = 3.1 Hz), 131.50, 130.18, 128.98 (d, J = 8.4 Hz), 125.43, 124.50, 116.09 (d, J = 21.6 Hz), 95.47, 12.02. LC−MS (ESI, pos. mode) m/z: 333.1 $[M + 1]^+$, t_R = 4.40 min.

*N-(5-Methylisoxazol-3-yl)-4′-(trifluoromethyl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 72**).*



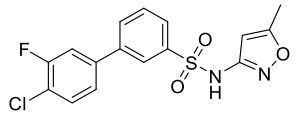
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (4-(trifluoromethyl)-phenyl)boronic acid (0.142 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−60%, 40 min) to afford the desired product **compound 72** as a yellowish solid (0.10 g, 0.27 mmol, 54%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.52 (s, 1H), 8.16 (t, J = 1.8 Hz, 1H), 8.06 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 7.94−7.87 (m, 5H), 7.76 (t, J = 7.8 Hz, 1H), 6.20 (d, J = 1.0 Hz, 1H), 2.29 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.53, 157.41, 142.26, 140.33, 139.62, 131.98, 130.40, 128.70 (q, J = 31.9 Hz), 127.76, 126.43, 126.08 (q, J = 3.8 Hz), 124.94, 124.20 (q), 95.48, 12.03. LC−MS (ESI, pos. mode) m/z: 383.2 $[M + 1]^+$, t_R = 4.71 min.

*N-(5-Methylisoxazol-3-yl)-3′-(trifluoromethyl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 73**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (3-(trifluoromethyl)-phenyl)boronic acid (0.142 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−80%, 40 min) to afford the desired product **compound 73** as a yellowish solid (0.11 g, 0.28 mmol, 55%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.49 (s, 1H), 8.16 (t, J = 1.9 Hz, 1H), 8.08 (ddd, J = 7.8, 2.0, 1.0 Hz, 1H), 8.01 (dt, J = 7.7, 1.4 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H), 7.90 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 7.82 (dt, J = 8.0, 1.1 Hz, 1H), 7.76 (dt, J = 15.8, 7.8 Hz, 2H), 6.22 (d, J = 1.0 Hz, 1H), 2.29 (d, J = 0.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.53, 157.45, 140.28, 139.61, 139.36, 131.99, 131.07, 130.39, 130.34, 129.98 (q, J = 31.9 Hz), 126.22, 125.10−124.98 (m), 126.94−121.13 (q, J = 3.8 Hz), 124.87, 123.37 (q, J = 3.8 Hz), 95.52, 12.00. LC−MS (ESI, pos. mode) m/z: 383.3 $[M + 1]^+$, t_R = 2.69 min.

*4′-Chloro-3′-fluoro-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 74**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (4-chloro-3-fluorophenyl)boronic acid (0.131 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1.5 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−80%, 40 min) to afford the desired product **compound 74** as a yellow solid (0.096 g, 0.26 mmol, 52%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.48 (s, 1H), 8.13 (t, J = 1.9 Hz, 1H), 8.03 (ddd, J = 7.8, 2.0, 1.1 Hz, 1H), 7.88 (ddd, J = 7.9, 1.9, 1.0 Hz, 1H), 7.80 (dd, J = 10.7, 2.1 Hz, 1H), 7.74 (dt, J = 12.5, 8.0 Hz, 2H), 7.60−7.55 (m, 1H), 6.21 (d, J = 1.0 Hz, 1H), 2.29 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.52, 157.63 (d, J = 246.6 Hz), 157.42, 140.28, 139.35 (d, J = 7.2 Hz), 138.77 (d, J = 1.9 Hz), 131.73, 131.34, 130.32, 126.30, 124.70, 124.04 (d, J = 3.3 Hz), 119.65 (d, J = 17.6 Hz), 115.31 (d, J = 22.0 Hz), 95.48, 12.03. LC−MS (ESI, pos. mode) m/z: 367.3 $[M + 1]^+$, t_R = 2.64 min.

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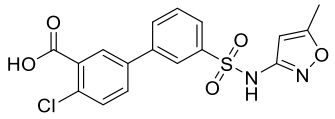
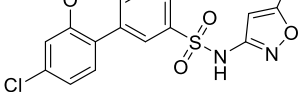
*4-Chloro-3′-(N-(5-methylisoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-3-carboxylic Acid (**Compound 75**).*



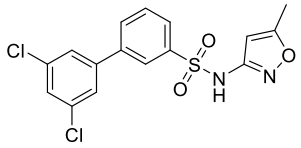
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), 5-borono-2-chlorobenzoic acid (0.150 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M HCl (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were extracted with 1 M NaOH (3× 10 mL). The combined aqueous layers were acidified with conc. HCl until pH 1−2 and then extracted with EtOAc (3× 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−55%, 40 min) to afford the desired product **compound 75** as a yellow solid (0.14 g, 0.36 mmol, 73%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.61 (s, 1H), 11.50 (s, 1H), 8.12 (t, J = 1.9 Hz, 1H), 8.05−8.02 (m, 2H), 7.88 (ddd, J = 7.9, 1.9, 1.0 Hz, 1H), 7.86 (dd, J = 8.4, 2.4 Hz, 1H), 7.73 (t, J = 7.9 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 6.21 (d, J = 1.0 Hz, 1H), 2.29 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 171.04, 166.90, 157.92, 140.75, 139.54, 137.61, 132.72, 132.22, 132.15, 131.99, 131.14, 130.85, 129.31, 126.64, 125.02, 95.98, 12.51. LC−MS (ESI, pos. mode) m/z: 393.3 $[M + 1]^+$, t_R = 2.16 min.

*4′-Chloro-2′-methoxy-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 76**).*



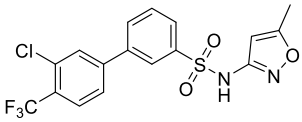
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (4-chloro-2-methoxyphenyl)boronic acid (0.140 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−65%, 40 min) to afford the desired product **compound 76** as a yellow solid (0.12 g, 0.30 mmol, 61%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.48 (s, 1H), 7.95 (t, J = 1.8 Hz, 1H), 7.82 (ddd, J = 7.9, 2.0, 1.1 Hz, 1H), 7.76 (ddd, J = 7.8, 1.8, 1.2 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 8.1, 2.0 Hz, 1H), 6.17 (d, J = 1.0 Hz, 1H), 3.80 (s, 3H), 2.30 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.40, 157.46, 156.77, 139.39, 137.89, 134.04, 133.93, 131.49, 129.35, 127.13, 126.59, 125.33, 120.85, 112.38, 95.39, 56.10, 12.04. LC−MS (ESI, pos. mode) m/z: 379.3 $[M + 1]^+$, t_R = 2.64 min.

*3′,5′-Dichloro-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 77**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (3,5-dichlorophenyl)-boronic acid (0.143 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−80%, 40 min) to afford the desired product **compound 77** as a light-yellow solid (0.089 g, 0.23 mmol, 46%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 8.14 (t, J = 1.9 Hz, 1H), 8.06 (dt, J = 7.9, 1.3 Hz, 1H), 7.90 (dt, J = 8.1, 1.3 Hz, 1H), 7.78−7.68 (m, 4H), 6.23 (d, J = 1.0 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.53, 157.44, 141.75, 140.24, 138.29, 134.88, 132.01, 130.31, 127.82, 126.60, 125.69, 124.97, 95.53, 12.03. LC−MS (ESI, pos. mode) m/z: 383.1 $[M + 1]^+$, t_R = 4.86 min.

*3′-Chloro-N-(5-methylisoxazol-3-yl)-4′-(trifluoromethyl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 78**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (3-chloro-4-(trifluoromethyl)phenyl)boronic acid (0.168 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−65%, 40 min) to afford the desired product **compound**

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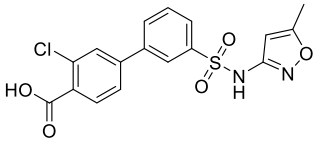
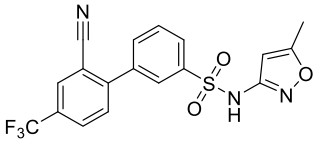
78 as a light-yellow solid (0.063 g, 0.15 mmol, 30%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.51 (s, 1H), 8.19 (t, J = 1.8 Hz, 1H), 8.10 (dt, J = 7.9, 1.4 Hz, 1H), 8.06 (d, J = 1.7 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.94 (dt, J = 7.9, 1.3 Hz, 1H), 7.87 (dd, J = 8.1, 1.7 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 6.21 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.53, 157.39, 143.95, 140.37, 138.12, 132.20, 131.62, 130.44, 129.77, 128.72, 128.67, 126.97, 126.14, 125.14, 124.23, 95.50, 12.03. LC−MS (ESI, pos. mode) m/z: 417.0 $[M + 1]^+$, t_R = 4.80 min.

*3-Chloro-3′-(N-(5-methylisoxazol-3-yl)sulfamoyl)-[1,1′-biphenyl]-4-carboxylic Acid (**Compound 79**).*



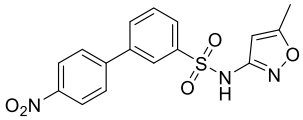
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), 4-borono-2-chlorobenzoic acid (0.150 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−100%, 40 min) to afford the desired product **compound 79** as a white solid (0.123 g, 0.31 mmol, 62%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.49 (s, 1H), 11.49 (s, 1H), 8.16 (t, J = 1.9 Hz, 1H), 8.07 (ddd, J = 7.9, 1.9, 1.1 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.91 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H), 7.77−7.72 (m, 2H), 6.22 (d, J = 1.0 Hz, 1H), 2.30 (d, J = 0.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.55, 166.29, 157.43, 142.25, 140.30, 138.67, 132.65, 131.99, 131.78, 130.76, 130.38, 128.78, 126.61, 125.60, 124.91, 95.51, 12.04. LC−MS (ESI, pos. mode) m/z: 393.1 $[M + 1]^+$, t_R = 3.85 min.

*2′-Cyano-N-(5-methylisoxazol-3-yl)-4′-(trifluoromethyl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 80**).*



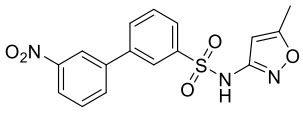
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzonitrile (0.223 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−60%, 40 min) to afford the desired product **compound 80** as a white solid (0.050 g, 0.12 mmol, 24%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.62 (s, 1H), 8.51 (d, J = 1.9 Hz, 1H), 8.24−8.19 (m, 1H), 8.10 (t, J = 1.8 Hz, 1H), 8.03 (ddd, J = 7.9, 1.9, 1.1 Hz, 1H), 7.97 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 6.18 (d, J = 1.0 Hz, 1H), 2.28 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 171.00, 157.77, 146.86, 140.62, 137.99, 135.27, 134.26, 132.37, 131.88, 131.50, 131.48, 131.45, 130.78, 130.76, 130.74, 130.03, 129.81, 129.44, 129.37, 128.00, 127.35, 124.53, 122.72, 117.33, 112.22, 95.87, 12.52. LC−MS (ESI, pos. mode) m/z: 408.1 $[M + 1]^+$, t_R = 4.45 min.

*N-(5-Methylisoxazol-3-yl)-4′-nitro-[1,1′-biphenyl]-3-sulfonamide (**Compound 81**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(4-nitrophenyl)-1,3,2-dioxaborolane (0.187 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−55%, 40 min) to afford the desired product **compound 81** as a yellow solid (0.065 g, 0.18 mmol, 36%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.54 (s, 1H), 8.39−8.34 (m, 2H), 8.20 (t, J = 1.9 Hz, 1H), 8.10 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 8.00−7.96 (m, 2H), 7.94 (ddd, J = 7.9, 1.9, 1.0 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 6.20 (d, J = 1.0 Hz, 1H), 2.29 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.55, 157.38, 147.30, 144.56, 140.41, 138.91, 132.17, 130.51, 128.21, 126.91, 125.14, 124.33, 95.48, 12.03. LC−MS (ESI, pos. mode) m/z: 360.1 $[M + 1]^+$, t_R = 4.27 min.

*N-(5-Methylisoxazol-3-yl)-3′-nitro-[1,1′-biphenyl]-3-sulfonamide (**Compound 82**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (3-nitrophenyl)boronic acid (0.125 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the

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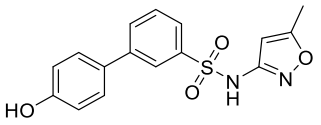
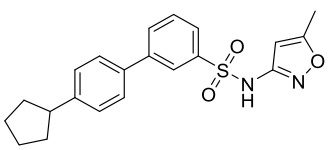
mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−60%, 40 min) to afford the desired product **compound 82** as a beige solid (0.055 g, 0.15 mmol, 30%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.52 (s, 1H), 8.46 (t, J = 2.1 Hz, 1H), 8.30 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 8.20 (t, J = 1.9 Hz, 1H), 8.18 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 8.12 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 7.93 (ddd, J = 7.9, 1.9, 1.0 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 6.22 (d, J = 1.0 Hz, 1H), 2.30 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.56, 157.42, 148.50, 140.36, 139.81, 138.91, 133.46, 132.02, 130.81, 130.47, 126.54, 124.92, 123.10, 121.45, 95.51, 12.03. LC−MS (ESI, pos. mode) m/z: 360.1 $[M + 1]^+$, t_R = 4.29 min.

*4′-Hydroxy-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 83**).*



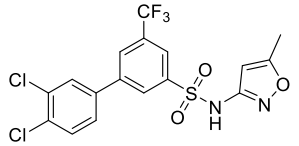
To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (4-hydroxyphenyl)-boronic acid (0.103 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL). The aqueous layer was acidified with 1 M HCl and further extracted with EtOAc (5 mL). The combined organic layers were washed with 1 M HCl (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−55%, 40 min) to afford the desired product **compound 83** as a white solid (0.099 g, 0.30 mmol, 60%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.43 (s, 1H), 9.72 (s, 1H), 8.01 (t, J = 1.9 Hz, 1H), 7.88 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.74 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.54−7.45 (m, 2H), 6.94−6.83 (m, 2H), 6.18 (d, J = 1.0 Hz, 1H), 2.29 (d, J = 0.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.45, 157.94, 157.51, 141.21, 140.03, 130.66, 129.96, 128.90, 127.97, 124.32, 123.68, 116.01, 95.45, 12.02. LC−MS (ESI, pos. mode) m/z: 331.1 $[M + 1]^+$, t_R = 3.81 min.

*4′-Cyclopentyl-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 84**).*



To a pressure vial charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19a**; 0.159 g, 0.50 mmol, 1.00 equiv), (4-cyclopentylphenyl)-boronic acid (0.143 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The vial was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with 1 M HCl (5 mL) and sat. Na_2CO_3 (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−75%, 40 min) to afford the desired product **compound 84** as a white solid (0.116 g, 0.30 mmol, 61%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.07 (t, J = 1.8 Hz, 1H), 7.95 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.81 (ddd, J = 7.9, 1.9, 1.0 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.61−7.54 (m, 2H), 7.43−7.35 (m, 2H), 6.19 (q, J = 0.9 Hz, 1H), 3.03 (tt, J = 9.8, 7.5 Hz, 1H), 2.29 (d, J = 0.9 Hz, 3H), 2.07−1.99 (m, 2H), 1.84−1.73 (m, 2H), 1.72−1.61 (m, 2H), 1.61−1.51 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.47, 157.48, 146.41, 141.13, 140.12, 135.74, 131.27, 130.10, 127.83, 126.68, 125.12, 124.28, 95.46, 44.94, 34.17, 25.04, 12.02. LC−MS (ESI, pos. mode) m/z: 383.2 $[M + 1]^+$, t_R = 5.14 min.

*3′,4′-Dichloro-N-(5-methylisoxazol-3-yl)-5-(trifluoromethyl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 85**).*



To a round-bottomed flask charged with a magnetic stirring bar were added 3-bromo-*N*-(5-methylisoxazol-3-yl)-5-(trifluoromethyl)benzenesulfonamide (**19b**; 0.47 g, 1.00 mmol, 1.00 equiv), (3,4-dichlorophenyl)boronic acid (0.286 g, 1.50 mmol, 1.50 equiv), K_2CO_3 (0.415 g, 3.00 mmol, 3.00 equiv), 1,4-dioxane (8.0 mL), and H_2O (2.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.058 g, 0.050 mmol, 0.05 equiv) against a positive flow of N_2. The flask was capped, and the mixture was stirred at 90 °C for 2.5 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3× 10 mL), and the combined organic layers were washed with 1 M HCl (10 mL) and sat. Na_2CO_3 (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−75%, 40 min) to afford the desired product **compound 85** as a white solid (0.186 g, 0.41 mmol, 41%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.73−11.61 (m, 1H), 8.43 (dt, J = 2.1, 1.1 Hz, 1H), 8.40 (d, J = 1.7 Hz, 1H), 8.15 (q, J = 1.3 Hz, 1H), 8.14−8.13 (m, 1H), 7.85−7.76 (m, 2H), 6.24 (d, J = 1.0 Hz, 1H), 2.30 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.84, 157.12, 141.33, 140.27, 137.33, 132.09, 132.08, 131.29, 130.92 (q, J = 33.1 Hz), 129.36, 128.66 (d, J = 6.7 Hz), 127.57, 123.09 (q, J = 273.2 Hz), 122.70 (t, J = 3.9 Hz), 95.61, 12.02. LC−MS (ESI, pos. mode) m/z: 451.0 $[M + 1]^+$, t_R = 5.07 min.

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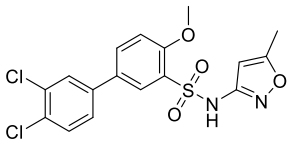
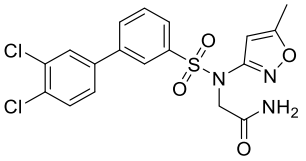
*3′,4′-Dichloro-4-methoxy-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 86**).*



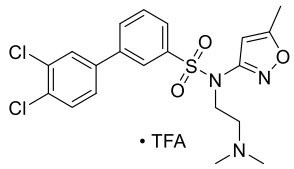
To a round-bottomed flask charged with a magnetic stirring bar were added 5-bromo-2-methoxy-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**19c**; 0.174 g, 0.50 mmol, 1.00 equiv), (3,4-dichlorophenyl)boronic acid (0.143 g, 0.75 mmol, 1.50 equiv), K_2CO_3 (0.207 g, 1.50 mmol, 3.00 equiv), 1,4-dioxane (4.0 mL), and H_2O (1.0 mL). The solution was degassed with N_2 for 10 min. To this solution was then added $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.05 equiv) against a positive flow of N_2. The flask was capped, and the mixture was stirred at 90 °C for 1 h. Upon reaction completion as determined by LC−MS, the reaction was quenched by the addition of 1 M HCl (5 mL). The mixture was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with sat. brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The crude was purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−80%, 40 min) to afford the desired product **compound 86** as a white solid (0.115 g, 0.28 mmol, 56%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.28 (s, 1H), 8.05 (d, J = 2.4 Hz, 1H), 8.00 (dd, J = 8.7, 2.5 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.65 (dd, J = 8.4, 2.2 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 6.11 (d, J = 1.0 Hz, 1H), 3.89 (s, 3H), 2.26 (d, J = 0.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.84, 157.60, 156.64, 138.90, 133.64, 131.83, 131.11, 130.23, 129.45, 128.20, 127.85, 127.39, 126.65, 113.94, 95.41, 56.48, 11.97. LC−MS (ESI, pos. mode) m/z: 413.0 $[M + 1]^+$, t_R = 4.79 min.

*2-((3′,4′-Dichloro-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl])-3-sulfonamido)acetamide (**Compound 87**).*



To a pressure vial charged with a magnetic stirring bar were added 3′,4′-dichloro-*N*-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**compound 70**; 0.038 g, 0.10 mmol, 1.00 equiv), 2-bromoacetamide (0.028 g, 0.20 mmol, 2.00 equiv), K_2CO_3 (0.041 g, 0.30 mmol, 3.00 equiv), and DMF (1.0 mL). The vial was capped, and the mixture was stirred at 80 °C for 2.5 h. Upon reaction completion as determined by LC−MS, the mixture was directly purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−60%, 40 min) to afford the desired product **compound 87** as a white solid (0.033 g, 0.074 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (t, J = 1.9 Hz, 1H), 8.08 (dt, J = 7.9, 1.3 Hz, 1H), 8.03 (d, J = 1.9 Hz, 1H), 7.95 (dt, J = 8.0, 1.3 Hz, 1H), 7.79−7.70 (m, 3H), 7.51 (s, 1H), 7.16 (s, 1H), 6.45 (d, J = 1.0 Hz, 1H), 4.43 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.69, 167.92, 159.12, 138.88, 138.76, 132.34, 131.92, 131.27, 131.15, 130.30, 128.96, 127.28, 126.95, 125.45, 96.69, 49.82, 12.08. LC−MS (ESI, pos. mode) m/z: 440.1 $[M + 1]^+$, t_R = 4.62 min.

*3′,4′-Dichloro-N-(2-(dimethylamino)ethyl)-N-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**Compound 88**).*



To a pressure vial charged with a magnetic stirring bar were added 3′,4′-dichloro-*N*-(5-methylisoxazol-3-yl)-[1,1′-biphenyl]-3-sulfonamide (**compound 70**; 0.077 g, 0.20 mmol, 1.00 equiv), 2-chloro-*N*,*N*-dimethylethan-1-amine hydrochloride (0.058 g, 0.40 mmol, 2.00 equiv), K_2CO_3 (0.166 g, 1.20 mmol, 6.00 equiv), and DMF (2.0 mL). The vial was capped, and the mixture was stirred at 80 °C for 16 h. Upon reaction completion as determined by LC−MS, the mixture was directly purified by reverse-phase preparative HPLC (buffer A/buffer B, 0−50%, 40 min) to afford the desired product **compound 88** as a white solid (0.033 g, 0.12 mmol, 60%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H), 8.15−8.08 (m, 2H), 8.00 (d, J = 2.1 Hz, 1H), 7.90−7.84 (m, 1H), 7.82−7.68 (m, 3H), 6.64 (s, 1H), 4.14 (t, J = 6.5 Hz, 2H), 3.40 (t, J = 6.5 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.64, 158.75, 139.21, 138.58, 137.37, 134.12, 132.97, 131.94, 131.43, 131.18, 130.75, 129.90, 129.06, 127.41, 126.68, 125.07, 99.49, 98.00, 54.04, 43.53, 42.67, 12.19. LC−MS (ESI, pos. mode) m/z: 454.3 $[M + 1]^+$, t_R = 2.29 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.1c01834.

GSH assay for **compound 2**, NMR data for selected ACM compounds, HPLC traces of ACM compounds, and analogues table for SAR study (PDF)

Molecular formula strings (CSV)

■ AUTHOR INFORMATION

Corresponding Authors

Anders Bach − *Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, 2100 Copenhagen, Denmark;* orcid.org/0000-0003-4305-9910; Email: anders.bach@sund.ku.dk

Morten Otto Alexander Sommer − *Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, 2800 Kongens Lyngby, Denmark;* orcid.org/0000-0003-4005-5674; Email: msom@bio.dtu.dk

Authors

Sang-Woo Lee − *Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, 2800 Kongens Lyngby, Denmark*

Kim Tai Tran − *Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, 2800 Kongens Lyngby, Denmark; Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, 2100 Copenhagen, Denmark*

Ruben Vazquez-Uribe − *Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, 2800 Kongens Lyngby, Denmark*

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Charlotte Held Gotfredsen − *Department of Chemistry, Technical University of Denmark, 2800 Kongens Lyngby, Denmark*

Mads Hartvig Clausen − *Center for Nanomedicine and Theranostics, Department of Chemistry, Technical University of Denmark, 2800 Kongens Lyngby, Denmark;* orcid.org/0000-0001-9649-1729

Blanca Lopez Mendez − *Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, 2100 Copenhagen, Denmark*

Guillermo Montoya − *Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, 2100 Copenhagen, Denmark*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jmedchem.1c01834

Author Contributions

[¶]S-W.L. and K.T.T. contributed equally.

Author Contributions

S.-W.L., R.V.-U., and M.O.A.S. conceived the project; S.-W.L., K.T.T., R.V.-U., C.H.G., M.H.C., A.B., and M.O.A.S. designed experiments; S.-W.L., K.T.T., R.V.-U., C.H.G., and B.L.M. performed the experiments; S.-W.L., K.T.T., R.V.-U., C.H.G., A.B., and M.O.A.S. analyzed data; and S.-W.L., K.T.T., R.V.-U., C.H.G., G.M., A.B., and M.O.A.S. wrote the manuscript.

Notes

The authors declare the following competing financial interest(s): G.M. is co-founder of Twelve BIO. The other authors declare no competing interests.

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■ ABBREVIATIONS

CRISPR, clustered regularly interspaced short palindromic repeats; SpyCas9, *Streptococcus pyogenes* Cas9; GFP, green fluorescent protein; ACM, anti-CRISPR molecule; HTS, high-throughput screening; SAR, structure−activity relationship; GSH, glutathione; gRNA, guide RNA; EMSA, electrophoretic mobility shift assay

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