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Rapid, Structure-Based Exploration of Pipecolic Acid Amides as Novel Selective Antagonists of the FK506-Binding Protein 51

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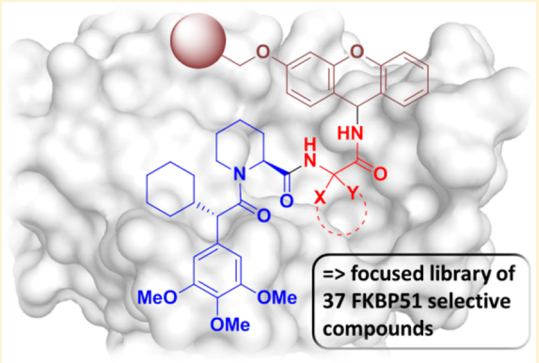
Supporting Information

ABSTRACT: The FK506-binding protein 51 (FKBP51) is a key regulator of stress hormone receptors and an established risk factor for stress-related disorders. Drug development for FKBP51 has been impaired by the structurally similar but functionally opposing homologue FKBP52. High selectivity between FKBP51 and FKBP52 can be achieved by ligands that stabilize a recently discovered FKBP51-favoring conformation. However, drug-like parameters for these ligands remained unfavorable. In the present study, we replaced the potentially labile pipecolic ester group of previous FKBP51 ligands by various low molecular weight amides. This resulted in the first series of pipecolic acid amides, which had much lower molecular weights without affecting FKBP51 selectivity. We discovered a geminally substituted cyclopentyl amide as a preferred FKBP51-binding motif and elucidated its binding mode to provide a new lead structure for future drug optimization.



INTRODUCTION

The FK506-binding protein 51 (FKBP51) plays an important role in the pathogenesis of depression and other stress-related diseases. It inhibits signaling of the glucocorticoid receptor, a key receptor for the stress hormone cortisol, and its upregulation in the brain causes depression-like behaviors.[1−3] In animal models of anxiety and depression, depletion of FKBP51 led to improved stress hormone signaling and stress-coping behavior.[4−6] Recently, FKBP51 deficiency was also shown to ameliorate chronic pain states.[37] Moreover, in humans FKBP51 has repeatedly been associated genetically with psychiatric endophenotypes and diseases.[7,8] Taken together, FKBP51 has emerged as a compelling target for stress-related disorders.[9,10]

Ligands for FKBPs have been traditionally derived from the natural product FK506 (Figure 1a) through structure-based design.[11−15] For FKBP51 drug discovery, the key challenge is to achieve selectivity over its closest homologue FKBP52, which is the functional counter-player of FKBP51 and has opposing effects on the endocrine system and on behavior.[1−3] The active site residues of FKBP51 and FKBP52 are strictly conserved,[16−22] and almost all ligands tested so far did not discriminate between these two proteins.[23−27]

Recently, we discovered the first FKBP51-selective ligands based on a novel, FKBP51-specific binding mode.[28] The resulting tool compounds, SAFit1 (**1**) and SAFit2 (**2**) (Figure 1b), for the first time allowed to pharmacologically probe the role of FKBP51. This enabled the proof-of-concept that inhibition of FKBP51 is neuritotrophic, enhances stress hormone regulation, has anxiolytic and antidepressant-like effects, and suppresses NF-κB signaling, a key pathway in melanoma cancers.[28−31]

Despite these encouraging findings, it is currently unclear if drug-like FKBP51-selective inhibitors can be developed. SAFit1 and 2 deviate substantially from the physicochemical properties required for CNS-directed drugs.[32] Clearly, the molecular weight (748 and 803 g/mol, compared to 426 g/mol for 90% of CNS drugs), lipophilicity (clogD = 3.5 and 7.1, vs <3.8 for CNS drugs), polar surface area (139 and 114 Å^2, vs <86 for CNS drugs), and hydrogen bond acceptors (HA = 14 and 12) are much too high, while the ligand efficiency is too low (LE = 0.21 and 0.19). Furthermore, there are biological stability issues that require attention. Therefore, we set out to identify improved lead structures that are better suited for further FKBP51 drug development.

RESULTS AND DISCUSSION

Cocrystal Structure of 3. Replacing a labile ester linkage with a metabolically more stable amide group is a common strategy to enhance bioavailability. When we replaced the pipecolic ester moiety of SAFit1 by the analogous amide we were delighted to see that the SAFit1 amide analogue **3** retained high-affinity binding toward FKBP51 (K_i = 39 nM, Figure 2a). No binding toward FKBP52 could be observed, in agreement with a SAFit-like FKBP51-selective binding mode.

We solved the cocrystal structure of **3** in complex with the FK1 domain of FKBP51 to confirm this assumption (Figure

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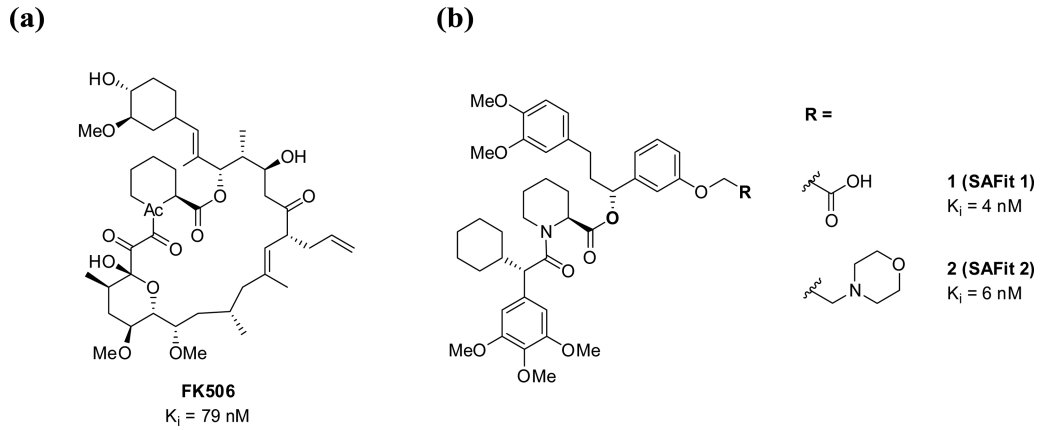

Figure 1. Chemical structures of (a) FK506 and (b) the FKBP51-selective ligands SAFit1 (**1**) and SAFit2 (**2**), and their binding affinities toward FKBP51.

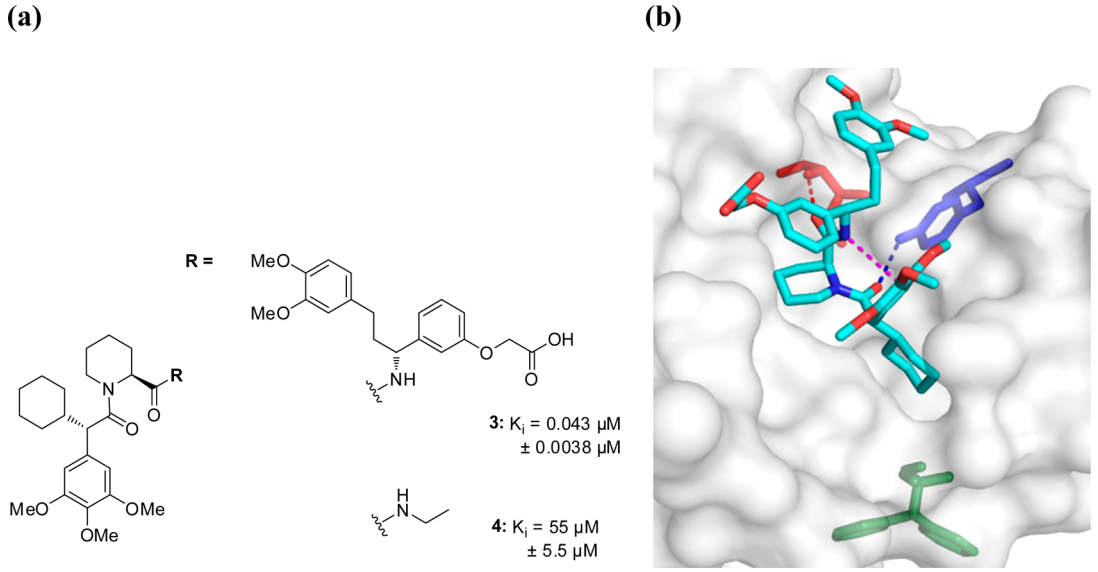

Figure 2. (a) Chemical structures of the SAFit1 amide analogue **3** and ethyl amide analogue **4** and their binding affinities toward FKBP51. (b) X-ray structure of **3** (cyan) in complex with the FK506-binding domain of FKBP51 (pdb: 5DIU). The hydrogen bonds to Tyr113 (blue), Ile 87 (red), and the intramolecular NH−C_{ar} interaction (magenta) are indicated as dotted lines. Phe67 (green) has been displaced by the cyclohexyl moiety upon binding of **3** and adopts two rotamers.

2b). The binding mode of **3** is virtually identical to the previously determined iFit1 and iFit4−FKBP51 complexes, including the key conformational rearrangement of Phe67 that is responsible for the strict selectivity over FKBP52.[28] The important hydrogen bonds to Tyr113 (red) and Ile 87 (blue) are preserved. Moreover, the conformation of the cyclohexyl ring conformation is similar to the cylcohexenyl moiety of iFit4. It is buried in the subpocket that is generated by the displacement of Phe67. The pipecolate amide of **3** points to the face of the trimethoxy phenyl ring but does not change its conformation.

Encouraged by this finding we started a systematic exploration of pipecolic acid amide substituents, starting with the small ethyl amide analogue **4**. As expected, the replacement of the large amide substituent of **3** by the simple ethyl group in **4** caused a substantial loss of binding affinity, resulting in a K_i value of 37 μM. Nevertheless, **4** represented a suitable starting point for further derivatization.

Efficient Synthetic Strategy for Pipecolic Acid Amide Screening. During the investigation on selective FKBP51 ligands, the carboxylic acid **5** proved to be the best building block, regarding binding affinity and selectivity.[28] We therefore developed an efficient, solid phase-assisted method (Figure 3) to couple **5** with a variety of pipecolic acid dipeptides. The synthesis started with the coupling of an Fmoc protected amino acid to the Sieber amide resin.[33] Then Fmoc-pipecolic acid and subsequently the carboxylic acid **5** were coupled to the free amines after Fmoc deprotection, respectively. Cleavage from the resin provided a variety of pipecolic acid amides in 20−90% overall yield and excellent purities (>90% for crude products). This approach allowed rapid incorporation and testing of a large variety of commercially available amino acid building blocks. Altogether, an FKBP51-focused library of 37 compounds was synthesized by this method (Tables 1−5). None of the ligands from this novel pipecolic acid amide series showed any binding to FKBP52.

Structure−Affinity Relationship (SAR) of the Amide Substituent. To perform a systematic investigation on the different amide substituents, we started our screening with simple unbranched side chains (Table 1). Entry **6**, which

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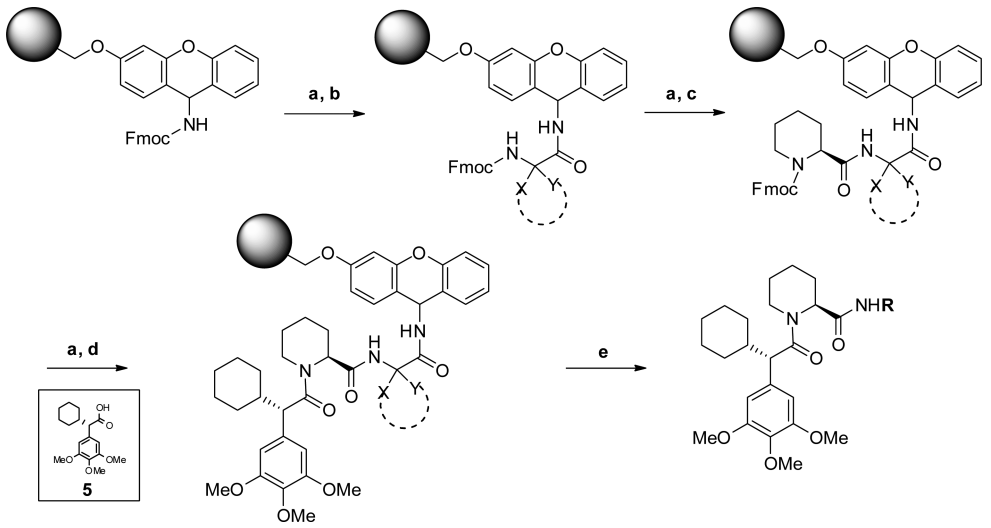
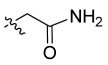
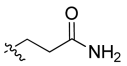
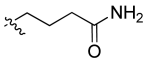
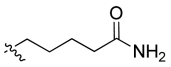


Figure 3. Solid phase synthesis for the pipecolic acid amide series. Reagents and conditions: (a) 20% 4-methylpiperidine/DCM; (b) 4.8 equiv of HBTU, 4.8 equiv of HOBt, 10 equiv of DIEA, 5 equiv of Fmoc-amino acid (X,Y = different substituents); (c) 3.8 equiv of HBTU, 3.8 equiv of HOBt, 8 equiv of DIEA, Fmoc-pipecolic acid; (d) 2 equiv of HATU, 4 equiv of DIEA, 2 equiv of **5**; (e) 1% TFA/1% TIS/98% DCM.

Table 1. Binding Affinities of Amide Analogues with Unbranched Amide Substituents to the FK1 Domain of FKBP51 and to FKBP12[a]

Entry	R	K_i [μM] FKBP51	K_i [μM] FKBP12
6		36.7 ± 3.4	>300
7		7.9 ± 0.7	49.2 ± 0.06
8		5.7 ± 0.2	22.3 ± 0.02
9		3.9 ± 0.2	4.2 ± 0.01

[a] K_i values were determined by competitive fluorescence polarization assay.[36]

derives from the simplest amino acid glycine, bound to FKBP51 in the same affinity range as the ethyl amide analogue **5** (35 and 37 μM, respectively). A significant affinity increase to 5.6 μM (**7**) was observed when an additional methylene group was added to the chain. Further prolongation of the chain, however, only resulted in a slight increase of the binding affinity (compounds **8** and **9**).

In the next series we assessed, whether branching with additional aliphatic groups would improve the binding affinity (Table 2). The addition of a methyl group (**10a,b**) increased the binding affinity irrespective of the configuration, compared to the linear analog **6**. Further enlargement of the branched side chains resulted only in a slight increase of the binding affinity (**11a,b**, **14a,b**, **15**, and **16a,b**). Interestingly, compounds with branched side chains with (*R*)-configuration showed higher binding affinities than their corresponding diastereomers with (*S*)-configuration (**14b** > **14a**, **16b** > **16a**). A clear improvement of the K_i value was observed when a geminally disubstituted amide was introduced (**12**, **13**).

We hypothesized that additional hydrophobic interactions might be beneficial for the binding to FKBP51 and therefore analyzed the effects of phenyl- and cyclohexyl rings branching off the linear precursor (Table 3). In general, compounds containing an aromatic ring showed better binding affinities than their aliphatic analog (e.g., **19a** vs **20**). Also shorter linkers tended to result in better affinities toward the protein. As observed in the previous series, ligands with the side chain in (*R*)-configuration were better than their corresponding diastereomers in (*S*)-configuration (**18b** > **18a** and **19b** > **19a**).

FKBP51 has two hydrogen bond acceptors, the carbonyls of Gly84 and of Gln85, that are close to the pipecolate ester substituents of FKBP51-bound ligands. The high-affinity ligands FK506 and rapamycin gain part of their binding energy by donating direct or water-mediated hydrogen bonds to these residues.[17,19] We thus analyzed the effect of substituents containing polar groups in the side chain. As shown in Table 4, this did not result in any affinity enhancement over the aliphatic counterparts. As for the branched aliphatic derivatives, we observed a preference for substituents with the (*R*)-configuration (**24b** > **24a**, **25b** > **25a**).

Intrigued by the promising ligand efficiency of the geminally disubstituted analogue **12**, we extended our studies to amide substituents containing geminally substituted carbocycles of different ring sizes (Table 5). While constraining the two geminal substituents by a cyclopropyl ring in **27** reduced affinity, the cyclobutyl (**28**) and six-membered ring analogues (**30**, **31**) had affinities comparable to **12**. A surprising discovery was the high affinity of the cyclopentyl compound **29**, which showed exceptionally strong inhibition (K_i = 0.1 μM). The beneficial effect of the cyclopentyl ring was confirmed by the close analogue **32** that also showed a significant higher binding affinity, compared to the other carbocycles.

Cocrystal Structure of 29. To better understand the basis for the surprisingly high affinity of **29** we solved the cocrystal structure of **29** in complex with the FK1 domain of FKBP51 (Figure 4). The cocrystal structure revealed that the pipecolic acid core and the 2-trimethoxyphenyl-2-cylcohexyl acetic acid moiety (derived from **5**) adopt the same conformation and engage in the same interactions as observed for **3** (Figure 2b). The pipecolic acid core sits tightly in the binding pocket in a

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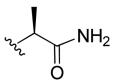
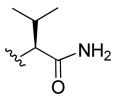
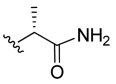
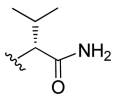
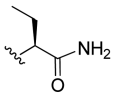
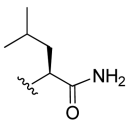
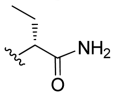
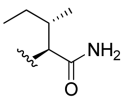
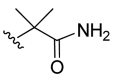
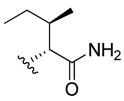
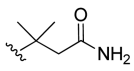
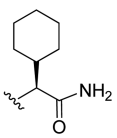
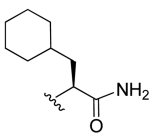
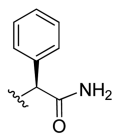
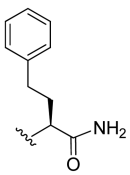
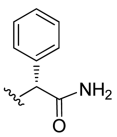
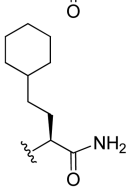
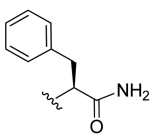
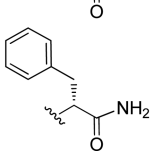
Table 2. Binding Affinities of Amide Analogues with Branched Aliphatic Side Chain to the FK1 Domain of FKBP51 and to FKBP12[a]

Entry	R	K_i [μM] FKBP51	K_i [μM] FKBP12	Entry	R	K_i [μM] FKBP51	K_i [μM] FKBP12
10a		17.1 ± 1.9	30.7 ± 0.1	14a		12.6 ± 0.9	11.5 ± 0.03
10b		10.0 ± 0.5	71.1 ± 0.3	14b		5.0 ± 0.3	39.7 ± 0.2
11a		3.6 ± 0.7	51.9 ± 0.05	15		8.7 ± 1.0	6.6 ± 0.1
11b		4.5 ± 0.3	6.0 ± 0.008	16a		7.1 ± 0.9	12.1 ± 0.02
12		2.2 ± 0.2	25.1 ± 0.2	16b		3.2 ± 0.3	8.7 ± 0.006
13		3.8 ± 0.3	3.2 ± 0.01				

[a] K_i values were determined by competitive fluorescence polarization assay.[36]

Table 3. Binding Affinities of Amide Analogues with Branched Side Chains Containing Aromatic and Nonaromatic Six-Membered Rings to the FK1 Domain of FKBP51 and to FKBP12[a]

Entry	R	K_i [μM] FKBP51	K_i [μM] FKBP12	Entry	R	K_i [μM] FKBP51	K_i [μM] FKBP12
17		4.3 ± 0.03	12.8 ± 0.03	20		17.8 ± 3.0	6.6 ± 0.03
18a		3.1 ± 0.5	7.5 ± 0.03	21		9.1 ± 0.5	30.1 ± 1.9
18b		1.5 ± 0.1	12.4 ± 0.08	22		12.0 ± 0.8	22.5 ± 0.6
19a		6.5 ± 0.6	10.9 ± 0.03				
19b		1.4 ± 0.09	5.6 ± 0.02				

[a] K_i values were determined by competitive fluorescence polarization assay.[36]

chair conformation, positioning both carbonyl groups optimally for forming hydrogen bonds with Ile87 (blue) and Tyr113 (red), respectively. Similar to ligand **3**, the cyclohexyl ring of **29** is deeply buried in a hydrophobic pocket formed by Gly59, Lys60, Leu61, Lys66, Asp68, and Ile122. This subpocket formed by the displacement of Phe67 is the key difference in the binding mode of the FKBP51-selective class of iFit ligands and of classical FK506-derived ligands, where Phe67 is always

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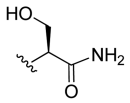
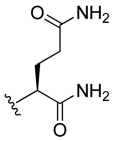
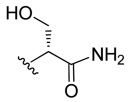
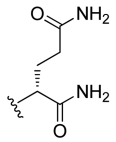
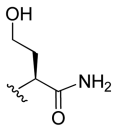
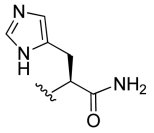
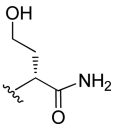
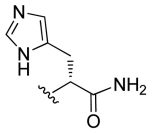
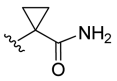
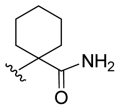
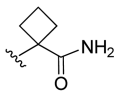
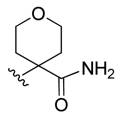
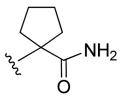
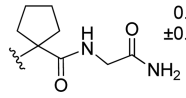
Table 4. Binding Affinities of Amide Analogues with Side Chains Containing Heteroatoms to the FK1 Domain of FKBP51 and to FKBP12[a]

Entry	R	K_i [μM] FKBP51	K_i [μM] FKBP12	Entry	R	K_i [μM] FKBP51	K_i [μM] FKBP12
23a		62.9 ± 7.2		25a		345 ± 54.4	
23b		2.8 ± 0.2	46.9 ± 0.1	25b		3.4 ± 0.7	120 ± 0.008
24a		13.0 ± 1.0	317 ± 1.2	26a		13.4 ± 0.9	101 ± 1.6
24b		4.2 ± 0.9	1.2 ± 0.02	26b		3.8 ± 0.2	26.9 ± 0.8

[a]K_i values were determined by competitive fluorescence polarization assay.[36]

Table 5. Binding Affinities of Amide Analogues Containing Geminally Substituted Carbocycles or Tetrahydropyran to the FK1 Domain of FKBP51 and to FKBP12[a]

Entry	R	K_i [μM] FKBP51	K_i [μM] FKBP12	Entry	R	K_i [μM] FKBP51	K_i [μM] FKBP12
27		19.5 ± 1.8	50.3 ± 2.6	30		1.9 ± 0.3	4.3 ± 0.01
28		4.9 ± 0.5	23.4 ± 0.02	31		1.8 ± 0.17	3.0 ± 0.005
29		0.14 ±0.02	3.8 ±0.006	32		0.8 ±0.07	2.0 ±0.0015

[a]K_i values were determined by competitive fluorescence polarization assay.[36]

observed in a conformation pointing inward to the binding pocket. The reduced capacity of FKBP52 to adopt the outward-facing conformation of Phe67 underlies the striking discrimination of the synthesized compounds against FKBP52.[28,34] The trimethoxyphenyl ring points toward the open space. In contrast to **3**, the terminal amide of the pipecolate substituent of **29** donates a hydrogen bond to the hydroxyl group of Tyr113, which in turn donates a hydrogen bond to the carbonyl group of the 2-trimethoxyphenyl-2-cylcohexyl acetic acid moiety. The cyclopentane of **29** neatly fills the space between the piperidine of **29**, the trimethoxyphenyl of **29**, and Phe77, Gln85, and Val86 of FKBP51 (Figure 4b). This tight, sandwich-like, intramolecular packing explains why even small deviations in the carbocycle size dramatically affect the interactions with FKBP51.

Neuritotrophic Properties of 29. We recently discovered that inhibition of FKBP51 induces neurite outgrowth in several neuronal cell types.[28] To test if this finding extends to the pipecolate amide series described here, we treated N2a cells with compound **29** and observed an increase in neurite length (Figure 5). Interestingly, **29** stimulated neurite outgrowth with a bell-shaped dose–response curve, as has observed previously by others and us for using several chemically distinct classes of unselective inhibitors.[10] In light of the opposing effects of FKBP51 and FKBP52 on neurite outgrowth we originally postulated inhibition of the neuritotrophic FKBP52 as a possible cause for the bell-shaped dose–response curve. However, compound **29** also showed this effect, although it did not inhibit FKBP52 up to 500 μM, suggesting a more

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J. Med. Chem. XXXX, XXX, XXX−XXX

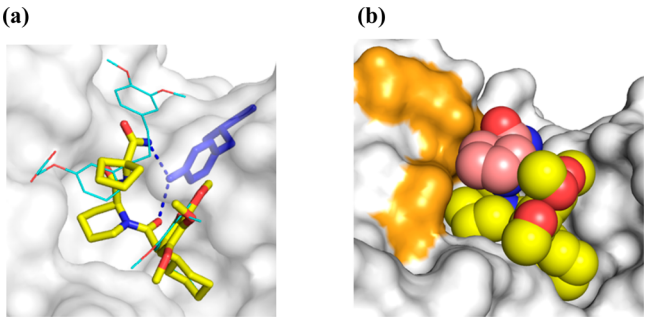

Figure 4. X-ray structure of **29** (yellow) in complex with the FK506-binding domain of FKBP51 (pdb: 5DIV). Lys121 is not shown for clarity. (a) The hydrogen bonds to Tyr113 (blue) are indicated by dotted lines. Compound **3** in complex with FKBP51 is superimposed and shown as cyan lines. (b) Compound **29** in complex with FKBP51 is shown as spheres. The cyclopentane ring and residues Phe77, Gln85, and Val86 have been highlighted in salmon and orange, respectively.

complex mechanism underlying the role of FKBPs in neurite outgrowth.

CONCLUSION

SAFit1 and SAFit2 were just recently reported as the best selective FKBP51 ligands so far, but they are too large for further drug optimization studies. In this study we have shown, that replacing the pipecolic ester moiety by a low molecular weight amide containing a geminally substituted cyclopentyl ring leads to ligands with high binding affinities (K_i = 0.1 μM) and low molecular weight. Importantly, most compounds bound weaker to FKBP12, and none of the compounds bound to FKBP52. Especially with **29** we were able to reduce the molecular weight by 34% (MW = 529.7 g/mol compared to 802 g/mol for SAFit2) and to improve key physicochemical parameters (clogD = 3.1, 9 HA, LE = 0.25). However, **29** is more polar compared to SAFit2 (tPSA = 120 Å^2 vs 114 Å^2) and also has more hydrogen bond donors (three compared to none), suggesting that further optimization is needed for optimal CNS activity. One of the terminal amide hydrogens points toward the solvent and thus should be dispensable. Due to the reduced size as well as the well-understood molecular binding mode, **29** represents a substantially improved starting point for the further development of FKBP51-directed drug candidates.

EXPERIMENTAL SECTION

Chemistry. Chromatographic separations were performed either by manual flash chromatography or automated flash chromatography using an Interchim Puriflash 430 with a UV detector. ^{1}H NMR spectra, ^{13}C NMR spectra, 2D HSQC, HMBC, and COSY of all intermediates were obtained from the Department of Chemistry and Pharmacy, LMU, on a Bruker Avance III HD 400/800 or a Varian NMR-System 300/400/600 at room temperature. Chemical shifts for ^{1}H or ^{13}C are given in ppm (δ) downfield from tetramethylsilane using residual protio solvent as an internal standard.

Mass spectra (m/z) were recorded on a Thermo Finnigan LCQ DECA XP Plus mass spectrometer at the Max Planck Institute of Psychiatry, while the high resolution mass spectrometry was carried out at MPI for Biochemistry (Microchemistry Core Facility) on Bruker Daltonics MicrOTOF.

The purity of the compounds was verified by reversed phase HPLC (see Supporting Information for detailed conditions). All of the final compounds synthesized and tested had a purity of >95%.

General Synthetic Procedure for Solid Phase Coupling Reaction. All steps were performed at RT. Sieber amide resin (108 mg, 80 μmol) was treated with 20% 4-methylpiperidine in DMF (2.0 mL) for 20 min for removing the Fmoc-group. The resin was filtered and washed with DMF (2.0 mL × 4). To the resin was added a solution of the Fmoc-protected amino acid (400 μmol, 5 equiv), HBTU (145 mg, 386 μmol, 4.8 equiv), HOBt (52 mg, 386 μmol, 4.8 equiv), and DIPEA (140 μL, 800 μmol, 10 equiv) in DMF (2.0 mL). The mixture was then mixed on a shaker for 2 h. In the following step the resin was filtered and washed with DMF (2 mL × 4). Fmoc deprotection and washing was performed as before. In the following step (*S*)-*N*-Fmoc-piperidine-2-carboxylic acid (112 mg, 320 μmol, 4 equiv), HBTU (115 mg, 304 μmol, 3.8 equiv), HOBt (41 mg, 304 μmol, 4.8 equiv), and DIPEA (120 μL, 640 μmol, 8 equiv) in DMF (2.0 mL) was added to the resin and mixed for 2 h. Washing and deprotecting was repeated as before, followed by the addition of **5** (48 mg, 136 μmol, 1.7 equiv), HATU (61 mg, 144 μmol, 1.8 equiv), and DIPEA (60 μL, 320 μmol, 4 equiv). The suspension was mixed for 16 h. Then the resin was washed with DMF, MeOH, DCM, and Et_2O (2 mL × 4 each) and dried in vacuo. The compounds were cleaved from the resin using DCM + 1% TFA + 1% TIS (2.0 mL) for 2 min. This was repeated 5 times, and after every step the solution, containing the cleaved product, was neutralized using saturated $NaHCO_3$ solution. The aqueous solution was then extracted three times with DCM. The combined organics were dried over $MgSO_4$ and filtered, and the solvent was removed to obtain the compounds after removing the solvent under reduced pressure. If necessary the compounds were purified by flash chromatography. (Note: The synthesis of **14a** + **b**, **19a** + **b**, and **20** were conducted starting with 160 μmol resin. The coupling step with **5** was performed with **5** (3 equiv), HATU (2.8 equiv), and DIPEA (6 equiv).) The purity of the compounds was verified by reversed phase HPLC. All of the final compounds synthesized and tested have a purity of more than 95%.

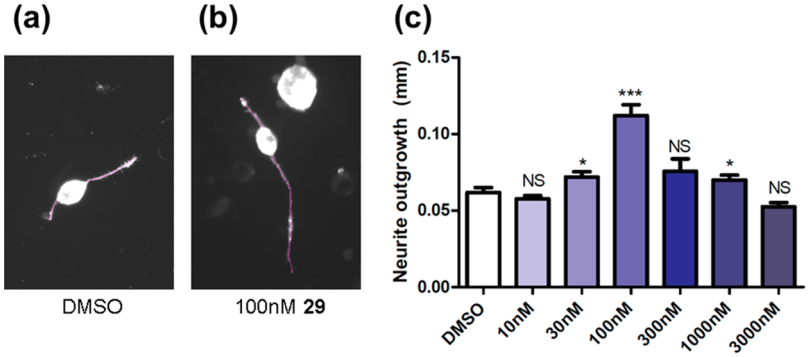

Figure 5. Neuritotrophic properties of **29**. N2a cells were transfected with myr-GFP and induced to differentiate in the absence (a) and presence (b) of 100 nM **29**. (c) Compound **29** stimulates neurite outgrowth of N2a cells with a bell-shaped dose−response curve.

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J. Med. Chem. XXXX, XXX, XXX−XXX

*2-(3-((R)-1-((S)-1-((S)-2-Cyclohexyl-2-(3,4,5-trimethoxyphenyl)-acetyl)piperidine-2-carboxamido)-3-(3,4-dimethoxyphenyl)propyl)-phenoxy)acetic Acid (**3**).* Compound **5** (30 mg, 0.20 mmol), HATU (110 mg, 0.29 mmol), and DIPEA (0.13 mL, 0.78 mmol) were dissolved in DCM (2.0 mL) at RT and stirred for 30 min.[35] Then **3**−**2** (50 mg, 0.20 mmol), dissolved in DCM (300 μL), was added, and the reaction mixture was stirred for 16 h at RT. The crude product was concentrated and purified by flash chromatography (0−20% EtOAc in cyclohexane). Then the carboxylic acid was liberated using 10% TFA in DCM (2.0 mL) at RT for 5 h. The reaction mixture was concentrated and flash purified by preparative HPLC (Gradient: 65−75% B in 20 min) to obtain the title compound (15 mg, 20 μmol, 24%) as a colorless oil.

HPLC [0−100% Solvent B, 20 min]: R_t = 11.7 min. **HRMS**: calculated 747.3857 [$C_{42}H_{55}N_2O_{10}$ + H]$^+$, found 747.3854 [M + H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.13−7.08 (m, 1H), 6.95−6.90 (m, 1H), 6.84 (t, *J* = 8.4 Hz, 1H), 6.75 (dq, *J* = 11.8, 2.0 Hz, 2H), 6.72−6.67 (m, 1H), 6.66−6.60 (m, 1H), 6.59−6.54 (m, 2H), 5.15−5.07 (m, 1H), 4.82−4.69 (m, 1H), 4.69−4.56 (m, 3H), 3.76−3.72 (m, 1H), 3.72−3.69 (m, 6H), 3.65−3.64 (m, 1H), 3.58−3.54 (m, 9H), 2.96−2.84 (m, 2H), 2.82−2.70 (m, 2H), 2.43−2.30 (m, 2H), 2.19−2.05 (m, 2H), 1.99−1.87 (m, 2H), 1.88−1.76 (m, 3H), 1.59 (d, *J* = 8.2 Hz, 2H), 1.34 (d, *J* = 9.6 Hz, 1H), 1.16−1.10 (m, 2H), 0.95−0.86 (m, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 171.99, 170.28, 170.12, 157.65, 152.52, 148.61, 147.00, 145.30, 135.97, 133.59, 130.71, 127.70, 120.01, 112.62, 112.31, 112.26, 111.74, 105.56, 64.33, 63.08, 59.70, 55.96, 55.52, 55.48, 55.34, 52.42, 51.79, 51.45, 42.79, 39.52, 38.52, 38.17, 31.59, 27.34, 27.03, 26.09, 24.87, 20.68, 19.97.

*(S)-1-((S)-2-Cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)-N-ethylpiperidine-2-carboxamide (**4**).* (*S*)-*N*-Ethylpiperidine-2-carboxamide (40.0 mg, 0.26 mmol) and **5** (60 mg, 0.39 mmol) were dissolved in DCM (1.0 mL). HATU (0.38 g, 0.26 mmol) and DIPEA (0.17 mL, 1.02 mmol) were added, and the reaction was stirred at RT for 16 h. Then the organic solvent was removed, and the title compound (68.0 mg, 0.15 mmol, 59.5%) was obtained after purification by flash chromatography (EtOAc/cyclohexane 1:2).

HPLC [0−100% Solvent B, 20 min]: R_t = 18.8 min. **HRMS**: calculated 447.2859 [$C_{25}H_{38}N_2O_5$ + H]$^+$, found 447.2863 [M + H]$^+$. **^{1}H NMR** (300 MHz, $CDCl_3$,) δ 6.52 (s, 2H), 5.50 (t, 1H), 5.23 (d, *J* = 5.3 Hz, 1H), 4.00 (d, *J* = 14.1 Hz, 1H), 3.84−3.83 (m, 6H), 3.82−3.80 (m, 3H), 3.42−3.29 (m, 2H), 3.08−2.97 (m, 2H), 2.78−2.71 (m, 1H), 2.38−2.31 (m, 1H), 2.22−2.08 (m, 2H), 1.91 (d, *J* = 12.6 Hz, 2H), 1.66−1.60 (m, 4H), 1.52−1.44 (m, 2H), 1.34−1.26 (m, 2H), 1.20−1.15 (m, 2H), 0.92−0.86 (m, 1H), 0.81 (t, *J* = 7.2, 0.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.77, 170.10, 153.41, 137.08, 133.71, 105.14, 60.75, 56.24, 55.23, 52.16, 43.71, 40.83, 34.03, 32.77, 30.49, 26.50, 26.10, 26.01, 25.84, 25.00, 20.61, 14.48.

*(S)-N-(2-Amino-2-oxoethyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**6**).* The general procedure was used with Fmoc-Gly-OH and **6** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (22 mg, 46 μmol, 57.5%).

HPLC [0−100% Solvent B, 20 min]: R_t = 19.2 min. **HRMS**: calculated 476.2761 [$C_{25}H_{38}N_3O_6$ + H]$^+$, found 476.2772 [M + H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.57 (d, *J* = 1.1 Hz, 1H), 6.52 (d, *J* = 1.1 Hz, 2H), 4.94−4.90 (m, 1H), 4.75 (d, *J* = 5.1 Hz, 1H), 4.31 (d, *J* = 13.0 Hz, 1H), 3.67−3.62 (m, 9H), 3.10 (d, *J* = 3.8 Hz, 1H), 2.68 (td, *J* = 12.9, 2.7 Hz, 1H), 2.45−2.40 (m, 4H), 1.88−1.76 (m, 2H), 1.68−1.44 (m, 8H), 1.34−1.27 (m, 2H), 1.05−0.89 (m, 4H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 172.90, 172.28, 170.97, 170.55, 153.08, 152.88, 136.32, 134.97, 134.22, 106.02, 105.82, 60.26, 56.32, 56.12, 53.56, 52.63, 48.98, 32.37, 32.19, 30.23, 27.17, 26.51, 26.05, 25.50, 21.14, 20.37.

*(S)-N-(3-Amino-3-oxopropyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**7**).* The general procedure was used with Fmoc-β-Ala-OH, and **7** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (19 mg, 39 μmol, 48.6%).

HPLC [0−100% Solvent B, 20 min]: R_t = 15.9 min. **HRMS**: calculated 490.2917 [$C_{26}H_{39}N_3O_6$ + H]$^+$, found 490.2945 [M + H]$^+$. **^{1}H NMR** (599 MHz, $CDCl_3$) δ 6.52 (s, 2H), 5.94−5.81 (m, 2H), 5.35 (s, 1H), 5.22−5.17 (m, 1H), 4.65−4.60 (m, 1H), 4.01−3.96 (m, 1H), 3.88−3.80 (m, 9H), 3.44−3.37 (m, 2H), 3.17−3.11 (m, 1H), 2.83−2.76 (m, 1H), 2.30 (d, *J* = 13.6, 3.3, 1.8 Hz, 1H), 2.19−2.13 (m, 1H), 2.12−2.04 (m, 2H), 1.90−1.85 (m, 1H), 1.73−1.61 (m, 4H), 1.60−1.55 (m, 1H), 1.50−1.42 (m, 2H), 1.37−1.29 (m, 2H), 1.19−1.10 (m, 2H), 0.93−0.85 (m, 1H), 0.76 (qd, *J* = 12.1, 3.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.00, 172.65, 170.80, 153.32, 136.90, 133.83, 105.41, 105.13, 60.87, 56.33, 56.26, 55.15, 52.30, 43.75, 40.97, 40.88, 35.29, 35.03, 32.70, 30.52, 26.48, 26.10, 26.01, 25.76, 25.25, 20.54, 14.18.

*(S)-N-(4-Amino-4-oxobutyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**8**).* The general procedure was used with Fmoc-GABA-OH, and **7** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (15 mg, 29 μmol, 36.3%).

HPLC [0−100% Solvent B, 10 min]: R_t = 16.2 min. **HRMS**: calculated 504.3074 [$C_{27}H_{41}N_3O_6$ + H]$^+$, found 504.3093 [M + H]$^+$. **^{1}H NMR** (599 MHz, $CDCl_3$) δ 6.52 (s, 2H), 6.30 (s_{br}, 1H), 5.69 (t, *J* = 6.1 Hz, 1H), 5.32 (s_{br}, 1H), 5.23 (d, *J* = 5.3, 2.2 Hz, 1H), 4.00 (d, 1H), 3.84−3.79 (m, 9H), 3.40 (d, *J* = 10.2 Hz, 1H), 3.23 (dq, *J* = 13.1, 6.5 Hz, 1H), 2.89 (h, 1H), 2.76−2.68 (m, 1H), 2.36−2.30 (m, 1H), 2.19−2.11 (m, 1H), 1.96−1.83 (m, 4H), 1.74−1.64 (m, 5H), 1.61−1.55 (m, 1H), 1.52−1.46 (m, 3H), 1.37−1.33 (m, 1H), 1.32−1.27 (m, 1H), 1.20−1.11 (m, 2H), 0.94−0.85 (m, 1H), 0.77 (qd, *J* = 12.2, 3.7 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.56, 172.93, 170.93, 153.42, 136.88, 133.89, 105.21, 60.86, 56.31, 55.20, 52.32, 43.85, 41.00, 40.87, 38.41, 32.73, 32.47, 30.49, 26.46, 26.09, 26.00, 25.74, 25.11, 20.58.

*(S)-N-(5-Amino-5-oxopentyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**9**).* The general procedure was used with Fmoc-Ava-OH, and **9** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (22 mg, 41.5 μmol, 51.9%).

HPLC [0−100% Solvent B, 10 min]: R_t = 16.9 min. **HRMS**: calculated 518.3230 [$C_{28}H_{43}N_3O_6$ + H]$^+$, found 518.3264 [M + H]$^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.44 (s, 2H), 6.01 (s, 1H), 5.47−5.37 (m, 1H), 5.32 (s_{br}, 1H), 5.15 (d, *J* = 4.6 Hz, 1H), 3.93 (d, *J* = 14.2 Hz, 1H), 3.78−3.70 (m, 9H), 3.32 (d, *J* = 10.2 Hz, 1H), 3.14−3.04 (m, 1H), 2.80−2.70 (m, 1H), 2.65 (td, *J* = 13.4, 2.7 Hz, 1H), 2.27 (d, *J* = 14.3 Hz, 1H), 2.12−2.03 (m, 1H), 2.02−1.91 (m, 4H), 1.82 (d, *J* = 12.5 Hz, 1H), 1.66−1.56 (m, 4H), 1.53−1.46 (m, 1H), 1.37 (m, 2H), 1.30−1.17 (m, 4H), 1.13−0.94 (m, 3H), 0.87−0.75 (m, 1H), 0.74−0.62 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.37, 172.80, 170.43, 153.38, 136.61, 134.04, 105.07, 60.87, 56.22, 55.18, 52.26, 43.84, 40.97, 40.88, 38.61, 34.84, 32.72, 30.48, 28.73, 26.48, 26.09, 25.99, 25.81, 25.04, 22.47, 20.63.

*(S)-N-((S)-1-Amino-1-oxopropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**10a**).* The general procedure was used with Fmoc-Ala-OH, and **10a** was obtained as colorless oil (15 mg, 31 μmol, 19.4%).

HPLC [0−100% Solvent B, 20 min]: R_t = 16.4 min. **HRMS**: calculated 490.2917 [$C_{26}H_{39}N_3O_6$ + H]$^-$, found 490.2945 [M + H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.63 (s, 1H), 6.59 (s, 2H), 5.04−4.98 (m, 1H), 4.82 (d, *J* = 5.2 Hz, 1H), 4.33−4.25 (m, 1H), 4.10−4.00 (m, 2H), 3.70 (d, *J* = 3.7 Hz, 9H), 3.60 (s, 2H), 2.04 (d, *J* = 10.0 Hz, 1H), 1.96−1.90 (m, 2H), 1.70 (d, *J* = 12.5 Hz, 2H), 1.60−1.46 (m, 5H), 1.42−1.35 (m, 2H), 1.24−1.17 (m, 2H), 1.11−1.03 (m, 2H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.82−0.70 (m, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 174.22, 172.67, 170.28, 153.14, 153.03, 136.48, 134.34, 106.02, 60.44, 60.28, 56.45, 56.17,53.46, 51.74, 48.27, 47.95, 43.26, 41.23, 32.31, 32.17, 30.20, 26.59, 26.09, 25.82,19.29, 18.84.

*(S)-N-((R)-1-Amino-1-oxopropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**10b**).* The general procedure was used with Fmoc-D-Ala-OH, and **10b** was obtained as colorless oil (8 mg, 17 μmol, 21.3%).

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J. Med. Chem. XXXX, XXX, XXX−XXX

HPLC [0−100% Solvent B, 20 min]: R_t = 17.1 min. **HRMS**: calculated 490.2917 $[C_{26}H_{39}N_3O_6 + H]^+$, found 490.2923 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.65 (s, 1H), 6.54 (s, 2H), 4.93−4.87 (m, 1H), 4.85 (d, J = 5.3 Hz, 1H), 4.31−4.24 (m, 1H), 4.10−3.99 (m, 2H), 3.70−3.68 (m, 6H), 3.60−3.58 (m, 3H), 3.08−2.96 (m, 1H), 2.78−2.68 (m, 1H), 1.98 (t, J = 12.2 Hz, 2H), 1.71 (d, J = 11.9 Hz, 2H), 1.64−1.46 (m, 6H), 1.06 (s, 2H), 1.04 (s, 2H), 1.02−1.02 (m, 3H), 0.95 (d, J = 0.7 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 174.38, 173.07, 170.90, 153.10, 152.98, 136.38, 135.02, 134.13, 105.98, 60.44, 60.27, 56.39, 56.18, 52.75, 48.05, 41.13, 30.24, 26.96, 26.10, 25.43, 20.29, 19.67, 19.28, 18.53.

*(S)-N-((S)-1-Amino-1-oxobutan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**11a**).* The general procedure was used with Fmoc-Abu-OH, and **11a** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as pale yellow oil (29 mg, 58 μmol, 72.5%).

HPLC [0−100% Solvent B, 20 min]: R_t = 17.8 min. **HRMS**: calculated 504.3074 $[C_{27}H_{41}N_3O_6 + H]^+$, found 504.3086 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.63 (s, 1H), 6.52 (s, 2H), 4.97−4.89 (m, 1H), 4.31 (d, J = 13.3 Hz, 1H), 3.73−3.60 (m, 9H), 3.45−3.38 (m, 1H), 3.02 (t, J = 12.5 Hz, 1H), 2.06−1.80 (m, 4H), 1.73−1.63 (m, 3H), 1.55−1.46 (m, 6H), 1.31−1.20 (m, 3H), 1.06−0.98 (m, 3H), 0.94−0.82 (m, 3H), 0.69−0.60 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 173.54, 172.98, 171.00, 152.91, 136.34, 134.97, 134.13, 105.93, 60.37, 60.19, 56.35, 56.10, 53.44, 52.60, 43.18, 41.09, 32.29, 30.18, 27.22, 26.50, 26.04, 25.93, 25.40, 20.32, 10.30.

*(S)-N-((R)-1-amino-1-oxobutan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**11b**).* The general procedure was used with Fmoc-D-Abu-OH, and **11b** was obtained after purification by flash chromatography (0−90% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (10 mg, 20 μmol, 24.8%).

HPLC [0−100% Solvent B, 20 min]: R_t = 17.3 min. **HRMS**: calculated 504.3074 $[C_{27}H_{41}N_3O_6 + H]^+$, found 504.3100 $[M + H]^+$. **^{1}H NMR** (599 MHz, $CDCl_3$) δ 6.51 (s, 2H), 6.03 (d, J = 7.9 Hz, 1H), 5.85 (s_{br}, 1H), 5.34 (s_{br}, 1H), 5.22−5.18 (m, 1H), 4.16−4.13 (m, 1H), 4.05 (dt, J = 13.7, 3.4 Hz, 1H), 3.84−3.78 (m, 11H), 3.41 (d, J = 10.2 Hz, 1H), 3.04−2.96 (m, 1H), 2.32−2.27 (m, 1H), 2.17−2.11 (m, 1H), 1.86 (d, J = 12.5 Hz, 1H), 1.71−1.64 (m, 8H), 1.39−1.31 (m, 3H), 1.18−1.09 (m, 3H), 0.94−0.86 (m, 2H), 0.77−0.69 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.63, 173.50, 171.12, 153.36, 137.11, 133.46, 105.24, 60.77, 60.37, 56.22, 55.03, 53.94, 52.60, 43.89, 41.06, 32.63, 30.47, 26.47, 26.07, 26.02, 25.61, 25.30, 24.73, 20.42, 14.18, 9.79.

*(S)-N-(1-Amino-2-methyl-1-oxopropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**12**).* The general procedure was used with Fmoc-Aib-OH, and **12** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as pale white oil (29 mg, 58 μmol, 72.5%).

HPLC [0−100% Solvent B, 20 min]: R_t = 17.1 min. **HRMS**: calculated 504.3074 $[C_{27}H_{41}N_3O_6 + H]^+$, found 504.3108 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.59 (s, 1H), 6.51 (s, 2H), 4.86−4.76 (m, 1H), 3.95 (d, J = 13.5 Hz, 1H), 3.68−3.60 (m, 7H), 3.60−3.51 (m, 4H), 2.86 (td, J = 14.3, 13.8, 2.9 Hz, 1H), 1.96−1.83 (m, 2H), 1.71−1.61 (m, 2H), 1.57−1.46 (m, 4H), 1.35−1.25 (m, 2H), 1.13 (d, J = 3.7 Hz, 6H), 1.09−0.96 (m, 4H), 0.85−0.70 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 176.37, 172.96, 170.58, 152.91, 136.31, 134.11, 105.97, 60.21, 56.13, 55.93, 53.68, 52.78, 43.13, 32.36, 30.18, 26.53, 26.03, 25.43, 24.88, 24.51, 20.18.

*(S)-N-(4-Amino-2-methyl-4-oxobutan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**13**).* The general procedure was used with Fmoc-3-amino-3-methyl-butyric acid, and **13** was obtained as colorless oil (34 mg, 66 μmol, 82.5%).

HPLC [0−100% Solvent B, 15 min]: R_t = 14.6 min. **HRMS**: calculated 518.3230 $[C_{28}H_{43}N_3O_6 + H]^+$, found 518.3264 $[M + H]^+$. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.52 (s, 2H), 5.99 (s_{br}, 1H), 5.70 (s, 2H), 5.14 (d, J = 4.1 Hz, 1H), 4.05 (d, J = 14.0 Hz, 1H), 3.90−3.73 (m, 9H), 3.39 (d, J = 10.2 Hz, 1H), 2.97−2.86 (m, 1H), 2.66−2.48 (m, 2H), 2.30−2.10 (m, 2H), 1.84 (d, J = 13.2 Hz, 1H), 1.70−1.57 (m, 4H), 1.51−1.41 (m, 3H), 1.31−1.22 (m, 2H), 1.17−1.12 (m, 3H), 1.06−1.00 (m, 6H), 0.93−0.86 (m, 1H), 0.79−0.67 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.45, 173.23, 170.88, 153.35, 137.14, 133.68, 105.32, 60.73, 56.24, 54.92, 52.75, 52.22, 44.74, 43.68, 40.97, 32.61, 30.44, 27.57, 27.52, 26.46, 26.04, 25.97, 25.72, 25.11, 20.51, 17.67, 12.27.

*(S)-N-((S)-1-Amino-3-methyl-1-oxobutan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**14a**).* The general procedure was used with Fmoc-Val-OH, and **14a** was obtained after purification by flash chromatography (50−100% [EtOAc + 0.1% TEA] in cyclohexane) as white crystals (24 mg, 46 μmol, 28.8%).

HPLC [0−100% Solvent B, 20 min]: R_t = 15.1 min. **HRMS**: calculated 518.3230 $[C_{28}H_{43}N_3O_6 + H]^+$, found 518.3264 $[M + H]^+$. **^{1}H NMR** (599 MHz, $CDCl_3$) δ 6.54 (s, 2H), 6.17 (d, J = 8.9 Hz, 1H), 5.23−5.18 (m, 1H), 4.10−4.07 (m, 2H), 3.83 (s, 6H), 3.78 (s, 3H), 3.37 (s, 1H), 2.87−2.79 (m, 1H), 2.34−2.27 (m, 1H), 2.14 (qt, J = 11.0, 3.4 Hz, 2H), 1.93−1.88 (m, 1H), 1.85−1.81 (m, 1H), 1.73−1.67 (m, 3H), 1.66−1.59 (m, 2H), 1.55−1.47 (m, 2H), 1.36−1.25 (m, 2H), 1.19−1.09 (m, 3H), 0.97 (dd, J = 29.5, 6.8 Hz, 1H), 0.91−0.84 (m, 1H), 0.77−0.69 (m, 1H), 0.62 (d, J = 6.8 Hz, 3H), 0.35 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.81, 172.93, 171.06, 153.46, 137.12, 133.32, 105.18, 60.67, 57.82, 56.18, 55.18, 52.73, 43.84, 41.51, 32.54, 30.43, 29.26, 26.44, 26.01, 25.95, 25.63, 24.91, 20.46, 19.16, 16.71.

*(S)-N-((R)-1-Amino-3-methyl-1-oxobutan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**14b**).* The general procedure was used with Fmoc-D-Val-OH, and **14b** was obtained after purification by flash chromatography (50−100% [EtOAc + 0.1% TEA] in cyclohexane) as colorless solid (31 mg, 63 μmol, 39.4%).

HPLC [0−100% Solvent B, 20 min]: R_t = 15.6 min. **HRMS**: calculated 518.3230 $[C_{28}H_{43}N_3O_6 + H]^+$, found 518.3254 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.58 (s, 2H), 5.07−5.02 (m, 1H), 4.95 (d, J = 5.1 Hz, 1H), 4.10 (d, J = 13.9 Hz, 1H), 4.02−3.98 (m, 1H), 3.69 (s, 6H), 3.58 (s, 3H), 2.87−2.80 (m, 1H), 2.08−2.02 (m, 1H), 1.88−1.79 (m, 2H), 1.73−1.61 (m, 3H), 1.58−1.48 (m, 6H), 1.07−1.00 (m, 3H), 0.90−0.86 (m, 3H), 0.83 (dd, J = 6.7, 3.6 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H), 0.59 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 173.07, 172.83, 171.00, 152.98, 136.65, 136.44, 135.02, 134.27, 106.00, 60.41, 60.23, 57.12, 56.42, 56.13, 53.39, 52.50, 46.55, 43.29, 41.23, 35.51, 32.29, 32.22, 31.33, 30.43, 30.24, 27.46, 26.56, 26.50, 26.09, 26.03, 25.65, 20.50, 19.84, 19.69, 18.17, 17.51, 14.51.

*(S)-N-((S)-1-Amino-4-methyl-1-oxopentan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**15**).* The general procedure was used with Fmoc-Leu-OH, and **15** was obtained after purification by flash chromatography (0−80% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (8 mg, 15 μmol, 18.8%).

HPLC [0−100% Solvent B, 20 min]: R_t = 18.8 min. **HRMS**: calculated 532.3387 $[C_{29}H_{45}N_3O_6 + H]^+$, found 532.3215 $[M + H]^+$. **^{1}H NMR** (599 MHz, $CDCl_3$) δ 6.53 (s, 2H), 6.26 (s, 1H), 5.84 (d, J = 8.4 Hz, 1H), 5.34 (s, 1H), 5.22−5.17 (m, 1H), 4.26 (ddd, J = 10.1, 8.4, 4.9 Hz, 1H), 4.10−4.04 (m, 1H), 3.87−3.77 (m, 9H), 3.37 (d, J = 10.2 Hz, 1H), 2.83−2.71 (m, 1H), 2.40−2.32 (m, 1H), 2.13 (qt, J = 10.9, 3.8 Hz, 1H), 1.76−1.61 (m, 6H), 1.60−1.48 (m, 4H), 1.37−1.29 (m, 1H), 1.18−1.06 (m, 3H), 0.99−0.85 (m, 3H), 0.78−0.71 (m, 1H), 0.70 (d, J = 6.6 Hz, 3H), 0.66 (d, J = 6.6 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.89, 173.74, 170.91, 153.51, 137.21, 133.22, 104.98, 60.81, 56.20, 55.30, 52.85, 51.07, 43.83, 41.43, 39.60, 32.66, 30.41, 26.45, 26.04, 25.97, 25.49, 24.93, 24.85, 22.73, 21.21, 20.49.

*(S)-N-((2S,3S)-1-Amino-3-methyl-1-oxopentan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**16a**).* The general procedure was used with Fmoc-Ile-OH, and **16a** was obtained after purification by flash chromatography (0−80% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) obtained as colorless oil (13 mg, 25 μmol, 31.3%).

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J. Med. Chem. XXXX, XXX, XXX−XXX

HPLC [0−100% Solvent B, 20 min]: R_t = 18.3 min. **HRMS**: calculated 532.3387 $[C_{29}H_{45}N_3O_6 + H]^+$, found 532.3417 $[M + H]^+$. **^{1}H NMR** (599 MHz, $CDCl_3$) δ 6.55 (s, 2H), 6.17 (d, J = 8.9 Hz, 1H), 6.08 (s, 1H), 5.51 (s, 1H), 5.21 (d, J = 5.1 Hz, 1H), 4.16 (dd, J = 8.9, 6.0 Hz, 1H), 4.10−4.04 (m, 1H), 3.85 (s, 9H), 3.36 (d, J = 10.2 Hz, 1H), 2.90−2.77 (m, 1H), 2.35−2.29 (m, 1H), 2.13 (qt, J = 11.0, 3.5 Hz, 1H), 1.86−1.79 (m, 1H), 1.76−1.59 (m, 6H), 1.56−1.47 (m, 2H), 1.38−1.30 (m, 1H), 1.29−1.22 (m, 1H), 1.19−1.07 (m, 2H), 1.02−0.95 (m, 1H), 0.95−0.85 (m, 2H), 0.78−0.70 (m, 1H), 0.68−0.56 (m, 6H), 0.48−0.41 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.86, 172.97, 170.94, 153.40, 153.31, 137.13, 133.32, 105.12, 60.72, 57.07, 56.17, 55.14, 52.81, 43.86, 41.69, 35.64, 32.56, 30.47, 26.45, 26.02, 25.97, 25.63, 24.99, 24.00, 20.51, 15.45, 10.86.

*(S)-N-((2R,3R)-1-Amino-3-methyl-1-oxopentan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**16b**).* The general procedure was used with Fmoc-D-Ile-OH, and **16b** was obtained after purification by flash chromatography (0−80% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (26 mg, 49 μmol, 61.3%).

HPLC [0−100% Solvent B, 20 min]: R_t = 18.0 min. **HRMS**: calculated 532.3387 $[C_{29}H_{45}N_3O_6 + H]^+$, found 532.3411 $[M + H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.45 (s, 2H), 6.13 (d, J = 8.8 Hz, 1H), 5.70 (s, 1H), 5.39 (s, 1H), 5.14−5.08 (m, 1H), 4.24 (dd, J = 8.7, 4.4 Hz, 1H), 3.99 (d, J = 13.2 Hz, 1H), 3.73 (d, J = 12.1 Hz, 9H), 3.34 (d, J = 10.2 Hz, 1H), 2.97 (ddd, J = 13.8, 12.3, 2.7 Hz, 1H), 2.24−2.15 (m, 1H), 2.07 (qt, J = 11.0, 3.4 Hz, 1H), 1.80−1.70 (m, 2H), 1.65−1.54 (m, 5H), 1.48−1.36 (m, 2H), 1.30−1.21 (m, 2H), 1.19−1.12 (m, 2H), 1.10−0.97 (m, 3H), 0.90−0.82 (m, 1H), 0.78 (t, J = 7.4 Hz, 3H), 0.72−0.62 (m, 1H), 0.54 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.97, 173.65, 171.20, 153.32, 137.10, 133.48, 105.36, 60.78, 56.19, 55.84, 54.97, 52.81, 43.95, 41.32, 36.45, 32.58, 30.50, 26.46, 26.40, 26.06, 26.03, 25.62, 25.35, 20.40, 14.00, 11.60.

*(S)-N-((S)-2-Amino-1-cyclohexyl-2-oxoethyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**17**).* The general procedure was used with Fmoc-Chg-OH, and **17** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (22 mg, 39 μmol, 48.8%).

HPLC [0−100% Solvent B, 20 min]: R_t = 18.7 min. **HRMS**: calculated 558.3543 $[C_{31}H_{47}N_3O_6 + H]^+$, found 558.3574 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.62 (s, 2H), 6.57 (s, 1H), 5.04 (d, J = 4.1 Hz, 1H), 4.19−4.10 (m, 1H), 4.02 (dd, J = 8.8, 5.6 Hz, 1H), 3.69−3.64 (m, 6H), 3.55−3.52 (m, 3H), 2.72−2.60 (m, 1H), 2.45−2.40 (m, 3H), 2.00 (d, J = 12.6 Hz, 1H), 1.94−1.82 (m, 2H), 1.66−1.57 (m, 4H), 1.53−1.41 (m, 5H), 1.39−1.25 (m, 5H), 1.13−0.90 (m, 8H), 0.79−0.60 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 172.79, 172.53, 170.15, 153.02, 136.33, 134.11, 105.56, 60.36, 60.04, 56.31, 56.08, 55.94, 53.33, 51.74, 46.04, 43.45, 41.58, 32.23, 30.10, 29.78, 27.29, 26.50, 26.08, 25.93, 25.87, 25.60, 20.74.

*(S)-N-((S)-2-Amino-2-oxo-1-phenylethyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**18a**).* The general procedure was used with Fmoc-Phg-OH, and **18a** was obtained as pale yellow oil (38 mg, 69 μmol, 86.3%).

HPLC [0−100% Solvent B, 20 min]: R_t = 18.6 min. **HRMS**: calculated 552.3074 $[C_{31}H_{41}N_3O_6 + H]^+$, found 552.3057 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.35−7.24 (m, 5H), 6.60 (s, 2H), 5.83 (s, 1H), 5.62 (s, 2H), 5.24 (t, J = 3.3 Hz, 1H), 3.74−3.70 (m, 10H), 3.45−3.41 (m, 1H), 2.97 (dt, J = 12.3, 5.3 Hz, 1H), 2.41−2.32 (m, 1H), 2.12−2.02 (m, 1H), 1.92−1.65 (m, 5H), 1.62−1.39 (m, 7H), 1.32−1.22 (m, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 176.49, 172.83, 172.02, 155.39, 138.52, 137.39, 130.48, 128.88, 128.38, 127.05, 108.27, 60.70, 57.77, 57.51, 57.41, 56.83, 43.29, 41.29, 32.44, 26.81, 26.27, 26.02, 25.47, 22.24.

*(S)-N-((R)-2-Amino-2-oxo-1-phenylethyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**18b**).* The general procedure was used with Fmoc-D-Phg-OH, and **18b** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as pale yellow oil (24 mg, 43 μmol, 53.2%).

HPLC [0−100% Solvent B, 20 min]: R_t = 17.8 min. **HRMS**: calculated 552.3074 $[C_{31}H_{41}N_3O_6 + H]^+$, found 552.3065 $[M + H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44−7.33 (m, 2H), 7.34−7.29 (m, 2H), 7.16−7.06 (m, 2H), 6.83−6.76 (m, 1H), 6.62 (s, 1H), 6.54 (s, 1H), 5.88 (s_{br}, 1H), 5.78−5.75 (m, 2H), 5.34−5.30 (m, 1H), 5.29−5.24 (m, 1H), 3.84−3.77 (m, 9H), 3.39 (dd, J = 32.2, 10.1 Hz, 1H), 2.57−2.44 (m, 1H), 2.31−2.10 (m, 3H), 1.95−1.83 (m, 1H), 1.75−1.56 (m, 7H), 1.22−1.10 (m, 3H), 0.98−0.86 (m, 1H), 0.83−0.69 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.32, 171.74, 170.38, 153.35, 153.23, 138.16, 137.12, 133.73, 29.11, 128.89, 127.01, 126.61, 105.19, 60.81, 60.40, 56.91, 56.74, 55.36, 52.68, 43.57, 41.56, 32.74, 26.53, 25.67, 25.38, 21.06, 20.35.

*(S)-N-((S)-1-amino-1-oxo-3-phenylpropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**19a**).* The general procedure was used with Fmoc-Phe-OH, and **19a** was obtained after purification by flash chromatography (EtOAc + 0.1% TEA) as colorless solid (15 mg, 23 μmol, 28.8%).

HPLC [0−100% Solvent B, 20 min]: R_t = 19.1 min. **HRMS**: calculated 566.3230 $[C_{32}H_{43}N_3O_6 + H]^+$, found 566.3253 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.21−7.16 (m, 1H), 7.15−7.12 (m, 4H), 6.60 (s, 2H), 6.45 (s, 2H), 5.08 (t, J = 7.3 Hz, 1H), 5.01 (t, J = 3.2 Hz, 1H), 3.78−3.67 (m, 10H), 3.56 (dd, J = 12.4, 7.2 Hz, 1H), 3.39 (d, J = 1.8 Hz, 1H), 3.02 (dd, J = 12.4, 7.3 Hz, 1H), 2.88 (dt, J = 12.5, 5.3 Hz, 1H), 2.61−2.50 (m, 1H), 2.29−2.18 (m, 1H), 1.90−1.78 (m, 1H), 1.73−1.59 (m, 4H), 1.55−1.40 (m, 8H), 1.35−1.20 (m, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 173.39, 172.96, 170.95, 153.11, 152.90, 138.43, 138.20, 136.67, 136.40, 134.95, 134.23, 129.67, 129.44, 128.38, 128.33, 126.54, 106.14, 105.97, 60.44, 60.27, 56.43, 56.16, 53.75, 52.56, 41.23, 37.92, 30.27, 26.54, 26.11, 20.03.

*(S)-N-((R)-1-Amino-1-oxo-3-phenylpropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**19b**).* The general procedure was used with Fmoc-D-Phe-OH, and **19b** was obtained after purification by flash chromatography (50% [EtOAc + 0.1% TEA] − 100% [EtOAc + 1% TEA] in hexane) as white solid (19 mg, 34 μmol, 21.3%).

HPLC [0−100% Solvent B, 20 min]: R_t = 19.4 min. **HRMS**: calculated 566.3230 $[C_{32}H_{43}N_3O_6 + H]^+$, found 566.3248 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.29 (s, 1H), 7.21−7.12 (m, 3H), 7.10−7.04 (m, 1H), 6.55 (s, 1H), 6.51 (s, 2H), 4.91−4.81 (m, 1H), 4.67 (d, J = 4.8 Hz, 1H), 4.35−4.26 (m, 1H), 3.92 (d, J = 13.4 Hz, 1H), 3.72−3.62 (m, 7H), 3.61−3.51 (m, 3H), 3.30−3.24 (m, 3H), 2.98−2.84 (m, 2H), 1.92−1.83 (m, 1H), 1.77−1.67 (m, 2H), 1.62−1.52 (m, 3H), 1.45 (d, J = 12.9 Hz, 1H), 1.32−1.21 (m, 2H), 1.12−0.98 (m, 4H), 0.92−0.83 (m, 2H), 0.78−0.60 (m, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 173.39, 172.96, 170.95, 153.11, 152.90, 138.43, 138.20, 136.67, 136.40, 134.95, 134.23, 129.67, 129.44, 128.38, 128.33, 126.54, 106.14, 105.97, 60.44, 60.27, 56.43, 56.16, 53.75, 52.56, 41.23, 37.92, 30.27, 26.54, 26.11, 20.03.

*(S)-N-((S)-1-Amino-3-cyclohexyl-1-oxopropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**20**).* The general procedure was used with Fmoc-Cha-OH, and **20** was obtained after purification by flash chromatography (50−100% [EtOAc + 0.1% TEA] in cyclohexane) as white solid (19 mg, 34 μmol, 21.3%).

HPLC [30−100% Solvent B, 10 min]: R_t = 18.5 min. **HRMS**: calculated 572.3700 $[C_{32}H_{49}N_3O_6 + H]^+$, found 572.3736 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.00 (s, 1H), 6.64 (s, 2H), 6.57 (s, 2H), 5.09−5.06 (m, 2H), 4.74 (d, J = 4.6 Hz, 1H), 4.39−4.29 (m, 2H), 4.23−4.12 (m, 2H), 3.72 (s, 3H), 3.70 (s, 6H), 2.71 (t, J = 12.3 Hz, 2H), 2.08 (d, J = 10.3 Hz, 1H), 1.99−1.90 (m, 2H), 1.65−1.51 (m, 9H), 1.44−1.34 (m, 4H), 1.22−1.15 (m, 4H), 0.85−0.76 (m, 3H), 0.67−0.58 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 174.17, 172.78, 170.20, 153.10, 136.32, 134.23, 105.51, 60.14, 55.97, 55.48, 54.11, 53.48, 51.77, 50.48, 49.67, 43.39, 41.46, 34.06, 33.52, 32.28, 32.22, 31.78, 30.15, 26.39, 26.29, 26.12, 26.05, 20.79, 19.67, 18.28, 12.51, 10.09.

*(S)-N-((S)-1-Amino-1-oxo-4-phenylbutan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**21**).* The general procedure was used with Fmoc-Homophe-OH, and **21**

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J. Med. Chem. XXXX, XXX, XXX−XXX

was obtained after purification by flash chromatography (40−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as white solid (34 mg, 58 μmol, 72.5%).

HPLC [0−100% Solvent B, 10 min]: R_t = 19.2 min. **HRMS**: calculated 580.3387 $[C_{33}H_{45}N_3O_6 + H]^+$, found 580.3434 $[M + H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.23−7.12 (m, 2H), 6.98−6.80 (m, 3H), 6.63 (s, 2H), 5.06 (s, 1H), 4.37 (s, 1H), 4.24−4.01 (m, 2H), 3.64−3.48 (m, 3H), 3.06−2.93 (m, 9H), 2.93−2.82 (m, 1H), 2.42−2.16 (m, 2H), 2.05−1.90 (m, 3H), 1.74 (d, *J* = 12.6 Hz, 2H), 1.58−1.44 (m, 5H), 1.23−1.04 (m, 5H), 0.90−0.71 (m, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 173.39, 172.96, 170.95, 153.11, 152.90, 138.43, 138.20, 136.67, 136.40, 134.95, 134.23, 129.67, 129.44, 128.38, 128.33, 126.54, 106.14, 105.97, 60.44, 60.27, 56.43, 56.16, 53.75, 52.56, 41.23, 37.92, 30.27, 26.54, 26.11, 20.03.

(S)-N-((S)-1-Amino-4-cyclohexyl-1-oxobutan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (***22***). The general procedure was used with Fmoc-L-HomoCha-OH and **22** was obtained after purification by flash chromatography (0−80% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as pale white oil (37 mg, 63 μmol, 78.8%).

HPLC [0−100% Solvent B, 10 min]: R_t = 19.2 min. **HRMS**: calculated 586.3856 $[C_{33}H_{51}N_3O_6 + H]^+$, found 586.3893 $[M + H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.44 (s, 2H), 6.14 (s_{br}, 1H), 5.90 (d, *J* = 8.3 Hz, 1H), 5.49 (s_{br}, 1H), 5.19−5.09 (m, 1H), 4.15−4.07 (m, 1H), 3.94 (d, *J* = 6.5 Hz, 1H), 3.79−3.67 (m, 12H), 3.28 (d, *J* = 10.1 Hz, 1H), 2.77−2.65 (m, 1H), 2.32−2.23 (m, 1H), 2.09−2.01 (m, 1H), 1.82−1.74 (m, 1H), 1.69−1.44 (m, 12H), 1.11−0.98 (m, 6H), 0.94−0.81 (m, 3H), 0.74−0.66 (m, 3H), 0.63−0.52 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.68, 173.61, 170.92, 153.49, 137.18, 133.19, 104.93, 60.74, 60.38, 56.14, 55.36, 52.78, 52.53, 43.79, 41.49, 36.36, 33.26, 32.94, 32.90, 32.74, 30.45, 28.40, 26.91, 26.48, 26.47, 26.21, 26.15, 26.07, 26.01, 25.58, 24.96, 21.04, 20.53, 14.19.

(S)-N-((S)-1-Amino-3-hydroxy-1-oxopropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (***23a***). The general procedure was used with Fmoc-L-Ser(OTrt)-OHm and **23a** was obtained as pale yellow oil (32 mg, 63 μmol, 78.8%).

HPLC [0−100% Solvent B, 20 min]: R_t = 15.8 min. **HRMS**: calculated 506.2866 $[C_{26}H_{39}N_3O_7 + H]^+$, found 506.2865 $[M + H]^+$. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.49 (s, 2H), 6.03 (s, 1H), 5.18−5.10 (m, 2H), 4.35−4.25 (m, 2H), 3.99 (d, *J* = 13.6 Hz, 2H), 3.82 (s, 6H), 3.79 (s, 3H), 3.70 (dd, *J* = 11.3, 3.9 Hz, 2H), 3.37−3.24 (m, 6H), 2.96−2.87 (m, 2H), 2.27−2.20 (m, 1H), 2.14−2.08 (m, 1H), 1.61−1.50 (m, 3H), 1.17−1.09 (m, 3H), 0.95−0.86 (m, 2H), 0.74−0.68 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.75, 173.27, 171.70, 153.28, 143.86, 137.02, 133.32, 129.40, 128.25, 126.24, 105.49, 61.78, 60.79, 56.27, 55.32, 53.00, 45.65, 43.75, 41.14, 32.64, 30.45, 26.45, 26.04, 25.35, 20.27, 17.67.

(S)-N-((R)-1-Amino-3-hydroxy-1-oxopropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (***23b***). The general procedure was used with Fmoc-D-Ser(OTrt)-OH, and **23b** was obtained after purification by flash chromatography (0−100% [EtOAc + 5% MeOH] in cyclohexane) as colorless oil (7 mg, 14 μmol, 17.3%).

HPLC [0−100% Solvent B, 20 min]: R_t = 16.9 min. **HRMS**: calculated 506.2866 $[C_{26}H_{39}N_3O_7 + H]^+$, found 506.2881 $[M + H]^+$. **^{1}H NMR** (599 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.0 Hz, 1H), 6.47 (s, 2H), 6.44 (s_{br}, 1H), 5.43 (s_{br}, 1H), 5.08 (t, *J* = 4.3 Hz, 1H), 4.38−4.30 (m, 1H), 4.01−3.94 (m, 2H), 3.82 (d, *J* = 12.4 Hz, 9H), 3.53 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.37 (d, *J* = 10.0 Hz, 1H), 3.02 (td, *J* = 13.7, 13.0, 2.9 Hz, 1H), 2.23−2.15 (m, 2H), 2.11 (ddt, *J* = 10.8, 6.8, 3.3 Hz, 1H), 1.84 (d, *J* = 12.6 Hz, 1H), 1.72−1.61 (m, 5H), 1.33−1.27 (m, 3H), 1.18−1.10 (m, 2H), 0.93−0.84 (m, 2H), 0.79−0.70 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.92, 172.88, 171.73, 153.28, 137.11, 133.17, 105.52, 62.13, 60.82, 56.31, 55.37, 53.68, 53.23, 43.88, 41.16, 32.76, 30.51, 29.67, 26.47, 26.09, 25.48, 25.33, 20.22.

(S)-N-((S)-1-Amino-4-hydroxy-1-oxobutan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (***24a***). The general procedure was used with Fmoc-L-Homoser(Trt)-OH, and **24a** was obtained after purification by flash chromatography (40−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (25 mg, 39 μmol, 48.8%).

HPLC [0−100% Solvent B, 20 min]: R_t = 14.8 min. **HRMS**: calculated 503.2995 $[C_{27}H_{40}N_3O_6 + H]^+$, found 503.2771 $[M - O]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.64 (s, 1H), 6.60 (s, 2H), 5.09−5.04 (m, 1H), 4.80 (d, *J* = 5.1 Hz, 1H), 4.31−4.27 (m, 1H), 4.23−4.13 (m, 2H), 4.08−3.97 (m, 2H), 3.72−3.71 (m, 6H), 3.63−3.62 (m, 3H), 3.10−2.99 (m, 1H), 2.76−2.68 (m, 1H), 2.36−2.26 (m, 2H), 2.09−2.00 (m, 2H), 1.95−1.88 (m, 1H), 1.84−1.67 (m, 2H), 1.62−1.54 (m, 4H), 1.51−1.43 (m, 2H), 1.42−1.32 (m, 3H), 1.14−1.01 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 175.63, 175.61, 172.62, 171.11, 152.89, 148.19, 136.37, 134.45, 128.78, 128.19, 127.95, 106.18, 65.62, 60.33, 56.38, 56.17, 52.02, 48.17, 43.30, 41.57, 32.38, 30.32, 28.51, 28.30, 27.93, 27.00, 26.56, 26.11, 25.72, 24.53, 20.54, 18.29.

(S)-N-((R)-1-Amino-4-hydroxy-1-oxobutan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (***24b***). The general procedure was used with Fmoc-L-Homoser(Trt)-OH, and **24b** was obtained as colorless oil (4 mg, 8 μmol, 10.0%).

HPLC [0−100% Solvent B, 20 min]: R_t = 14.9 min. **HRMS**: calculated 503.2995 $[C_{27}H_{40}N_3O_6 + H]^+$, found 503.2774 $[M - O]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.64 (s, 1H), 6.60 (s, 2H), 5.09−5.04 (m, 1H), 4.80 (d, *J* = 5.1 Hz, 1H), 4.31−4.27 (m, 1H), 4.23−4.13 (m, 2H), 4.08−3.97 (m, 2H), 3.72−3.71 (m, 6H), 3.63−3.62 (m, 3H), 3.10−2.99 (m, 1H), 2.76−2.68 (m, 1H), 2.36−2.26 (m, 2H), 2.09−2.00 (m, 2H), 1.95−1.88 (m, 1H), 1.84−1.67 (m, 2H), 1.62−1.54 (m, 4H), 1.51−1.43 (m, 2H), 1.42−1.32 (m, 3H), 1.14−1.01 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 175.63, 175.61, 172.62, 171.11, 152.89, 148.19, 136.37, 134.45, 128.78, 128.19, 127.95, 106.18, 65.62, 60.33, 56.38, 56.17, 52.02, 48.17, 43.30, 41.57, 32.38, 30.32, 28.51, 28.30, 27.93, 27.00, 26.56, 26.11, 25.72, 24.53, 20.54, 18.29.

(S)-2-((S)-1-((S)-2-Cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)-piperidine-2-carboxamido)pentanediamide (***25a***). The general procedure was used with Fmoc-Gln-OH, and **25a** was obtained as colorless oil (25 mg, 46 μmol, 57.5%).

HPLC [0−100% Solvent B, 20 min]: R_t = 15.1 min. **HRMS**: calculated 547.3132 $[C_{28}H_{42}N_4O_7 + H]^+$, found 547.3187 $[M + H]^+$. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.77 (s_{br}, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 6.54 (s_{br}, 2H), 6.14 (s_{br}, 1H), 5.76 (s_{br}, 1H), 5.52 (s_{br}, 1H), 5.17−5.07 (m, 1H), 4.42−4.30 (m, 1H), 4.00 (d, *J* = 14.2 Hz, 1H), 3.81 (dd, *J* = 14.3, 0.8 Hz, 9H), 3.38 (d, *J* = 10.1 Hz, 1H), 2.94 (t, *J* = 12.9 Hz, 1H), 2.24−1.99 (m, 3H), 1.96−1.77 (m, 3H), 1.73−1.52 (m, 6H), 1.38−1.22 (m, 3H), 1.18−1.08 (m, 2H), 1.00−0.85 (m, 2H), 0.78−0.56 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.79, 173.56, 173.10, 171.24, 153.23, 136.70, 133.79, 105.45, 60.81, 56.24, 55.21, 52.92, 51.63, 43.72, 41.35, 32.59, 30.76, 30.51, 27.96, 26.46, 26.07, 26.00, 25.38, 20.27.

(R)-2-((S)-1-((S)-2-Cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)-piperidine-2-carboxamido)pentanediamide (***25b***). The general procedure was used with Fmoc-D-Gln-OH, and **25b** was obtained as colorless oil (28 mg, 51 μmol, 64.4%).

HPLC [0−100% Solvent B, 20 min]: R_t = 14.8 min. **HRMS**: calculated 547.3132 $[C_{28}H_{42}N_4O_7 + H]^+$, found 547.3196 $[M + H]^+$. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.79 (s_{br}, 1H), 6.51 (s, 2H), 6.35 (s_{br}, 1H), 5.85 (s_{br}, 1H), 5.72 (s_{br}, 1H), 5.16−5.08 (m, 1H), 4.38−4.28 (m, 1H), 4.02 (d, *J* = 13.7 Hz, 1H), 3.86−3.74 (m, 9H), 3.44 (d, *J* = 10.0 Hz, 1H), 3.20−3.06 (m, 2H), 2.56−2.41 (m, 2H), 2.28−2.19 (m, 1H), 2.16−2.06 (m, 3H), 1.83 (d, *J* = 11.8 Hz, 1H), 1.73−1.54 (m, 4H), 1.39−1.27 (m, 3H), 1.18−1.09 (m, 2H), 0.97−0.84 (m, 3H), 0.82−0.69 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.02, 173.79, 173.24, 171.24, 153.22, 136.92, 133.60, 105.53, 60.78, 56.24, 54.98, 53.24, 40.97, 32.62, 30.54, 27.97, 26.89, 26.46, 26.07, 25.44, 20.34, 17.68, 12.28.

(S)-N-((S)-1-Amino-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (***26a***). The general procedure was used with Fmoc-His(Trt)-OH. The trityl protection group was cleaved with 1% TFA and 1% TIS in DCM at RT for 5 h. The crude product was loaded on silica and purified by flash chromatography (50% [EtOAc + 2% MeOH + 0.1% TEA] − 100% [EtOAc + 10% MeOH + 0.1% TEA] in cyclohexane) to obtain **26a** as colorless oil (20 mg, 36 μmol, 45.0%).

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J. Med. Chem. XXXX, XXX, XXX−XXX

HPLC [0−100% Solvent B, 20 min]: R_t = 13.2 min. **HRMS**: calculated 556.3135 $[C_{29}H_{41}N_5O_6 + H]^+$, found 556.3229 $[M + H]^+$. **^{1}H NMR** (599 MHz, $CDCl_3$) δ 7.30 (s_{br}, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.57 (s, 2H), 6.33 (s, 1H), 6.18 (s_{br}, 1H), 5.10−5.04 (m, 1H), 4.71−4.64 (m, 1H), 4.02−3.93 (m, 1H), 3.79 (d, J = 57.4 Hz, 9H), 3.41 (d, J = 10.0 Hz, 1H), 2.98 (dd, J = 15.1, 4.9 Hz, 1H), 2.75−2.66 (m, 1H), 2.54−2.46 (m, 1H), 2.17−2.08 (m, 1H), 2.03 (d, J = 12.8 Hz, 1H), 1.82 (d, J = 12.1 Hz, 1H), 1.74−1.59 (m, 4H), 1.59−1.52 (m, 2H), 1.48−1.41 (m, 2H), 1.34−1.25 (m, 3H), 1.15 (q, J = 12.7 Hz, 2H), 0.95−0.86 (m, 1H), 0.82−0.73 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.85, 172.04, 171.54, 153.30, 136.71, 133.81, 133.30, 129.38, 116.83, 105.45, 60.78, 56.21, 55.11, 52.62, 51.50, 43.74, 41.19, 40.92, 32.50, 30.46, 28.08, 26.41, 26.03, 25.98, 25.12, 25.05, 19.94.

*(S)-N-((R)-1-Amino-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**26b**).* The general procedure was used with Fmoc-D-His(Trt)-OH. The trityl protection group was cleaved with 1% TFA and 1% TIS in DCM at RT for 5 h. The crude product was loaded on silica and purified by flash chromatography (50% [EtOAc + 2% MeOH + 0.1% TEA] − 100% [EtOAc + 10% MeOH + 0.1% TEA] in cyclohexane) to obtain **26b** as colorless oil (13 mg, 23 μmol, 28.8%).

HPLC [0−100% Solvent B, 20 min]: R_t = 13.7 min. **HRMS**: calculated 556.3135 $[C_{29}H_{41}N_5O_6 + H]^+$, found 556.3217 $[M + H]^+$. **^{1}H NMR** (599 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.10−7.01 (m, 2H), 6.77−6.70 (m, 1H), 6.47 (s, 2H), 5.61 (s, 1H), 5.02−4.95 (m, 1H), 4.59−4.52 (m, 1H), 3.99−3.92 (m, 0H), 3.84−3.72 (m, 9H), 3.66−3.60 (m, 1H), 3.43 (d, J = 10.0 Hz, 1H), 3.23−3.12 (m, 1H), 2.94−2.81 (m, 2H), 2.18−2.03 (m, 2H), 1.80 (d, J = 12.4 Hz, 1H), 1.70−1.58 (m, 5H), 1.48 (tdd, J = 13.0, 8.2, 4.6 Hz, 2H), 1.34−1.28 (m, 3H), 1.17−1.07 (m, 2H), 0.98−0.86 (m, 1H), 0.79−0.70 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.15, 173.14, 171.19, 153.17, 136.88, 134.53, 133.44, 105.60, 60.80, 56.28, 56.20, 55.14, 53.82, 52.48, 44.01, 41.07, 40.96, 32.67, 30.57, 28.73, 26.44, 26.10, 25.84, 25.19, 20.11.

*(S)-N-(1-Carbamoylcyclopropyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**27**).* The general procedure was used with Fmoc-1-amino-cyclopropane carboxylic acid, and **27** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (18 mg, 36 μmol, 45.0%). **HPLC** [0−100% Solvent B, 20 min]: R_t = 16.8 min. **HRMS**: calculated 502.2917 $[C_{27}H_{39}N_3O_6 + H]^+$, found 502.2950 $[M + H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.39 (s, 2H), 6.21 (s, 1H), 5.33 (s, 1H), 4.94−4.83 (m, 1H), 3.89 (d, J = 13.8 Hz, 1H), 3.75 (d, J = 5.1 Hz, 9H), 3.30 (d, J = 10.1 Hz, 1H), 2.70 (ddd, J = 14.5, 11.6, 3.2 Hz, 1H), 2.21−2.10 (m, 1H), 2.04 (qt, J = 11.0, 3.3 Hz, 1H), 1.67−1.40 (m, 9H), 1.36−1.16 (m, 5H), 1.14−0.99 (m, 2H), 0.83 (qd, J = 12.3, 3.3 Hz, 1H), 0.76−0.62 (m, 2H), 0.42 (ddd, J = 10.3, 7.6, 4.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.08, 173.91, 172.17, 153.63, 137.31, 132.96, 105.12, 60.85, 56.26, 55.62, 53.44, 43.83, 40.95, 34.33, 32.77, 30.42, 26.46, 26.08, 26.03, 25.05, 24.79, 19.98, 17.37, 16.87.

*(S)-N-(1-Carbamoylcyclobutyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**28**).* The general procedure was used with Fmoc-1-amino-cyclobutane carboxylic acid, and **28** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (17 mg, 33 μmol, 41.3%).

HPLC [0−100% Solvent B, 20 min]: R_t = 18.9 min. **HRMS**: calculated 516.3074 $[C_{28}H_{41}N_3O_6 + H]^+$, found 516.3069 $[M + H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 6.44 (s, 2H), 6.11 (s, 1H), 5.13−5.03 (m, 2H), 4.02−3.96 (m, 1H), 3.76−3.67 (m, 9H), 3.33 (d, J = 10.2 Hz, 1H), 2.80 (ddd, J = 13.9, 12.3, 2.8 Hz, 1H), 2.54−2.42 (m, 2H), 2.21 (dd, J = 13.5, 3.5 Hz, 1H), 2.13−2.03 (m, 1H), 1.83−1.70 (m, 2H), 1.69−1.52 (m, 8H), 1.52−1.39 (m, 3H), 1.31−1.21 (m, 2H), 1.13−1.00 (m, 2H), 0.88−0.75 (m, 1H), 0.68 (qd, J = 12.0, 3.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.20, 173.73, 171.13, 153.55, 137.28, 133.33, 105.14, 60.76, 59.06, 56.28, 55.27, 52.59, 43.87, 41.10, 32.66, 31.42, 31.02, 30.42, 26.91, 26.47, 26.06, 26.00, 25.47, 24.84, 20.29, 15.53.

*(S)-N-(1-Carbamoylcyclopentyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**29**).* The general procedure was used with Fmoc-1-amino-cyclopentane carboxylic acid, and **29** was obtained as colorless oil (32 mg, 60 μmol, 75.0%).

HPLC [0−100% Solvent B, 20 min]: R_t = 18.1 min. **HRMS**: calculated 530.3230 $[C_{29}H_{43}N_3O_6 + H]^+$, found 530.3266 $[M + H]^+$. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.52 (s, 2H), 5.94 (s, 1H), 5.19 (s_{br}, 1H), 5.10−5.03 (m, 1H), 4.06 (dd, J = 13.2, 4.2 Hz, 1H), 3.88−3.73 (m, 9H), 3.39 (d, J = 10.2 Hz, 1H), 2.95−2.82 (m, 1H), 2.26 (d, J = 13.4 Hz, 1H), 2.17−1.98 (m, 3H), 1.88−1.75 (m, 2H), 1.74−1.44 (m, 10H), 1.41−1.24 (m, 4H), 1.23−1.06 (m, 3H), 0.96−0.84 (m, 1H), 0.83−0.68 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.86, 173.91, 171.21, 153.49, 137.33, 133.37, 105.24, 66.96, 60.73, 56.28, 55.10, 52.98, 43.82, 41.28, 37.23, 36.25, 32.54, 30.40, 26.42, 26.01, 25.96, 25.44, 24.88, 23.87, 23.67, 20.23.

*(S)-N-(1-Carbamoylcyclohexyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl) acetyl)piperidine-2-carboxamide (**30**).* The general procedure was used with Fmoc-1-amino-cyclohexane carboxylic acid, and **30** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (21 mg, 38 μmol, 47.8%).

HPLC [0−100% Solvent B, 20 min]: R_t = 18.9 min. **HRMS**: calculated 544.3387 $[C_{30}H_{45}N_3O_6 + H]^+$, found 544.3438 $[M + H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.55 (s, 3H), 5.95 (s, 1H), 5.28 (s_{br}, 1H), 5.20−5.12 (m, 1H), 4.19−4.14 (m, 1H), 3.88−3.77 (m, 9H), 3.63 (ddt, J = 24.9, 12.1, 4.0 Hz, 2H), 3.45 (d, J = 10.3 Hz, 1H), 3.24 (td, J = 11.6, 2.6 Hz, 1H), 3.14−2.95 (m, 2H), 2.37−2.25 (m, 1H), 2.22−2.12 (m, 1H), 2.10−2.06 (m, 1H), 2.05−1.96 (m, 2H), 1.86−1.73 (m, 4H), 1.73−1.63 (m, 4H), 1.62−1.55 (m, 2H), 1.55−1.41 (m, 2H), 1.39−1.29 (m, 2H), 1.17 (qd, J = 12.3, 2.9 Hz, 2H), 0.93 (qd, J = 12.3, 3.4 Hz, 1H), 0.77 (qd, J = 12.0, 3.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.06, 174.24, 171.35, 153.51, 137.37, 133.30, 105.29, 62.96, 62.70, 60.74, 57.22, 56.33, 54.99, 53.23, 44.04, 41.30, 32.79, 32.51, 31.83, 30.43, 26.43, 26.01, 25.98, 25.45, 24.89, 20.27.

*(S)-N-(1-Carbamoylcyclohexyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl) acetyl)piperidine-2-carboxamide (**31**).* The general procedure was used with Fmoc-4-amino-tetrahydropyran-4-carboxylic acid, and **31** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (19 mg, 35 μmol, 43.5%).

HPLC [0−100% Solvent B, 20 min]: R_t = 18.9 min. **HRMS**: calculated 546.3179 $[C_{29}H_{44}N_3O_7 + H]^+$, found 546.3201 $[M + H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.55 (s, 3H), 5.95 (s, 1H), 5.28 (s, 1H), 5.20−5.12 (m, 1H), 4.19−4.14 (m, 1H), 3.88−3.77 (m, 9H), 3.63 (ddt, J = 24.9, 12.1, 4.0 Hz, 2H), 3.45 (d, J = 10.3 Hz, 1H), 3.24 (td, J = 11.6, 2.6 Hz, 1H), 3.14−2.95 (m, 2H), 2.37−2.25 (m, 1H), 2.22−2.12 (m, 1H), 2.10−2.06 (m, 1H), 2.05−1.96 (m, 2H), 1.86−1.73 (m, 4H), 1.73−1.63 (m, 4H), 1.62−1.55 (m, 2H), 1.55−1.41 (m, 2H), 1.39−1.29 (m, 2H), 1.17 (qd, J = 12.3, 2.9 Hz, 2H), 0.93 (qd, J = 12.3, 3.4 Hz, 1H), 0.77 (qd, J = 12.0, 3.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.06, 174.24, 171.35, 153.51, 137.37, 133.30, 105.29, 62.96, 62.70, 60.74, 60.40, 57.22, 56.33, 54.99, 53.23, 44.04, 41.30, 32.79, 32.51, 31.83, 30.43, 26.43, 26.01, 25.98, 25.45, 24.89, 20.27, 14.20.

*(S)-N-(1-((2-Amino-2-oxoethyl)carbamoyl)cyclopentyl)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxamide (**32**).* The general procedure was used with Fmoc-Gly-OH and Fmoc-1-amino-cyclopentane carboxylic acid (first coupling step repeated). Compound **32** was obtained after purification by flash chromatography (0−100% [EtOAc + 2% MeOH + 0.1% TEA] in cyclohexane) as colorless oil (14 mg, 24 μmol, 30.2%).

HPLC [0−100% Solvent B, 20 min]: R_t = 19.1 min. **HRMS**: calculated 587.3445 $[C_{31}H_{46}N_4O_7 + H]^+$, found 587.3530 $[M + H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.81 (t, 1H), 6.47 (s, 2H), 6.11 (s, 1H), 5.34 (s, 1H), 4.97 (t, 1H), 4.00 (d, 1H), 3.86 (dd, 1H), 3.76 (s, 6H), 3.72 (s, 3H), 3.62 (dd, 1H), 3.34 (d, 1H), 2.86 (m, 1H), 2.19−2.02 (m, 3H), 1.90−1.84 (m, 3H), 1.74 (d, 2H), 1.65−1.52 (m, 8H), 1.32−1.16 (m, 5H), 1.11−1.01 (m, 2H), 0.82 (qd, 1H), 0.75−0.57 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.27, 173.39, 172.17, 172.03, 153.56, 137.39, 133.37, 105.23, 66.78, 60.77, 56.32,

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J. Med. Chem. XXXX, XXX, XXX−XXX

55.10, 53.26, 44.12, 43.10, 41.30, 37.56, 36.40, 32.52, 30.39, 26.41, 26.00, 25.96, 25.38, 24.82, 23.88, 20.31.

■ ASSOCIATED CONTENT

Supporting Information

can be found in the Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.5b01355.

Full characterization and synthetic procedures of all intermediates (PDF)
Crystallography information (CSV)
Crystallography information (XLS)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

FKBP, FK506-binding protein; HA, hydrogen bond acceptor; FP, fluorescence polarization

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