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BRIEF ARTICLE

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4-Aminothiazolyl Analogues of GE2270 A: Antibacterial Lead Finding

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ABSTRACT: 4-Aminothiazolyl analogues of the antibacterial natural product GE2270 A (**1**) were designed, synthesized, and evaluated for Gram positive bacteria growth inhibition. The aminothiazole-based chemical template was evaluated for chemical stability, and its decomposition revealed a novel, structurally simplified, des-thiazole analogue of **1**. Subsequent stabilization of the 4-aminothiazolyl functional motif was achieved and initial structure activity relationships defined.

INTRODUCTION

In 1991, Selva and co-workers from Lepetit Research Institute reported the structure and antibiotic activity of GE2270 A (**1**), a thiopepetide-based natural product isolated from a fermentation broth of *Planobispora rosea*.[1] The in vitro antibiotic profile against methicillin resistant staphylococci (MRSA) and vancomycin resistant enterococci (VRE) was exquisite, with minimum inhibitory concentrations <1 μg/mL. Structurally related thiopeptide natural products are known in the literature and have been reported in preclinical drug discovery campaigns. These thiopeptides include the Thiostreptons (Figure 1), Nocathiacins, Amythiamicins (not shown), and the Thiomuracins.[2]

Thiazolyl actinomycetes metabolites are characterized by their highly modified, sulfur containing macrocyclic peptide structures, which possess a tri- or tetra-substituted nitrogen-containing heterocycle core (circled, Figure 1). Nearly all of the thiopeptides inhibit bacterial growth by inhibiting protein synthesis, however, their cellular targets are distinct. For example, the structurally complex polycycles of the Nocathiacins and Thiostreptons bind to the 23s rRNA component of the bacterial 50S ribosomal subunit at the same site as the L11 ribosomal subunit, while **1** and the Thiomuracin monocycles target the prokaryotic chaperone, elongation factor Tu (EF-Tu).[3]

Recently there has been increased interest in **1**. In 2003, Vicuron, Inc., reported semisynthetic derivatives of **1** intended for parenteral administration.[4] In that report, the previously described acid-mediated decomposition of the oxazoline side chain allowed for SAR investigation of carbon-based side chain analogues.[5] One compound was reportedly selected for advancement to the clinic as a topical treatment for acne.[6] In addition, partial and total syntheses of **1** have been achieved by several academic groups.[7] Structural papers[8] and solution conformation studies[9] of related natural products have also recently been reported.

The discovery of antibiotics which act via a novel mechanism of action remains a pressing unmet medical need in infectious disease care. Clinical resistance to marketed drugs is becoming increasingly common.[10] Toward this end, a high-throughput screen of the Novartis compound library was conducted to identify compounds with potent antibiotic activity.[11] Most notably, **1** and several fermentation metabolites thereof were identified as potent inhibitors of Gram positive bacterial growth. Fortunately, large-scale fermentation and isolation of the thiopeptides was possible in order to further investigate the chemotype as an antibacterial drug-lead.[12] Considering the potent antibiotic activity of the thiopeptide class of molecules, we embarked on our own drug discovery efforts with the aim to discover and develop a novel class of antibiotics for parenteral use.

In view of the chemical instability of the oxazoline-based side chain of **1** and the previously reported carbon-based side chain analogues thereof, we envisioned the use of a nitrogen-linked side chain strategy to prosecute our discovery efforts (**5**, Scheme 1), vis à vis a 4-aminothiazolyl moiety. In 1991, South reported the chemical instability of 2,5-dichloro, 4-aminothiazolyl rings via polymerization.[13] More recently, others have successfully synthesized and manipulated amides, ureas, and carbamates derived from 4-aminothiazoles.[14] In these reports, the 4-aminothiazole was synthesized via Curtius rearrangement of an activated 4-carboxylic acid-thiazole derivative. The intermediate isocyanate was subsequently trapped by a nucleophile, providing the requisite amide, carbamate, or urea. To facilitate a thorough SAR investigation of N-linked thiazolyl side chains of **1**, and to evaluate the chemical stability of this functional motif, we investigated trapping of the 4-thiazolyl isocyanate as well as chemistries derived from the 4-aminothiazole.

RESULTS

In a retrosynthetic sense, 4-aminothiazole **5** was envisioned from the Boc-protected 4-aminothiazole (**6**, Scheme 1). This strategic intermediate would from a Curtius rearrangement of known acid **7**,[1,4] a derivative of **1**. In the forward synthetic direction, **1** (Scheme 2) was first subjected to acid-catalyzed rearrangement and basic hydrolysis,[4] which afforded acid **7** in high yield. The resulting 4-thiazolylcarboxylic acid was next activated with ethylchloroformate to form the ethylacylcarbonate, which was

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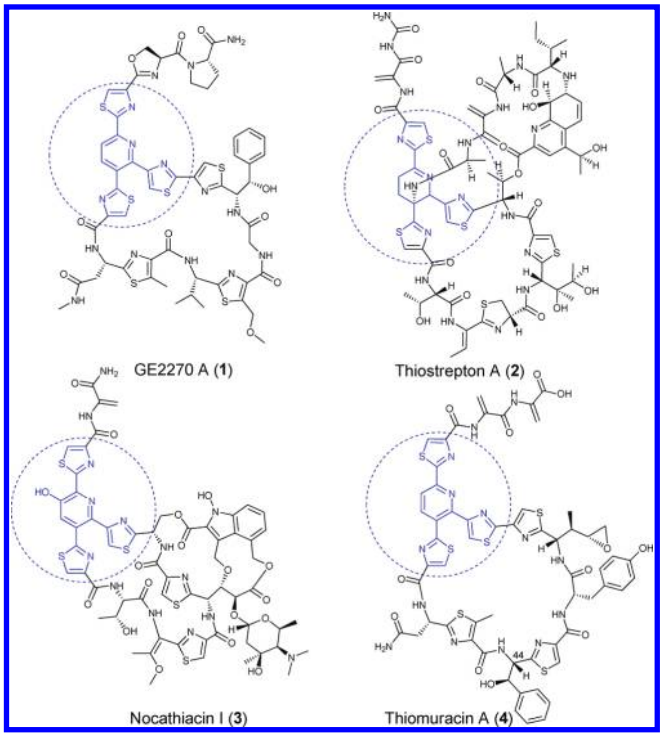
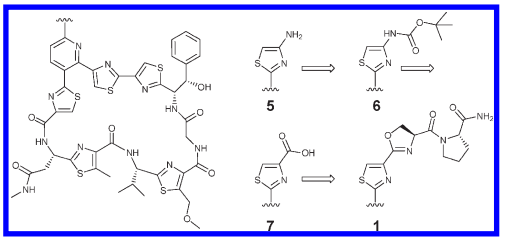


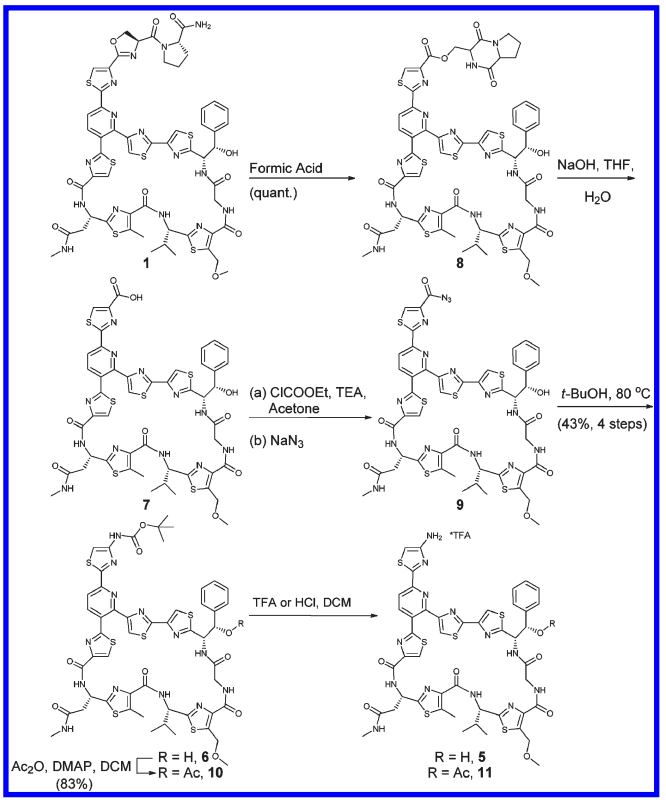
Figure 1. Thiopepetide-based natural products.

Scheme 1. Retrosynthesis of 4-Aminothiazolyl Analogues

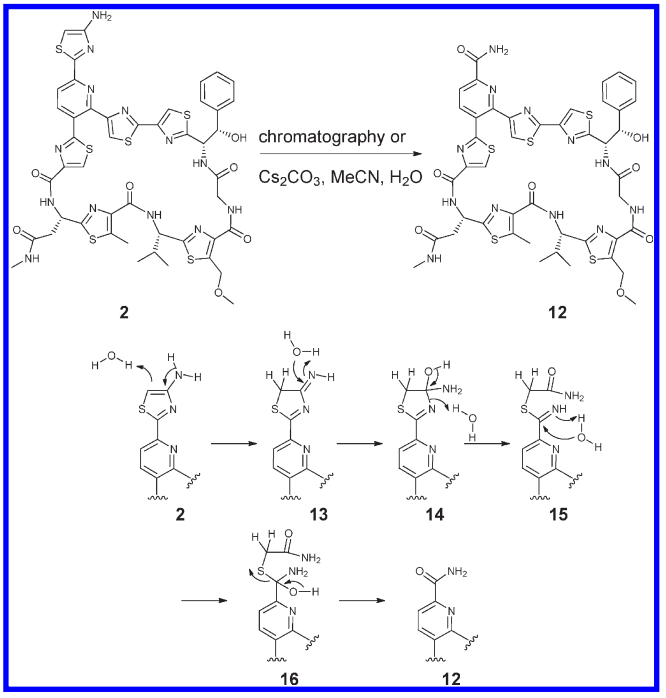


displaced in situ by azide. This three-step, one-pot process furnished acylazide **9** and also set the stage for the Curtius event. Interestingly, direct acylazide formation from the carboxylate utilizing diethylphosphorylazide led to low, irreproducible yields. In the Curtius rearrangement, the acylazide was heated in *tert*-butyl alcohol at 80 °C to furnish the Boc protected 4-aminothiazole **6** (43%, 4 steps). Acetylation of the alcohol (i.e., **10**, **11**) increased the organic solubility and improved the recovery from column chromatography. Subsequent deprotection of either **6** or **10** under acidic conditions (TFA or HCl in DCM) afforded the corresponding 4-aminothiazole salt. Unfortunately, attempts to obtain the freebase of **5** (or **11**) proved challenging. Basic aqueous workup, chromatography, or storage of the 4-aminothiazole freebase (**5**) led to chemical decomposition (Scheme 3). The major decomposition product identified was 2-picolinamide **12**, the product of likely aminothiazole hydrolysis. Mechanistically, we speculate that the 4-aminothiazole ring tautomerizes to afford the thiazol-4(5*H*)imine (**13**). Subsequent hydration of the imine promoted by advantageous water under column chromatography (or via aqueous workup) would provide intermediate **14**. Ring-opening leading to amide formation would then afford intermediate **15**. Further hydration of **15** (e.g., **16**) and

Scheme 2. Synthesis of 4-Aminothiazole 5



Scheme 3. 4-Aminothiazole Decomposition and Proposed Mechanism



elimination of 2-mercapto-acetamide would furnish the 2-picolinamide, **12**. Of note, the synthesis of 2-picolinamide (**12**) could also be purposely accomplished under basic aqueous reaction conditions (Cs_2CO_3, MeCN, H_2O).

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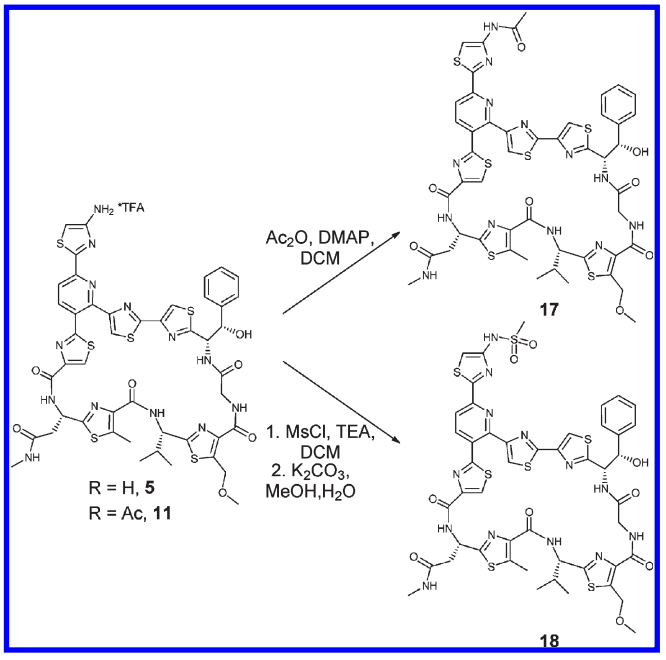
To circumvent the 4-aminothiazole hydrolysis and enable the evaluation of structure activity relationships of amine-based thiazole linkers, chemical stabilization of the 4-aminothiazole was necessary. Boc removal via acidolysis revealed the aminothiazole salt (Scheme 2: **5**, **11**), which was successfully stored without decomposition (room temperature, > 14 days) and used directly in amidation and sulfonylation reactions (Scheme 4), affording amide **17** and sulfonamide **18**. We surmise that salting, acylation, or sulfonylation precludes tautomerization and thus prevents the subsequent hydrolytic decomposition.

1 and novel analogues **6**, **12**, **17**, and **18** were then evaluated in minimum inhibitory concentration (MIC) assays[15] against Gram positive bacteria (Table 1). Four organisms comprised our antibacterial screen and included *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, and *Streptococcus pyogenes*. Boc protected aminothiazole **6** proved significantly less potent (MICs > 32 μg/mL) than the natural product (**1**: MICs < 1 μg/mL). The structurally simplified des-thiazolyl 2-picolinamide **12** also failed to retain activity against all organisms. The amide and sulfonamide analogues (**17**, **18**), however, retained good to moderate potency (1 > 32 μg/mL) in 3 out of 4 target organisms.

Scheme 4. 4-Aminothiazole Stabilization



Thus, a stabilized and structurally simplified chemical platform for further medicinal chemistry optimization had been identified.

DISCUSSION AND CONCLUSIONS

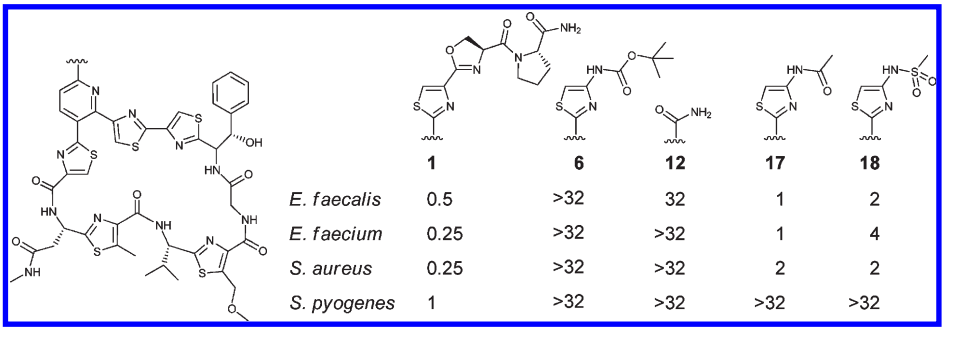
4-Aminothiazolyl analogues of the antibiotic natural product GE2270 A were designed, synthesized, and evaluated for Gram positive bacterial growth inhibition. An unexpected 4-aminothiazolyl decomposition pathway was identified that led to a structurally simplified des-thiazole analogue (**12**). The chemical instability of the 4-aminothiazolyl moiety was then controlled by salting, amidation, and sulfonylation, which resulted in analogues with moderate in vitro potency (**17**, **18**). Because of the improved chemical stability and promising initial antibacterial results, the 4-aminothiazolyl template was selected for further medicinal chemistry lead optimization. Furthermore, the 4-aminothiazolyl-based chemical template described herein represents an original chemotype for antibacterial drug discovery. Indeed, to combat increasing clinical resistance to marketed antibiotics, the discovery of innovative chemical scaffolds that address underexploited antibacterial mechanisms of action remains a pressing need in infectious disease care. Thus, the biological activity exhibited by this unique class of thiopeptides represents a significant and promising lead for antibiotic drug discovery. In addition, these lead identification efforts also serve as a reminder of the importance and relevance of natural product-based, industrial drug discovery. The details of these continued efforts will be the subject of additional correspondence.

EXPERIMENTAL SECTION

NMR: proton NMR spectra were recorded on a Bruker 400 MHz ultrashield spectrometer. Chemical shifts are reported relative to methanol (δ 3.31), dimethyl sulfoxide (δ 2.50), or chloroform (δ 7.26). LCMS: compounds were analyzed on an Inertsil ODS-3 column (C18, 50 mm × 4.6 mm, 3 μm) with a 2 min gradient elution (25% acetonitrile/H_2O/5 mM ammonium formate) and a flow rate of 4 mL/min. HPLC purification utilizes a C8 or C18 column (30 mm × 100 mm, 5 μm, brand: Sunfire or XTerra) and 10 mM NH_4OH in 40−95%ACN in H_2O. LC analysis utilizes an Atlantis brand C18 column (150 mm) with a 20 min gradient elution (0−95% acetonitrile in water +0.1% TFA).

Preparation of Acylazide 9. To a solution of the ester (**5**, 1.5 g, 1.16 mmol) in THF (300 mL) is added 20 mL of H_2O and NaOH (60 mg, 1.50 mmol). The reaction is stirred at 60 °C for 1.5 h and monitored by TLC (10% MeOH/DCM) and LCMS. After completion, the reaction is concentrated to dryness. The off-white solid is suspended

Table 1. Minimum Inhibitory Concentrations[15] (μg/mL) of 1 and Analogues 6, 12, 17, and 18



	1	6	12	17	18
E. faecalis	0.5	>32	32	1	2
E. faecium	0.25	>32	>32	1	4
S. aureus	0.25	>32	>32	2	2
S. pyogenes	1	>32	>32	>32	>32

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in toluene (100 mL) and concentrated to dryness (repeat 3×), which affords the acid, an off-white solid. The crude solid is stored in vacuo (0.1 Torr) for 12 h. LCMS: R_t = 1.12 min, $[M + H]^+$ 1125.

The carboxylic acid **7** was suspended in 300 mL of acetone. The flask was sonicated and the solid scraped down the sides of the flask for 15 min. To this suspension was added TEA (2.0 mL, 14.2 mmol) and ethylchloroformate (2.0 mL, 20.91 mmol). The precipitate slowly dissolved. Further sonication and vigorous stirring was used to break up all particles. After 1 h, the reaction appeared complete via LCMS and NaN_3 (500 mg, 7.69 mmol) was added. The suspension (white/yellow in appearance) was stirred for 1 h at 60 °C and monitored by LCMS. Two additional aliquots of NaN_3 (500 mg, 7.69 mmol) were added and the reaction stirred for 20 min. The reaction was concentrated onto SiO_2 and purified by flash chromatography (1.5 in. × 1.5 in. SiO_2 column, 3 L of EtOAc). This afforded 920 mg of crude acyl-azide (**6**), a white solid. The crude material was taken on to the next step with no further purification. LCMS: R_t = 1.55 min, $[M + H]^+$ 1150.

Preparation of Boc-amine 6. A suspension of acyl-azide (**9**, 920 mg) was heated (80 °C) in *t*-BuOH (100 g). After 2 h complete dissolution occurred and after 12 h the reaction appeared complete by LCMS. The solution was concentrated directly onto SiO_2 and chromatographed (gradient elution: 50−70% EtOAc/hexanes) which afforded 600 mg (43%, 4 steps) of Boc-amine (**6**), a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (br s, 1 H), 9.00 (d, 1 H), 8.70 (app d, 2 H), 8.58 (s, 1 H), 8.44−8.41 (m, 1 H), 8.38 (d, 1 H), 8.23 (s, 1 H), 8.11 (d, 1 H), 7.48 (br s, 1 H), 7.38−7.23 (m, 7 H), 6.02 (br s, 1 H), 5.31−5.18 (m, 3 H), 5.01−5.00 (m, 1 H), 4.97 (s, 2 H), 4.30−4.24 (dd, 1 H), 3.79 (dd, 1 H), 3.38 (s, 3 H), 2.75−2.68 (m, 1 H), 2.47 (d, 3 H), 2.22−2.13 (m, 1 H), 1.49 (s, 9 H), 1.37−1.31 (m, 1 H), 0.87 (d, 3 H), 0.84 (d, 3 H). LCMS: R_t = 1.72 min, $[M + H]^+$ 1196. LC: R_t = 17.96 min. HRMS: 1196.2437, calcd 1196.2492.

Step 5, Preparation of Boc-amine-acetate 10. To a solution of the Boc-amine (**6**, 540 mg, 0.451 mmol) in DCM (250 mL) was added acetic anhydride (0.100 mL, 0.979 mmol), pyridine (1.0 mL, 12.4 mmol), and DMAP (20 mg, 0.169 mmol). The reaction stirred for 3 h, was concentrated directly onto SiO_2, and chromatographed (gradient elution: 50−70% EtOAc/hexanes), which provided 465 mg (83%) of Boc-amine-acetate (**10**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (br s, 1 H), 9.20 (br d, 1 H), 8.79 (br d, 1 H), 8.61 (br d, 1 H), 8.56 (s, 1 H), 8.44−8.41 (m, 1 H), 8.38 (d, 1 H), 8.24 (s, 1 H), 8.11 (d, 1 H), 7.48 (br s, 1 H), 7.42 (s, 2 H), 7.35−7.29 (m, 6 H), 6.14 (s, 1 H), 5.47 (t, 1 H), 5.31−5.26 (m, 1 H), 5.19 (dd, 1 H), 4.97 (s, 3 H), 4.26 (dd, 1 H), 3.72 (dd, 1 H), 3.38 (s, 3 H), 2.70−2.65 (m, 1 H), 2.59 (s, 3 H), 2.45 (d, 3 H), 2.22−2.14 (m, 1 H), 1.96 (s, 3 H), 1.57−1.50 (m, 1 H), 1.49 (s, 9 H), 0.88 (d, 3 H), 0.84 (d, 3 H). LCMS: R_t = 1.81 min, $[M + H]^+$ 1238. LC: R_t = 18.89 min. HRMS: 1238.2559, calcd 1238.2597.

Preparation of 2-Picolinamide 12. To a solution of Boc-amine (**6**, 911 mg, 0.761 mmol) in DCM (100 mL) was added excess TFA (0.5 mL). The reaction was stirred for 2 h then concentrated from DCM three times and stored under reduced pressure (0.1 Torr) for 30 min. The residue was suspended in acetonitrile and H_2O (80 mL, 10:1), and excess Cs_2CO_3 were added. The reaction was stirred at RT for 72 h and then concentrated onto silica gel for purification. The compound was first purified by flash chromatography (0−10% MeOH in DCM), followed by a second flash chromatography (0−5% MeOH in DCM) and finally purified by HPLC (20−70% acetonitrile in H_2O with 0.1% TFA), which afforded 33 mg of final compound. ^{1}H NMR (DMSO-d_6): δ 9.00 (d, 1H), 8.80 (s, 1H), 8.73 (d, 1H), 8.68 (d, 1H), 8.62 (s, 1H), 8.41−8.46 (m, 2H), 8.35 (d, 1H), 8.13 (d, 1H), 7.86 (bs, 1H), 7.21−7.34 (m, 7H), 5.99 (bs, 1H), 5.27−5.32 (m, 1H), 5.18−5.21 (m, 2H), 4.97−5.00 (m, 3H), 4.23−4.29 (m, 1H), 3.75−3.81 (m, 1H), 3.38 (s, 3H), 2.68−2.73 (m, 1H), 2.57 (s, 3H), 2.44 (d, 3H), 2.12−2.17 (m, 1H), 1.22−1.28 (m, 1H), 0.83−0.89 (m, 6H). LC/MS: R_t 1.14 min, $[M + H]^+$1041. LC: R_t = 13.50 min. HRMS: 1041.2062, calcd 1041.2087.

Preparation of Amide 17. To a solution of the Boc-amine (**6**, 10 mg, 0.0083 mmol) in DCM (10 mL) was added TFA (1 mL, 13.46 mmol). The reaction was stirred for 30 min and concentrated. The resultant yellow foam was dissolved in DCM (10 mL) and concentrated (repeat 3×). The crude amine salt was taken on with no further purification. LCMS: R_t = 1.33 min, $[M + H]^+$ 1096.0.

To a solution of the amine (0.0083 mmol) in pyridine (1 mL) is added acetic anhydride (0.100 mL, 0.979 mmol). The solution is stirred at RT for 10 min and poured into a saturated aq solution of sodium bicarbonate (100 mL). The mixture is extracted with EtOAc (3×) and the combined organic extracts are dried over $MgSO_4$, filtered, and concentrated directly onto SiO_2. The crude product is purified by flash chromatography (gradient elution: 0−5% MeOH/DCM) to afford 6 mg of amide (**17**) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6 δ 11.14 (br s, 1 H), 9.00 (br d, 1 H), 8.68−8.66 (m, 2 H), 8.59 (s, 1 H), 8.45−8.42 (m, 1 H), 8.40 (d, 1 H), 8.24 (s, 1 H), 8.13 (d, 1 H), 7.80 (s, 1 H), 7.38−7.21 (m, 7 H), 6.01 (br d, 1 H), 5.32−5.17 (m, 3 H), 5.01−4.99 (m, 1 H), 4.97 (s, 2 H), 4.27 (dd, 1 H), 3.79 (dd, 1 H), 3.38 (s, 3 H), 2.73−2.68 (m, 1 H), 2.46 (d, 3 H), 2.19−2.14 (m, 1 H), 2.10 (s, 3 H), 1.35−1.28 (m, 1 H), 0.87 (d, 3 H), 0.84 (d, 3 H). LCMS: R_t = 1.35 min, $[M + H]^+$1138.0. HRMS $[M + H]^+$ 1138.2046, calcd 1138.2073.

Preparation of Sulfonamide 18. To a solution of Boc-amine-acetate (**10**, 100 mg, 0.081 mmol) in DCM (25 mL) was added TFA (5 mL, 67.3 mmol). The reaction was stirred for 30 min and concentrated. The resultant yellow foam was dissolved in DCM (10 mL) and concentrated (repeat 3×). The crude amine is taken on with no further purification. LCMS: R_t = 1.45 min, $[M + H]^+$1138.0.

To a solution of the amine (0.081 mmol) in pyridine (5 mL) was added methanesulfonylchloride (0.050 mL, 0.646 mmol). The solution was stirred for 30 min and poured into a saturated aq solution of sodium bicarbonate (100 mL). The mixture was extracted with EtOAc (3×) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated directly onto SiO_2. The crude acetate was taken on to the next step without any further purification. LCMS: R_t = 1.42 min, $[M + H]^+$1216.1.

To a solution of the acetate-sulfonamide in MeOH (10 mL) was added K_2CO_3 (50 mg, 0.362 mmol). The reaction was stirred 5 min, concentrated, and purified by HPLC to afford 15 mg of sulfonamide **18**. ^{1}H NMR (400 MHz, DMSO-d_6 δ 10.62 (br s, 1 H), 9.00 (br d, 1 H), 8.68−8.66 (m, 2 H), 8.58 (s, 1 H), 8.44−8.41 (m, 1 H), 8.37 (d, 1 H), 8.23 (s, 1 H), 8.15 (d, 1 H), 7.39−7.20 (m, 7 H), 7.07 (br s, 1 H), 6.02 (d, 1 H), 5.31−5.18 (m, 3 H), 5.01−4.98 (m, 1 H), 4.97 (s, 2 H), 4.27 (dd, 1 H), 3.77 (dd, 1 H), 3.38 (s, 3 H), 3.12 (s, 3 H), 2.73−2.67 (m, 1 H), 2.58 (s, 3 H), 2.47 (d, 3 H), 2.19−2.13 (m, 1 H), 1.36−1.28 (m, 1 H), 0.87 (d, 3 H), 0.84 (d, 3 H). LCMS: R_t = 1.31 min, $[M + H]^+$1174.0. HRMS $[M + H_2O]$ 1192.1843, calcd 1192.1849.

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