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# 1,4-Pyrazolyl-Containing SAFit-Analogues are Selective FKBP51 Inhibitors With Improved Ligand Efficiency and Drug-Like Profile

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The FK506 binding protein 51 (FKBP51) is an appealing drug target due to its role in several diseases such as depression, anxiety, chronic pain and obesity. Towards this, selectivity versus the close homolog FKBP52 is essential. However, currently available FKBP51-selective ligands such as SAFit2 are too large and lack drug-like properties. Here, we present a structure activity relationship (SAR) analysis of the pipecolic ester moiety of SAFit1 and SAFit2, which culminated in the discovery of the 1,4-pyrazolyl derivative **23 d**, displaying a binding affinity of 0.077 μM for FKBP51, reduced molecular weight (541.7 g/mol), lower hydrophobicity (cLogP = 3.72) and higher ligand efficiency (LE = 0.25). Cocrystal structures revealed the importance of the 1,4- and 1,3,4- substitution patterns of the pyrazole ring versus the 1,4,5 arrangement.

## Introduction

The FK506-binding protein 51 (FKBP51, encoded by the FKBP5 gene) has repeatedly been shown to be a key factor in the pathophysiology of stress-related diseases such as depression, anxiety, chronic pain, and obesity.[1] An important issue in the development of FKBP51-directed drugs is selectivity against its closest homolog and functional counterplayer FKBP52.[2] The serendipitous discovery of a FKBP51-specific cryptic subpocket[3–5] laid the foundation for FKBP51-selective inhibitors such as SAFit1 and SAFit2 (Figure 1), which was instrumental to provide a first proof-of-concept in animal models.[1] However, SAFit2 suffers from a poor physicochemical profile and unfavorable pharmacokinetics, and despite numerous derivatization strategies, optimization remained challenging.[6–11] Further medicinal chemistry studies are therefore needed, starting with SAFit analogues with reduced molecular weight and lipophilicity.

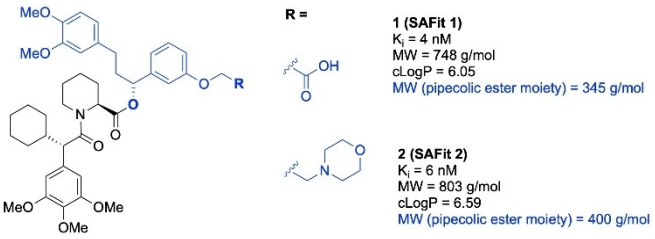


**Figure 1.** Chemical structures of SAFit1and SAFit2. The SAFit pipecolic ester moiety is shown in blue.[5]

The pipecolic ester moiety (shown in blue, Figure 1) of SAFit2 (**2**) represents a large proportion of the total molecular weight of both compounds (50%). However, this part of the ligand makes only limited contact with the surface of the protein.

In this study, we systematically analyzed the effects of variations of the pipecolic ester moiety of SAFit-like ligands with the specific aims of retaining selectivity for FKBP51 over FKBP52, while improving the drug-like properties and increasing ligand efficiency.

## Results and Discussion

We started our SAR study by gradually reducing the size of the bulky SAFit pipecolic ester moiety. All compounds were tested in a competitive fluorescence polarization assay[12] for binding

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toward FKBP51 and the homologues FKBP12, FKBP12.6, and FKBP52 (Table 1 and 4 and Table S4).

In compound **3**, synthesized by using a precursor reported by Wang et al.[13] (Scheme S1a), the removal of the morpholinoethyl moiety resulted in 40-fold drop in binding affinity when compared to SAFit2 (Table 1). To assess the importance of the dimethoxyphenylethyl arm of SAFit2, we synthesized compound **4** (Scheme S1b). Similarly, truncation of the dimethoxyphenylethyl arm reduced binding affinity 88-fold. Further reducing the size of the SAFit-pipecolic ester substituent to a benzyl ring resulted in compound **5** (Scheme S1c) showing a binding affinity of 0.46 μM. Truncation to a simple methyl ester, as in compound **6**,[9] drastically reduced binding affinity towards FKBP51. As expected, the complete removal of the two SAFit branches, resulting in the free pipecolic acid analogue **7**,[9][14] abolished binding to FKBP51 (Table 1). Importantly, all analogs retained high selectivity *vs* FKBP52 (Table SI S4).

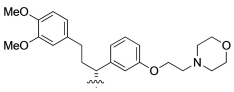
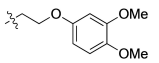
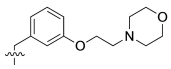
### Bioisosteric Replacement of the Phenyl Ring

Having identified a benzyl in compound **5** as a minimal pipecolic ester moiety (Table 1), we continued our analysis by investigating the tolerability of various 5-membered heterocycles as potential pipecolic ester moiety replacements. Toward this end, we synthesized compounds **11a–j** by Steglich esterification of precursor **7** and the corresponding alcohols **10a–j** (Scheme 1B). Alcohols **10a–j** were either commercially available or synthesized via reduction with $NaBH_4$, $LiAlH_4$ or boron dimethyl sulfide complex (Scheme 1A).

Among 5-membered heterocycles bearing a single heteroatom, the 2-thienyl derivative **11a** behaved similarly to **5**. For 5-membered heterocycles with 2 heteroatoms, the best derivative was the 5-thiazole analogue **15a** ($K_i = 0.26$ μM). A comparison of **15a** with the 2-thiazolyl derivative **11b** and especially the 4-thiazole analogue **11c** revealed the importance for correct positioning of the sulfur and nitrogen heteroatoms in the ring. A similar trend was observed for the 5-oxazole **11d** and the 4-oxazole **11e**. In contrast, 2- or 5-imidazoles as in **11g** and **11f** were less tolerated than the related moieties in **11d** and **15a**. For 5-membered rings with vicinal heteroatoms, such as the 4-isothiazole analogue **11h** and the 4-isoxazole derivative **11i**, binding affinity slightly decreased with $K_i$ values of 0.84 μM and 0.63 μM respectively. Surprisingly, an increase in binding affinity was observed when a 1,4-pyrazolyl moiety was introduced as in **23a** ($K_i = 0.27$ μM). However, introduction of a third heteroatom as in the triazole analogues **11k** and **11l** substantially reduced affinity for FKBP51 (Table 2 and Scheme S2).

Based on the preliminary results of our SAR analysis, **15a** ($K_i = 0.26$ μM, Table 2) and **23a** ($K_i = 0.27$ μM, Table 2) emerged as promising starting point for further optimization. We therefore decided to investigate these two scaffolds in a more systematic manner by exploring the substitution pattern of the 5-thiazolyl and the 4-pyrazolyl moieties.

**Table 1.** SAFit-like ligands derived by gradual truncation of the SAFit1/2 pipecolic ester moiety.

| Entry | R | FKBP51 $K_i$ [μM] * | synthetic method |
|---|---|---|---|
| **SAFit2** |  | 0.006 ± 0.002 | [5] |
| **3** |  | 0.25 ± 0.01 | a and [13] |
| **4** |  | 0.53 ± 0.07 | b |
| **5** |  | 0.46 ± 0.05 | c |
| **6** | -Me | 2.8 ± 0.5 | [9] |
| **7** | -H | > 200 | [9] |

* Affinities were measured by a competitive fluorescence polarization assay. Errors represent standard deviation from the mean from two technical replicates. [a] synthesized according to Scheme S1a and as reported by Wang et al.;[13] [b] synthesized according Scheme S1b. [c] synthesized according to Scheme S1c.

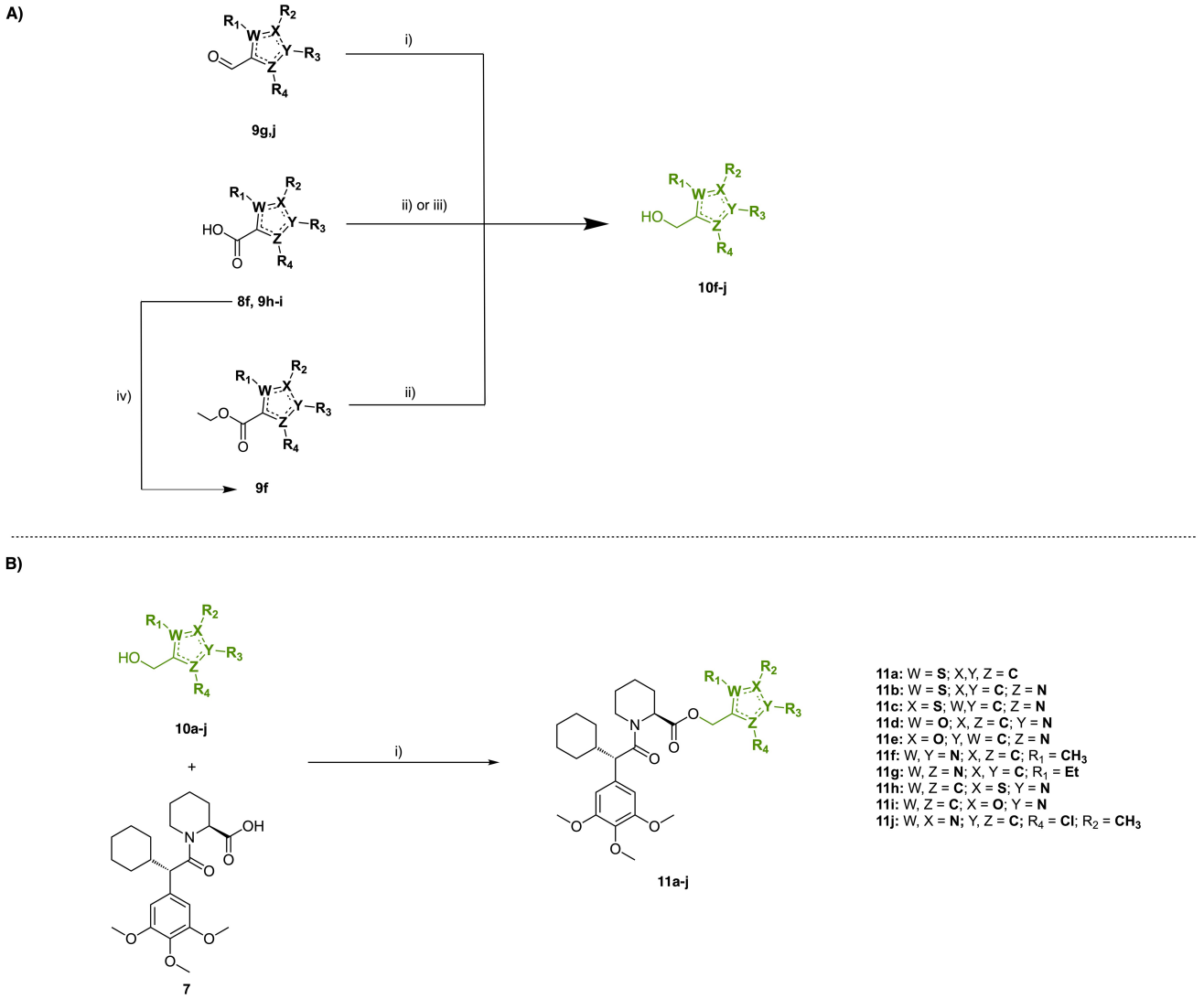
### Exploration of the Thiazole Moiety

Inspired by the promising binding affinity observed with **15a** for FKBP51, we sought to investigate the tolerability of various substituents in the 2- and 4-position of the 5-thiazole ring. To achieve this, alcohols **14a–k** were esterified with precursor **7** to give analogues **15a–k** (Scheme 2B). Alcohols **14a–c**, **14f** and **14h–i** were commercially available, while **14d–e**, **14g** and **14j–k** were synthesized according to Scheme 2A.

To assess position 2 of the 5-thiazolyl scaffold, we started by introducing small substituents such as a methyl as in **15b**, a chlorine as in **15c**, a bromine as in **15d**, and gradually expanding with bulkier groups such as methoxy as in **15e**, trifluoromethyl as in **15f**, and phenyl as in **15g**. Overall, all substituents were tolerated, with the exception of the trifluoromethyl analogue **15f**, which showed a 4-fold drop in binding affinity compared to **15a**. The introduction of a methyl (**15h**) or a chlorine (**15i**) in the 4-position of the 5-thiazole did not affect binding. In conclusion, the 2- and 4-positions are both suitable for modifications (Table 3). However, although various substitutions were possible, no net gain in binding affinity could be observed among the 5-thiazolyl series.

### Exploration of the Pyrazole Moiety

Since no substantial improvement in binding affinity could be derived from the 5-thiazolyl series (Table 3), we focused on **23a** ($K_i = 0.27$ μM, Table 2) and prepared a series of 4-pyrazolyl-containing analogues displaying various nitrogen 1 (N1) substituents. Like for previous derivatives, analogues **23a–m** and **24e–f** were synthesized through Steglich esterification with the corresponding alcohols **22a–m** and the precursor **7** (Scheme 3B). The alcohol precursors **22a–g** were synthesized via N-alkylation of the common precursor **17**. Intermediate **21k** was




**A**) i) $NaBH_4$, MeOH/THF, 0°C to rt, overnight; ii) LAH, THF, 0°C to rt, 2h; iii) Borane dimethyl sulfide complex (2M in THF), THF, 0°C to rt, overnight; iv) $H_2SO_4$, EtOH, reflux, 24h. **B**) i) for **11a** and **11c**: **7**, DIC, DMAP, DCM, 0° to rt, on; for **11b**: **7**, DMAP, EDC-HCl, DCM, 0° to rt, on; for **11d-j**: **7**, 4-(pyrrolidin-1-yl)pyridine, EDC-HCl, toluene, rt, on.

**Scheme 1.** Synthesis of analogues **11 a-j** by esterification with intermediate **7**.

synthesized through cyclization of the enaminone **19 k** with ethylhydrazine following the procedure reported by Ishimoto et al.[15] and Zanatta et al.,[16] yielding an 32 : 1 ratio in favour of the 1,5 regioisomer over the 1,3 regioisomer. Compounds **21 a**–**m** were treated either with $NaBH_4$ or $LiAlH_4$ to give the corresponding alcohols **22 a**–**m** (Scheme 3A).

When gradually increasing the size of the N1 substituent, such as with the unbranched ethyl in **23 b**, binding affinity improved by 2-fold compared to **23 a**. Further extension to a branched isopropyl (**23 c**) and a *n*-propyl residue (**23 d**) further increased binding affinity, showing values of 0.087 μM and 0.077 μM respectively (Table 4).

With the hope of engaging into a potential hydrogen bond interaction with the surroundings of the FK1 domain of FKBP51, we introduced more polar substituents as in the 1-(2-hydroxyethyl) and the 1-(3-hydroxypropyl) analogues **24 e** and **24 f**. Unfortunately, the increase in polarity was not beneficial for binding as a 3-3.5-fold drop in potency was observed compared to **23 d**. Similarly, **23 g**, the methylated analogue of **24 e**, showed a 5-fold drop in affinity.

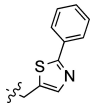
In parallel, we sought to investigate the tolerability of substitutions on the other positions of the 4-pyrazole ring. Analogues **23 h** (0.12 μM) and **23 i** (0.062 μM) showed that 1,3,4-pyrazolyl analogues are tolerated, but functionalization of the 3-position does not increase affinity substantially. Conversely, functionalisation of the 5-position of the 4-pyrazolyl moiety, resulting into 1,4,5-pyrazolyl analogues as **23 j** (0.92 μM) and **23 k** (2.0 μM) and the cyclized analogues **23 l** (2.5 μM) and **23 m** (0.97 μM), would be deleterious for binding. To prove the importance of the 4-pyrazolyl connectivity, we synthesized **11 j** (Scheme 1). The reduced binding affinity of this 3-pyrazolyl

**Table 2.** Affinities of SAFit-like ligands containing heterocycles as SAFit1/2 pipecolic ester moiety replacements.

| Entry | R | FKBP51 $K_i$ [μM] * | Synthetic method | Entry | R | FKBP51 $K_i$ [μM] * | Synthetic method |
|---|---|---|---|---|---|---|---|
| **5** |  | 0.46 ± 0.05 | a | **11f** |  | 0.97 ± 0.12 | b |
| **11a** |  | 0.46 ± 0.04 | b | **11g** |  | 3.6 ± 0.6 | b |
| **15a** [f] |  | 0.26 ± 0.01 | c | **11h** |  | 0.84 ± 0.12 | b |
| **11b** |  | 0.73 ± 0.10 | b | **11i** |  | 0.63 ± 0.09 | b |
| **11c** |  | 1.9 ± 0.2 | b | **23a** [g] |  | 0.27 ± 0.01 | d |
| **11d** |  | 0.57 ± 0.03 | b | **11k** |  | 1.0 ± 0.1 | e |
| **11e** |  | 1.5 ± 0.1 | b | **11l** |  | > 5.0 | e |

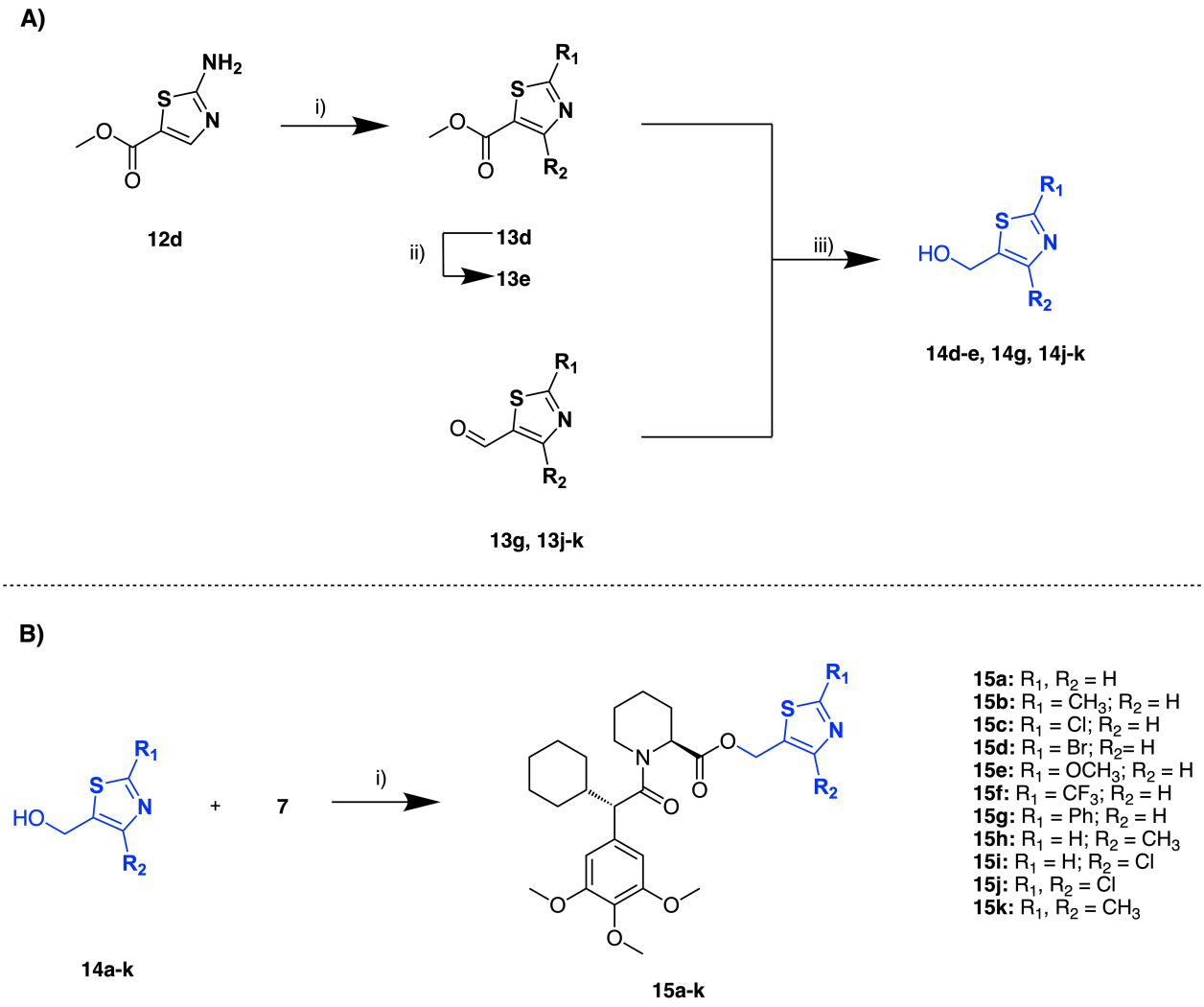
* Affinities were measured by a competitive fluorescence polarization assay. Errors represent standard deviation from the mean from two technical replicates.
[a] synthesized according to Scheme S1b; [b] synthesized according Scheme 1; [c] synthesized according to Scheme 2; [d] synthesized according to Scheme 3; [e] synthesized according to Scheme S2; [f] value obtained from the average of two independent measurements (representing two technical replicates each); [g] value obtained from the average of 3 independent measurements (representing two technical replicates each).

**Table 3.** Affinities of SAFit-like ligands containing 2- and 4-substituted 5-thiazoles.

| Entry | R | FKBP51 $K_i$ [μM] * | Synthetic method | Entry | R | FKBP51 $K_i$ [μM] * | Synthetic method |
|---|---|---|---|---|---|---|---|
| **15a** [b] |  | 0.26 ± 0.01 | a | **15g** |  | 0.32 ± 0.02 | a |
| **15b** |  | 0.24 ± 0.02 | a | **15h** |  | 0.26 ± 0.02 | a |
| **15c** |  | 0.56 ± 0.05 | a | **15i** |  | 0.46 ± 0.06 | a |
| **15d** |  | 0.23 ± 0.02 | a | **15j** |  | 0.30 ± 0.07 | a |
| **15e** |  | 0.19 ± 0.01 | a | **15k** |  | 0.45 ± 0.07 | a |
| **15f** |  | 1.1 ± 0.1 | a | | | | |

* Affinities were measured by a competitive fluorescence polarization assay. Errors represent standard deviation from the mean from two technical replicates. [a] synthesized according to Scheme 2; [b] value obtained from the average of two independent measurements (representing two technical replicates each).

analogue further underscores the importance of the 4-pyrazolyl series (Table 4).




**A**) i) HBr, KBr, CuBr, $NaNO_2$, $H_2O$, 60°C, 3h; ii) $NaOCH_3$ (0.5M in MeOH), MeOH, 50°C, 4d; iii) for **13d**: $NaBH_4$, EtOH/$H_2O$ (5:1, v/v), 0°C to rt, 4h; for **13e**, **13g** and **13j-k**: $NaBH_4$, MeOH/THF, 0°C to rt, overnight. **B**) i) **15a-b**: **7**, DIC, DMAP, DCM, 0° to rt, on; for **15c-g** and **15i-k**: **7**, PPY, EDC-HCl, toluene, rt, on; for **15h**: **7**, DMAP, EDC-HCl, DCM, 0° to rt, on.

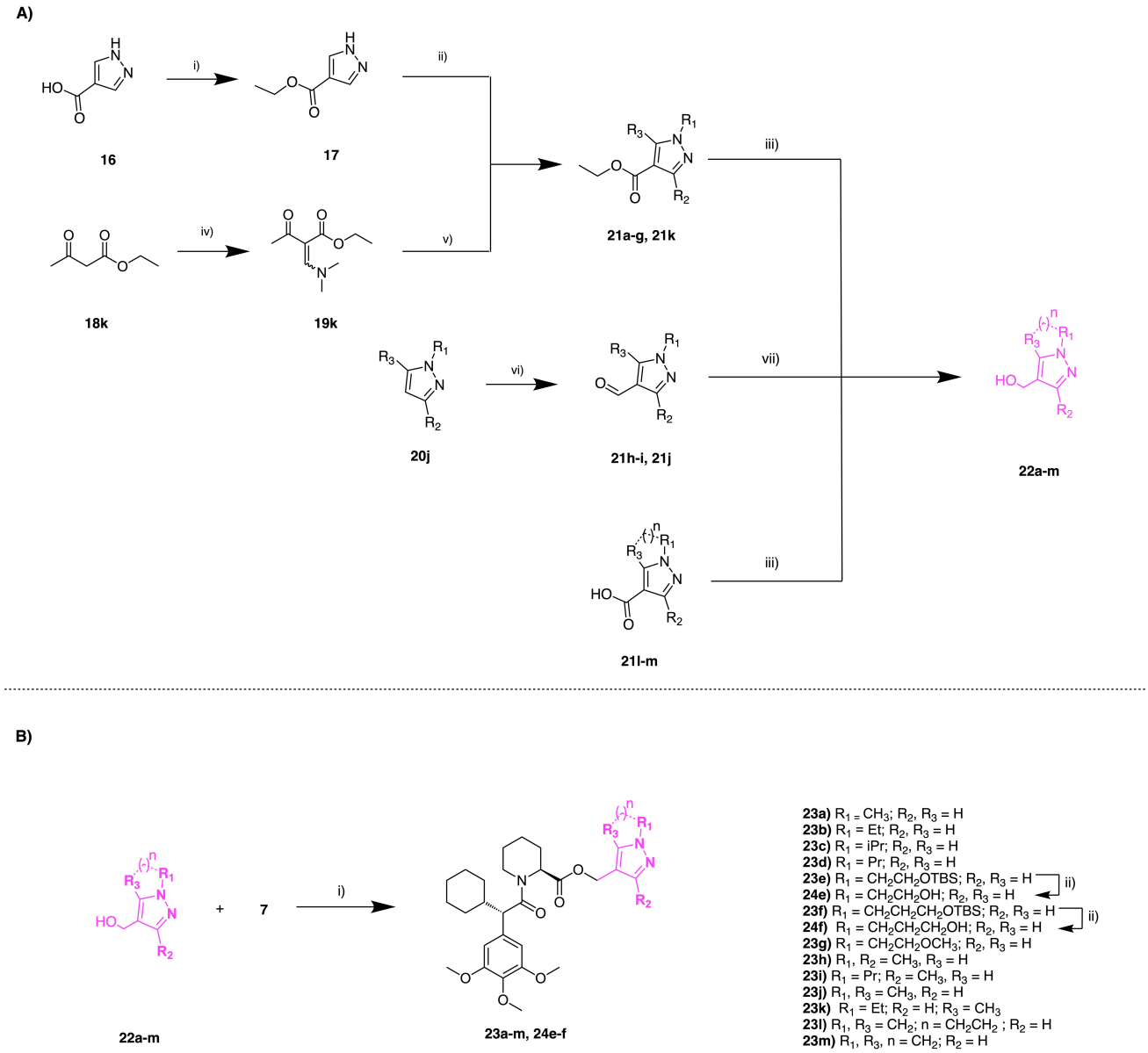
**Scheme 2.** Synthesis of analogues **15a-k**.

### Molecular Binding Mode

Intrigued by the promising binding affinity of the 5-thiazolyl and 4-pyrazolyl series (Table 3 and 4), we cocrystallized **15i**, **15b**, **15h**, **23a**, **23b**, **23c**, **23d**, **23j, and 24e** in complex with the FK1 domain of FKBP51. For all cocrystallized analogues, the basic binding mode is very similar to the previously determined cocrystal structures of SAFit1[11] and SAFit2.[17] Specifically, the positions of the three methoxy substituents of phenyl ring pointing towards the solvent, the cyclohexyl ring occupying the transient hydrophobic subpocket formed by the displacement of the Phe67, and the pipecolic amide core engaging into two key hydrogen bonds with Ile87 and Tyr113 were highly conserved (Figure 2).

In all cocrystallized analogues, the heterocycles introduced as pipecolic ester replacement sample a space corresponding to the phenyl group of the morpholinoethyl branch of SAFit2 (Figure 2B and 2 C).

In **23a**, **23c**, and **23d** the N1 substituent extends towards a surface-exposed hydrophobic area formed by Phe77, Val86 and the β-carbon of Phe79 (Figure 3A and S1 A & S1 C). In **23b** and **24e** (Figure S1B and S1D), the ethyl and the hydroxyethyl chains deviate by 90° when compared to the methyl (**23a**), propyl (**23d**) and isopropyl (**23c**) residues (Figure S1A, 3 A and S1 C). For the 1,4-pyrazolyl (**24a–d**) and the 1,3,4-pyrazolyl series (**23h–i**), it is interesting to notice that, by gradually increasing the size of the N1 substituent of the pyrazole ring a gain in binding affinity is correspondingly observed, starting from the methyl (**23a**, 0.27 μM and **23h**, 0.12 μM), to the ethyl (**23b**, 0.12 μM), to the isopropyl (**23c**, 0.087 μM) and culminating with the propyl (**23d**, 0.077 μM and **23i**, 0.062 μM). The 3.5-fold decrease in binding affinity observed with **24e** when compared to **23d** could be explained by the fact that the hydrophobic environment represented by Phe77, Phe79, and Val86 causes the terminal polar residue of the hydroxyethyl




**A**) i) $H_2SO_4$, EtOH, reflux, 24h; ii) for **21a**: $CH_3I$, $K_2CO_3$, DMF, rt, on; for **21b-d**: $R_1$-Br, $K_2CO_3$, acetone, rt, on; for **21e-f**: $R_1$-Br, $Cs_2CO_3$, acetone, rt; for **21g**: $R_1$-Br, $K_2CO_3$, DMSO, 0°C to rt, on; iii) $LiAlH_4$, THF, 0°C to rt, 2h; iv) DMF-DMA, rt, on; v) ethylhydrazine, $Na_2CO_3$ (1M in $H_2O$), MeOH/HCl (10:1 v/v), rt to reflux, on; vi) $POCl_3$, DMF, 0°C to rt, overnight; vii) $NaBH_4$, THF/MeOH (1.5:1, v/v), 0°C to rt, overnight. **B**) i) **7**, PPY, EDC-HCl, toluene, rt, on; ii) TBAF, THF, 0°C, 1h.

**Scheme 3.** Synthesis of analogues **23a-m** and **24e-f**.

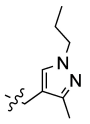
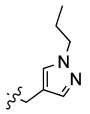
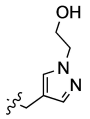
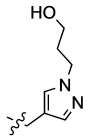
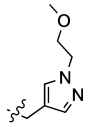
chain to shift, thus hindering the hydrophobic contacts. (Figure S1D).

In **23j** (Figure 4A and 4B), the methyl in the 5-position of the pyrazole ring points toward the trimethoxyphenyl ring, engaging in an intramolecular van-der-Waals contact with the conserved aromatic ring of SAFit1 and SAFit2.

Although we were unable to obtain a cocrystal structure for **23i**, we postulate that the orientation of the pyrazole ring of 1,3,4-analogues would mimic the one observed in 1,4-derivatives **23a–d** and **24e** (Figure 3A, S1 A, S1B, S1 C, S1D), with the additional methyl in the 3-position of the pyrazole ring interacting via the same van-der-Waals contact observed for **23j** (Figure 4A and 4B).

The correct positioning of the N-substituent explains the pronounced affinity difference between 1,3,4-pyrazolyl analogues (**23i** and **23h**) and 1,4,5-derivatives (**23j** and **23k**). While the substitution pattern of 1,3,4-pyrazoles allows the aliphatic chain of N1 to extend toward the solvent-exposed hydrophobic area represented by Phe77, Phe79 and Val86, this is not possible for 1,4,5-derivatives (Figure 4C). Indeed, in **23j**, the pyrazole ring is forced to twist by 180° to avoid clashes with the backbone carbonyl of Gln85. This causes the aliphatic chain in N1 to point away from the hydrophobic area, thus preventing the hydrophobic contact and likely weakening the overall interaction (Figure 4C).

**Table 4.** Affinities of SAFit-like ligands containing 4-pyrazolyl-containing analogues.

| Entry | R | FKBP51 $K_i$ [μM] * | Synthetic method | Entry | R | FKBP51 $K_i$ [μM] * | Synthetic method |
|---|---|---|---|---|---|---|---|
| **23a** [d] |  | 0.27 ± 0.01 | a | **23h** [d] |  | 0.12 ± 0.003 | a |
| **23b** [c] |  | 0.12 ± 0.001 | a | **23i** [e] |  | 0.062 ± 0.003 | a |
| **23c** [c] |  | 0.087 ± 0.003 | a | **23j** [c] |  | 0.92 ± 0.06 | a |
| **23d** [d] |  | 0.077 ± 0.003 | a | **23k** |  | 2.0 ± 0.3 | a |
| **24e** [d] |  | 0.27 ± 0.009 | a | **23l** |  | 2.5 ± 0.5 | a |
| **24f** [c] |  | 0.22 ± 0.001 | a | **23m** |  | 0.97 ± 0.19 | a |
| **23g** [c] |  | 0.36 ± 0.003 | a | **11j** |  | 0.57 ± 0.11 | b |

* Affinities were measured by a competitive fluorescence polarization assay. Errors represent standard deviation from the mean from two technical replicates. [a] synthesized according to Scheme 3; [b] synthesized according to Scheme 1; [c] value obtained from the average of 2 independent measurements (representing two technical replicates each); [d] value obtained from the average of 3 independent measurements (representing two technical replicates each); [e] value obtained from the average of 6 independent measurements (representing two technical replicates each).

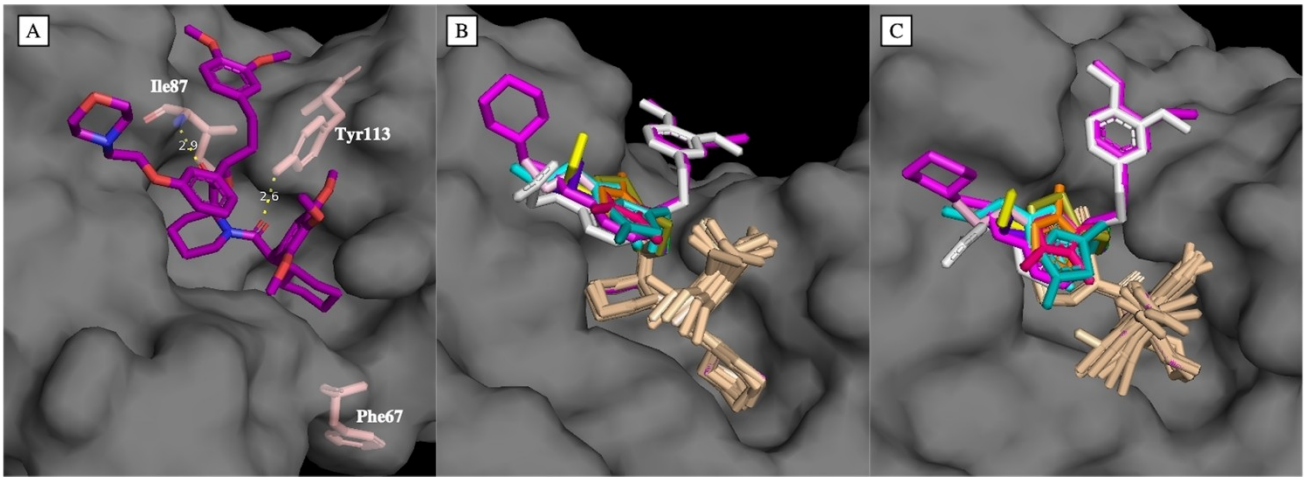



**Figure 2.** Binding mode of pipecolate ester moiety analogues of SAFit2. **A**) SAFit2 (magenta sticks) in complex with the FK1 domain of FKBP51 (gray surface, PDB: 6TXX,[17]). Key hydrogen bonds with Ile87 and Tyr113 (light pink) are indicated as yellow dotted lines. **B**) Overlay of SAFit1 (white, from PDB: 8CCA,[11]) and SAFit2 (magenta, PDB: 6TXX) with **15b** (teal, PDB: 9EU7), **15h** (deep olive, PDB: 9EU8) **15i** (orange, PDB: 9EU9), **23a** (blue sticks, PDB: 9EUE), **23b** (green, PDB: 9EUC), **23c** (purple blue, PDB: 9EUD), **23d** (light pink, PDB: 9EUA), **23j** (hot pink, PDB: 9EU6), **24e** (yellow, PDB: 9EUB) in complex with the FK1 domain of FKBP51. **C**) Compounds superimposed as in **B**), viewed from the top. In **B**) and **C**) K121 was removed for better visualization.

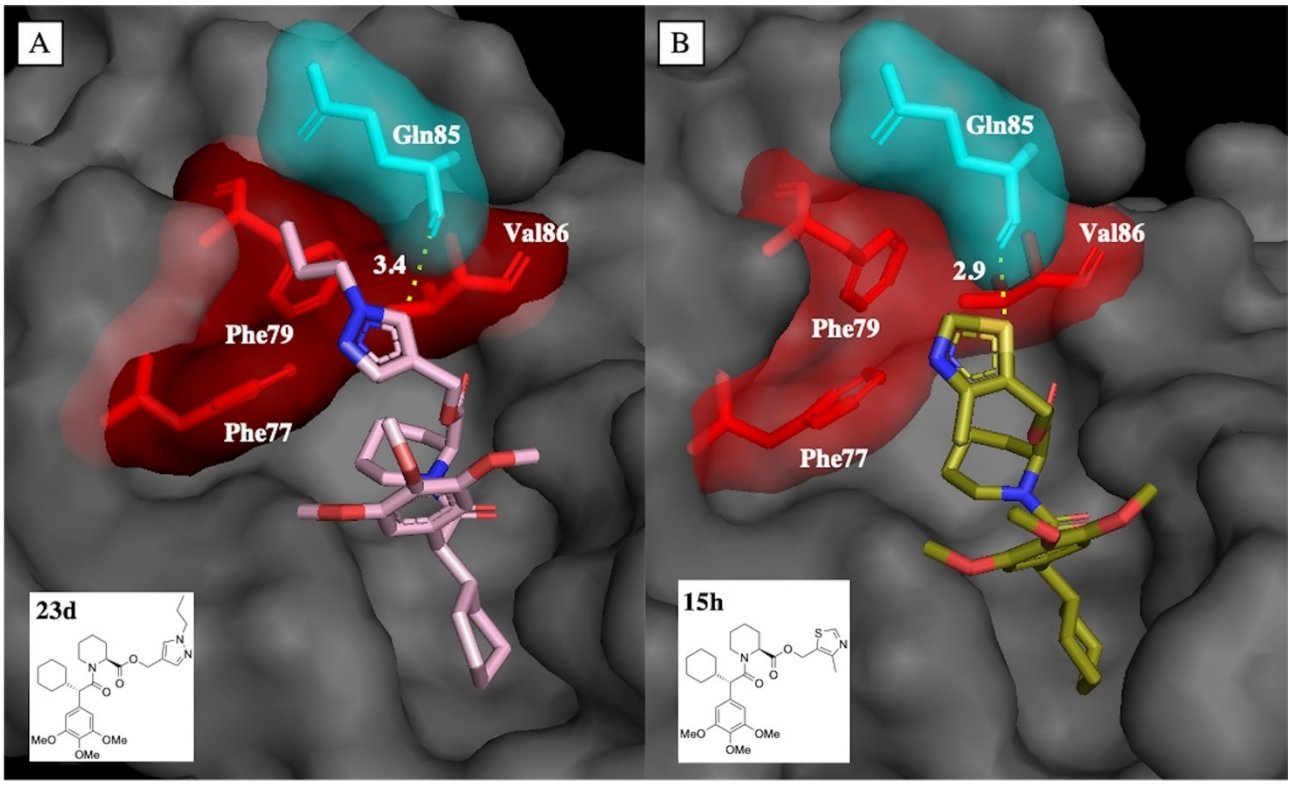



**Figure 3.** Cocrystal structure of the FK1 domain of FKBP51 with **23 d** (**A**, PDB: 9EUA, shown in light pink sticks), **15 h** (**B**, PDB: 9EU8, shown as olive sticks). The hydrophobic residues Phe77, Val78 and Phe79 are shown in red sticks, Gln85 is shown in cyan. The distance between the aromatic CH-hydrogen and the lone pair of the backbone carbonyl of Gln85, and the chalcogen bonds are indicated as yellow dotted lines. K121 was removed for better visualization.

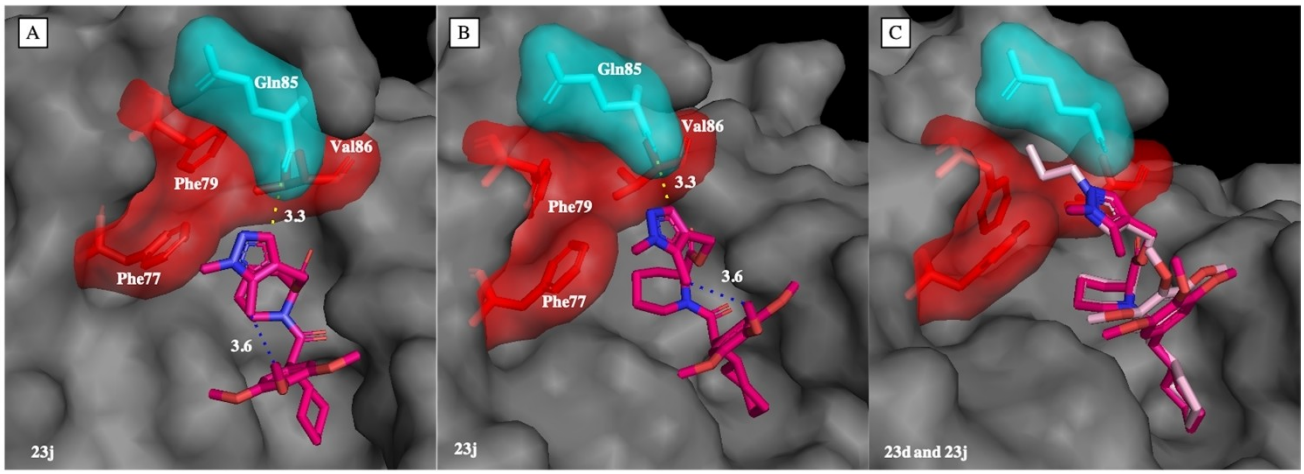



**Figure 4. A)** Cocrystal structure of **23 j** (PDB: 9EU6, shown as hot pink lines) viewed from the top. **B**) Compound **23 j** as in **A**), viewed from the side. **C)** Superposition of compound **23 d** (shown as light pink sticks, PDB: 9EUA) with **23 j** (shown as hot pink sticks, PDB: 9EU6). The hydrophobic residues Phe77, Val78 and Phe79 are shown in red sticks, Gln85 is shown in cyan. The distance of the van der Waals contact is shown as blue dotted line, while the distance between the aromatic CH-hydrogen and the lone pair of the backbone carbonyl of Gln85 is indicated as yellow dotted line. K121 was removed for better visualization.

All heterocyclic mimics of the phenyl group of SAFit1/2 stack on the edge of Phe77 and will benefit from the displacement of a unhappy water molecule that has repeatedly been observed in FKBP51 complexes.[18] All pyrazoles form a close contact with the backbone carbonyl of Gln85 (3.2-3.4 Å), with the CH-hydrogen pointing directly to the lone pair of the carbonyl group (Figure 3A and S1 A, S1B, S1 C, S1D). This interaction is replaced in the thiazoles **15 h** and **15 i** by a chalcogen bond from the sulfur to the carbonyl of Gln85 (2.7–3.0 Å) as seen in Figure 3B and S1E.

## Conclusions

FKBP51 is a promising target for several stress-related disorders, but so far it has been challenging to develop compounds with a desirable drug-like profile.[19] In this study we show that 1,4- and 1,3,4-pyrazolyl-containing analogues display promising binding affinities for FKBP51, with the best compound being the 1,4-analogue **23 d**, showing a $K_i$ of 0.077 μM. The substitution pattern analysis demonstrated that also 1,3,4-pyrazolyl moieties are tolerated (e.g., **23 h** and **23 i**), whereas the 1,4,5 substitution pattern is disfavored. Cocrystal structures with FKBP51 revealed that both the 1,4- and the 1,3,4-pyrazolyl analogues direct the alkyl chain of N1 in an optimal orientation for hydrophobic interactions at the surface of FKBP51, whereas 1,4,5-pyrazolyl derivatives as **23 j** fail to do so, thus explaining the 12-fold drop in binding affinity.

Despite the higher binding affinity of **23 i**, **23 d** was selected as the best compound of this series, based on the substantial improvements achieved in several key parameters (MW = 541.7 g/mol, cLogP = 3.72; tPSA = 92 Å$^2$; 9 HA, LE = 0.25) compared to the current gold standard SAFit2 (MW = 802 g/mol, cLogP = 6.59; tPSA = 114 Å$^2$; 12 HA, LE = 0.19),[1] suggesting it as a promising starting point for further optimization.

## Experimental Section

### Crystallization

Complexes were prepared by mixing FKBP51FK1 A19T, C103 A, C107I (14-140) at 7.5-15 mg/ml with a slight molar excess of ligand previously dissolved at 20 mM in DMSO. Crystallization was performed at room temperature using the hanging drop vapor-diffusion method, equilibrating mixtures of 1 μl protein complex and 1 μl reservoir against 500 μl reservoir solution. Crystals were obtained from reservoir solutions containing 12–18% PEG-3350, 0.1 M HEPES-NaOH pH 7.5, 0.2 M $NH_4$-acetate (**15 b**, **15 h**, **15 i** and **23 a**) or 0.2 M Na-thiocyanate (**23 b**, **23 c** and **24 e**) or 0.2 M $NH_4$-thioacetate (**23 d**) and for **23 a**, **23 b**, **23 c**, **23 d** and **24 e** additionally 10% ethylene glycol. Crystals with compound **23 j** were obtained from a reservoir solution containing 45% Pentaerythritol propoxylate 5/4 PO/OH and 15% ethanol. Crystals were fished and flash frozen in liquid nitrogen.

### Structure Solution and Refinement

The crystallographic experiments were performed on the BL14.1 and BL14.2 beamlines at the Helmholtz-Zentrum BESSY II synchrotron, Berlin, Germany as well as on the PX beamline at the Swiss Light Source (SLS), Villigen, Switzerland.[20] Diffraction data were integrated with XDS and further processed with the implemented programs of the CCP4i and CCP4i2 interface.[21–24] The data reduction was conducted with Aimless.[24–26] Crystal structures were solved by molecular replacement using Phaser.[27] Iterative model improvement and refinement were performed with Coot and Refmac5.[28–33] The dictionaries for the compounds were generated with AceDRG.[34] Residues facing solvent channels without detectable side chain density were truncated.

**General information**. Air and water-sensitive reactions were performed under an argon atmosphere with commercially available dry solvents. All commercially available chemicals and solvents were used as received. All reactions were monitored with TLC performed on precoated aluminum plates with a fluorescence indicator from Merck (silica gel 60 F254) or LCMS. Analytical LC–MS measurements were performed on an Agilent 1260 Infinity II System including a 1260 Infinity II flexible pump, a vial sampler, a multicolumn thermostat, and a diode array detector connected to a 6125B MSD single quadrupole detector or on a Beckman System Gold 125S Solvent Module with Beckman System Gold Diode Array Detector Module 168 equipped with Phenomenex Jupiter 4 μm Proteo 90 Å, 250×4.6 mm 4 micron. Eluents were 0.1% formic acid in water (Solvent A) and 0.1% formic acid in acetonitrile (Solvent B) or 95% $H_2O$, 5% MeCN, 0.1% TFA (Solvent A) and 95% MeCN, 5% $H_2O$, 0.1% TFA (Solvent B). The used methods were specified for each compound in the experimental section. Chromatographic separations were performed either by manual flash chromatography on silica ($SiO_2$) from Macherey-Nagel (particle size 0.04–0.063 mm) or by automated flash chromatography using a Biotage® Isolera One system with Biotage ® Sfär Silica HC D columns. Reverse phase purifications were performed with a Beckman System Gold Programmable Solvent Module 126 NMP equipped with a Phenomenex Jupiter 10 μm Proteo 90 Å, (250×21.2 mm 10 micron) or a Beckman Programmable Detector Module 166 using as eluents 95% $H_2O$, 5% MeOH, 0.1% TFA (solvent A) and 95% MeOH, 5% H2O, 0.1% TFA (solvent B).

$^1$H NMR spectra, $^{13}$C NMR spectra, 2D HSQC, HMBC, COSY, NOESY and $^{15}$N-$^1$H-HMBC were obtained from the NMR Department of the Technical University of Darmstadt, on a Bruker DRX 300 or 500 spectrometer at room temperature or 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. Proton chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the residual solvent ($^1$H: $CDCl_3$, δ = 7.26; DMSO-d6, δ = 2.50, MeOD, δ = 3.31; $^{13}$C: $CDCl_3$, δ = 77.16; DMSO-d6, δ = 39.52, MeOD, δ = 49.00). Coupling constants (J) are given in hertz (Hz). HRMS: mass spectra were recorded on an Impact II, quadrupol-time-of-flight spectrometer from Bruker Daltonics at TU Darmstadt or on a Bruker Daltonics MicrOTOF at MPI for Biochemistry (Microchemistry Core Facility).

All compounds had a purity > 95% as determined by reverse-phase HPLC (detection at 220 nm), unless otherwise noted. The compounds contained traces of the diastereomer (racemized at the alpha-C position of the pipecolate and determined by $^1$H-NMR). This is reported in the analytical sections for each compound. For three compounds the percentage of the wrong diastereomers were > 10%. To the best of our knowledge, the wrong diastereomers are inactive regarding binding to FKBP51 and do not interfere with the assay. The NMR analysis was complicated by rotamer signals of the pipecolyl amide bond in the $^1$H and $^{13}$C NMR spectra of all final compounds. Here we have only reported the signals corresponding to the major rotamer.

### Synthetic Procedures and Characterization Data

**General procedure A for the Steglich esterification (PPY, EDC-HCl)**: 4-(pyrrolidin-1-yl)pyridine (PPY, 4.00 equiv) and the corresponding alcohol (1.0 equiv) were added to a round bottom flask under argon. Precursor **7** (1.0 equiv) was dissolved in toluene and added to the previous reaction mixture. After stirring for 15 minutes at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 1.1 equiv) was added. The reaction mixture was stirred at 0 °C for 1 h, then warmed up to room temperature, and stirred overnight. After completion, the reaction was diluted with $H_2O$ and extracted with DCM (3×10 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced

pressure. The crude product was purified by flash column chromatography.

**General procedure B for the Steglich esterification (DIC, DMAP)**: Precursor **7** (1.00 equiv), the corresponding alcohol (1.0 equiv) and DMAP (3.0 equiv) were dissolved in DCM and the reaction mixture was cooled to 0 °C. While stirring, DIC (1.1 equiv) was added. Afterwards, the reaction mixture was warmed up to room temperature and stirred overnight. Upon completion, the reaction mixture was quenched with a 1 M solution of concentrated HCl, washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the crude product was purified by column flash chromatography.

**General procedure C for the Steglich esterification (EDC-HCl, DMAP)**: Precursor **7** (1.00 equiv), the corresponding alcohol (1.0 equiv), and DMAP (3.0 equiv) were dissolved in DCM and the reaction mixture was cooled to 0 °C. While stirring, EDC-HCl (1.1 equiv) was added and the reaction mixture was stirred from 0 °C to rt overnight. Upon complete conversion, the solvent was removed under reduced pressure and the crude was purified with flash column chromatography.

**General procedure D for the $NaBH_4$ reduction**: The corresponding aldehyde or ester (1.0 equiv) was added to a round-bottom flask, dissolved in THF (2.7 mL/mmol), and cooled to 0 °C. $NaBH_4$ (3.0 equiv) was dissolved in MeOH (1.8 mL/mmol) and added dropwise to the previous mixture. The reaction mixture was stirred while warming from 0 °C to rt until complete conversion as observed by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure, re-dissolved in $H_2O$ and extracted with EA (3×10 mL). The organic phases were combined, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the crude product was purified with column chromatography or used without further purification as specified.

**General procedure E for the $LiAlH_4$ reduction**: The carboxylic acid/ester (1.00 equiv) was added to a round-bottom flask under argon and dissolved in THF (0.15 M). The reaction mixture was cooled to 0 °C and $LiAlH_4$ (1.0 M in THF, 1.10 equiv) was added dropwise. The reaction mixture was warmed up to rt and stirred until complete conversion as monitored by TLC. Upon completion, the reaction was quenched by addition of a saturated aqueous solution of $Na_2SO_4$ and extracted with EA (3×10 mL). The organic phases were combined, washed with brine (1×20 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the obtained crude product was purified with flash column chromatography.

**General procedure F for the pyrazole alkylation ($K_2CO_3$ in acetone)**: **17** (1.0 equiv) and $K_2CO_3$ (5.0 equiv) were dissolved in acetone. Then, the corresponding alkyl bromide (1.0 equiv) was added dropwise and the reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified with flash column chromatography.

**General procedure G for the pyrazole alkylation**: ($Cs_2CO_3$ in acetone). **17** (300 mg, 2.14 mmol, 1.0 equiv) was dissolved in acetone at 0 °C. Then $Cs_2CO_3$ (1.5 equiv) the corresponding alkyl bromide (1.05 equiv) were added and the reaction mixture was stirred overnight, while warming from 0 °C to rt. The reaction mixture was filtered through celite and washed with EA (2×20 mL). The solvent was removed under reduced pressure and the crude product was used without further purification.

**General procedure H for TBS removal (TBAF)**: The TBS protected alcohol (33 mg, 0.05 mmol, 1.0 equiv) was dissolved in THF (0.03 M). The reaction mixture was cooled to 0 °C and then TBAF (1.0 equiv) was added. The reaction mixture was stirred at 0 °C until complete, then quenched with $H_2O$, and extracted with $Et_2O$ (3×10 mL). The organic phases were combined, washed with brine (1×10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

Compounds **8f**, **9g–j**, **10a–e**, **12d**, **13g**, **13j–k**, **14a–c**, **14f**, **14h–i**, **16**, **18k**, **20j**, **21h–l** and **21l–m** were commercially available.

### (S)-2-(3,4-Dimethoxyphenoxy)ethyl Piperidine-2-Carboxylat (25)

Synthesized as previously described in [13].

### (S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetic Acid (7)

Synthesized as previously described in [5].

### (S)-2-(3,4-Dimethoxyphenoxy)ethyl 1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (3)

**7** (37.0 mg, 0.12 mmol), HATU (46.1 mg, 0.12 mmol) and DIPEA were dissolved in DCM (0.5 mL). Then **25** (37.0 mg, 0.12 mmol), dissolved in DCM (0.5 mL), was added and stirred at rt overnight. After purification by flash column chromatography (CH/EA 1.5:1, v/v) the title compound was obtained as light-yellow oil (27.1 mg, 43.5 μmol, 36.3%). TLC (CH/EA, 1.5:1): $R_f = 0.27$. HPLC (0-100% Solvent B, 20 min): Rt = 21.1 min, purity (220 nm) = 98%. $^1$H NMR (400 MHz, DMSO-d6) δ 6.81 (d, J = 8.8 Hz, 1H), 6.58 (s, 2H), 6.49 (d, J = 2.8 Hz, 1H), 6.32 (dd, J = 8.7, 2.8 Hz, 1H), 5.17–5.14 (m, 1H), 4.19–4.12 (m, 2H), 4.04–3.96 (m, 2H), 3.87–3.79 (m, 1H), 3.71 (s, 3H), 3.69 (s, 6H), 3.68 (s, 3H), 3.63 (s, 3H), 3.55–3.47 (m, 1H), 2.85–2.76 (m, 2H), 2.09–1.99 (m, 2H), 1.92 (q, J = 10.9 Hz, 2H), 1.77–1.69 (m, 1H), 1.64–1.53 (m, 4H), 1.25–1.04 (m, 5H), 0.97–0.86 (m, 1H), 0.84–0.74 (m, 1H). $^{13}$C NMR (101 MHz, DMSO-d6) δ 172.17, 170.74, 152.55, 152.42, 149.66, 143.35, 136.02, 133.60, 112.72, 105.88, 104.33, 100.94, 65.96, 62.75, 59.89, 56.07, 55.73, 55.40, 53.04, 51.84, 39.52, 31.89, 29.81, 26.54, 26.34, 26.12, 25.65, 25.04, 24.21, 20.53. HRMS: calculated 600.3173 $[M+H]^+$, found 600.3189 $[M+H]^+$.

### (S)-3-(2-Morpholinoethoxy)benzyl 1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (4)

To a solution of **26** (200 mg, 0.57 mmol, 1.00 equiv) and **27** (149 mg, 0.63 mmol, 1.10 equiv) in DCM was added DMAP (6.95 mg, 0.06 mmol, 0.10 equiv) and EDC (120 mg, 0.63 mmol, 1.10 equiv) at 0 °C. The reaction mixture was then stirred at room temperature for 16 h. Purification by flash column chromatography (0-10% MeOH in CH/EA 1:1, v/v) gave the intermediate 1-((9H-fluoren-9-yl)methyl) 2-(3-(2-morpholinoethoxy)benzyl) (S)-piperidine-1,2-dicarboxylate. Fmoc deprotection was conducted in a 10% solution of 4-methylpiperidine in DCM (5 mL) at room temperature for 16 h. The solvent was removed under vacuo and the title compound **28** was obtained as yellow oil (172 mg, 87%) after purification by flash chromatography (0-10% MeOH in DCM). TLC [MeOH/DCM, 2:8]: Rf = 0.36. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 1H), 6.97–6.80 (m, 3H), 5.18–5.02 (m, 2H), 4.71–4.61 (m, 1H), 4.16–4.07 (m, 2H), 3.75–3.72 (m, 4H), 3.44 (dd, J = 10.0, 3.3 Hz, 1H), 3.14–3.08 (m, 1H), 2.80 (td, J = 5.7, 0.6 Hz, 3H), 2.72–2.63 (m, 1H), 2.60–2.56 (m, 4H), 2.05–1.94 (m, 1H), 1.85–1.71 (m, 1H), 1.65–1.38 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 172.97, 158.94, 158.81, 142.62, 137.18, 129.64, 129.58, 120.60, 119.25, 114.41, 114.36, 113.78, 112.94, 66.87, 66.86, 66.39, 65.73, 65.70, 65.13, 58.40, 57.61, 57.58, 54.05, 45.50, 29.68, 28.93, 25.49, 23.87.

**28** (35.0 mg, 0.10 mmol, 1.00 equiv), **7** (31.0 mg, 0.10 mmol, 1.00 equiv), HATU (57.3 mg, 0.15 mmol, 1.50 equiv) and DIPEA (70.2 μL, 0.40 mmol, 0.90 equiv) were stirred in DCM (1 mL) at room temperature for 3 h. After purification by preparative HPLC (65-75% B) the title compound **4** was obtained as colorless oil (12 mg, 20%). TLC (DCM + 1% MeOH): $R_f$ = 0.39; $^1$H NMR (599 MHz, DMSO-d6) δ 7.02–6.95 (m, 1H), 6.92–6.86 (m, 2H), 6.76–6.72 (m, 1H), 6.57 (s, 2H), 5.20–5.15 (m, 2H), 4.35–4.28 (m, 3H), 4.09–4.04 (m, 1H), 3.73–3.64 (m, 9H), 3.61–3.57 (m, 4H), 3.11–3.01 (m, 4H), 2.08–1.98 (m, 2H), 1.94–1.84 (m, 2H), 1.74–1.66 (m, 1H), 1.62–1.49 (m, 6H), 1.47–1.43 (m, 1H), 1.38–1.30 (m, 1H), 1.12–1.00 (m, 4H), 0.96–0.85 (m, 2H), 0.83–0.76 (m, 1H), 0.70–0.60 (m, 1H).$^{13}$C NMR (75 MHz, DMSO-d6) δ 172.66, 171.05, 157.91, 152.89, 138.16, 136.48, 134.12, 130.11, 120.68, 114.29, 106.33, 63.72, 60.37, 56.40, 56.20, 52.19, 46.18, 32.33, 26.57, 26.11. HPLC (0-100% Solvent B, 20 min): Rt = 16.2 min, purity (220 nm) = 100%. HRMS (ESI+): m/z: calculated 639.3645 $[M+H]^+$, found 639.3641 $[M+H]^+$.

### (S)-Benzyl 1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)Piperidine-2-Carboxylate (5)

**29** (100 mg, 0.44 mmol, 1.00 equiv), **30** (75.3 mg, 0.44 mmol, 1.00 equiv), NaI (32.7 mg, 0.22 mmol, 0.50 equiv) and DBU (329 μL, 2.18 mmol, 5.00 equiv) were stirred in DMF (5 mL) at room temperature for 16 h. The reaction mixture was diluted with $Et_2O$ and washed with brine. The organic layer was then dried over $MgSO_4$, filtered and the solvent was removed under vacuo. Purification by flash column chromatography (EA/CH = 0–5%) gave intermediate 2-benzyl 1-(tert-butyl) (S)-piperidine-1,2-dicarboxylate which was subjected to Boc-deprotection in TFA/DCM (4.0 mL, 1:1 v/v) at room temperature for 1 h. The reaction mixture was then quenched with $NaHCO_3$. In the following step the product was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under vacuo. After purification by flash chromatography (MeOH/DCM = 0–5%) the title compound **32** was obtained as colorless oil (50.9 mg, 54%). TLC (DCM + 5% MeOH): $R_f$ = 0.16. $^1$H NMR (599 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 5.19–5.10 (m, 2H), 3.40 (dd, J = 10.1, 3.3 Hz, 1H), 3.07 (dtd, J = 12.3, 3.8, 1.3 Hz, 1H), 2.69–2.59 (m, 1H), 1.99–1.92 (m, 1H), 1.80–1.72 (m, 1H), 1.61–1.49 (m, 2H), 1.47–1.39 (m, 2H). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 173.29, 135.73, 128.53, 128.25, 128.18, 66.46, 58.60, 45.68, 29.13, 25.77, 24.00.

Precursor **7** (40.0 mg, 0.13 mmol, 1.00 equiv), **31** (34.1 mg, 0.16 mmol, 1.20 equiv), HATU (54.3 mg, 0.14 mmol, 1.10 equiv) and DIPEA (68.0 μl, 0.39 mmol, 3 equiv) were stirred in DMF (1.5 mL) at room temperature for 16 h. The reaction mixture was diluted with $Et_2O$ and washed with brine. Then the organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuo. After purification by flash chromatography (0-15% EA in CH) the title compound **5** was obtained as colorless oil (36 mg, 55%). TLC (CH/EA = 4:1, v/v): $R_f$ = 0.19; $^1$H NMR (599 MHz, $CDCl_3$) δ 7.39–7.32 (m, 2H), 7.13–7.08 (m, 2H), 6.47 (s, 2H), 6.41 (s, 1H), 5.43–5.38 (m, 1H), 5.21 (d, J = 2.7 Hz, 1H), 5.13–5.04 (m, 1H), 4.98–4.90 (m, 1H), 3.93–3.85 (m, 1H), 3.82–3.79 (m, 9H), 3.35 (d, J = 9.7 Hz, 1H), 2.93–2.82 (m, 1H), 2.28–2.21 (m, 1H), 2.10–2.05 (m, 1H), 1.68–1.54 (m, 7H), 1.35–1.27 (m, 2H), 1.16–1.05 (m, 2H), 0.94–0.85 (m, 1H), 0.74 (qd, J = 12.1, 3.4 Hz, 1H), 0.66–0.57 (m, 1H). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 172.52, 170.97, 152.91, 128.63, 128.41, 128.02, 127.61, 105.77, 66.34, 60.80, 56.25, 56.11, 55.10, 52.24, 43.62, 41.27, 32.83, 30.71, 26.81, 26.56, 26.21, 25.48, 20.97. HPLC (50-100% Solvent B, 20 min): Rt = 17.1 min, purity (220 nm) = 98%.

**Ethyl 1-methyl-1H-imidazole-5-carboxylate (9f)**. The commercially available 1-methyl-1H-imidazole-5-carboxylic acid (**8f**) (300 mg, 2.38 mmol, 1.00 equiv.) was dissolved in EtOH (3 mL) and concentrated $H_2SO_4$ acid (0.50 mL, 9 mmol, 3.00 equiv) was added. The reaction mixture was heated at reflux for 24 hours. Upon completion, the solvent was removed under reduced pressure, the residue was neutralized with a saturated solution of $NaHCO_3$ and extracted with EA (3×10 mL). The organic phases were combined and dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **9f** (1.2 g, 96%). TLC (DCM/MeOH = 9:1, v/v): $R_f$ = 0.58; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.74 (s, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 160.12, 142.10, 135.74, 123.58, 60.88, 34.56, 14.38. HPLC (5–100% solvent B, 3 min) Rt = 0.782 min, purity (220 nm): > 99%.

**(1-methyl-1H-imidazol-5-yl)methanol (10f). 10f** was synthesized following the general procedure E starting from **9f** (100 mg, 0.65 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 0.70 mL, 0.70 mmol, 1.00 equiv) in THF (5 mL), stirring overnight. **10f** (56 mg, 78%) was obtained without further purification. TLC (DCM/MeOH = 9:1, v/v): $R_f$ = 0.13. $^1$H NMR (500 MHz, DMSO) δ 7.52 (d, J = 1.0 Hz, 1H), 6.77 (d, J = 1.1 Hz, 1H), 4.42 (s, 2H), 3.61 (s, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 138.94, 132.31, 127.57, 52.96, 31.39.

### (1-Ethyl-1H-Imidazol-2-Yl)methanol (10g)

**10g** was synthesized following the general procedure D with the commercially available 1-ethyl-1H-imidazole-2-carbaldehyde (**9g**) (212 mg, 1.71 mmol, 1.00 equiv) and $NaBH_4$ (122 mg, 3.22 mmol, 2.00 equiv) in MeOH (17 mL) and THF (8.5 mL). The crude product was purified with flash column chromatography (DCM/MeOH = 10:1, v/v) to yield **10g** (138 mg, 64%). TLC (DCM/MeOH = 10:1, v/v): $R_f$ = 0.19; $^1$H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, J = 3.0 Hz, 1H), 6.80 (d, J = 3.0 Hz, 1H), 5.63 (s, 1H), 4.58 (s, 2H), 4.03 (q, J = 7.3 Hz, 2H), 1.39 (t, J = 7.3 Hz, 3H).$^{13}$C NMR (75 MHz, $CDCl_3$) δ 147.57, 126.62, 119.28, 55.52, 40.95, 16.35.

### Isothiazol-4-Ylmethanol 14d (10h)

**10h** was synthesized following the general procedure E starting from the commercially available isothiazole-4-carboxylic acid (**9h**) (100 mg, 0.77 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 1.20 mL, 0.77 mmol, 1.00 equiv) in THF (5 mL), stirring for 2 h. **10h** (19 mg, 21%) was obtained after purification with flash column chromatography (CH/EA = 3:1, v/v). TLC (CH/EA = 1:1, v/v): $R_f$ = 0.25; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J = 0.8 Hz, 1H), 8.49 (s, 1H), 4.82 (d, J = 0.9 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 156.90, 144.81, 139.41, 58.03.

### Isoxazol-4-Ylmethanol (10i)

The commercially available isoxazole-4-carboxylic acid (**9i**) (50 mg, 0.44 mmol, 1.00 equiv) was dissolved in THF (7 mL) and the reaction mixture was cooled at 0 °C. Then, borane dimethyl sulfide complex (2 M in THF, 0.40 mL, 0.66 mmol, 1.50 equiv) was added dropwise and the reaction mixture was stirred from 0 °C to rt overnight. Upon completion, the reaction mixture was quenched with $H_2O$ and extracted with EA (3×10 mL). The organic phases were combined and washed with brine (1×20 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified with column chromatography (1:1 CH-EA, v/v) to yield **10i** (25 mg, 57%). TLC (CH/EA = 1:1 + 1% HCOOH, v/v/v): $R_f$ = 0.27; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 1.0 Hz, 1H), 8.32 (s, 1H), 4.64 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 155.17, 149.24, 119.56, 54.16. GC-MS: (splitless 10 min) Rt = 3.545, purity > 99%.

### (4-Chloro-1-Methyl-1H-Pyrazol-3-Yl)methanol (10 j)

**10 j** was synthesized following the general procedure D starting from the commercially available 4-chloro-1-methyl-1H-pyrazole-3-carbaldehyde (**9 j**) (200 mg, 1.38 mmol, 1.00 equiv) and $NaBH_4$ (104 mg, 2.76 mmol, 2.00 equiv) in THF (6.9 mL) and MeOH (13.5 mL). **10 j** (94 mg, 46 %) was obtained after purification by flash column chromatography (DCM/MeOH = 25 : 1 v/v). TLC (CH/EA 1 : 3, v/v): $R_f$ = 0.29; $^1$H NMR (300 MHz, $CDCl_3$) δ = 7.29 (s, 1H), 4.62 (d, 2H), 3.81 (s, 3H), 3.12 (t, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ = 148.47, 128.84, 108.41, 55.97, 39.45. HPLC (5–100 % solvent B, 3 min) Rt = 0.678 min, purity (220 nm): > 99 %.

### Thiophen-2-Ylmethyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 a)

The substrate **11 a** was synthesized following the general procedure B with precursor **7** (16 mg, 0.04 mmol, 1.00 equiv), the commercially available thiophen-2-ylmethanol (**10 a**) (4 μL, 4.9 mg, 0.04 mmol, 1.00 equiv), DMAP (13.90 mg, 0.11 mmol, 3.00 equiv) and DIC (6.5 μL, 5.3 mg, 0.04 mmol, 1.10 equiv) in DCM (1 mL). **11 a** (8 mg, 41 %) was obtained after purification by flash column chromatography (CH/EA = 7 : 1, v/v). TLC (CH/EA = 3 : 1 v/v): $R_f$ = 0.50; Diastereomer ratio: 8 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.25–7.23 (m, 1H), 6.91 (d, J = 3.9 Hz, 2H), 6.47 (s, 2H), 5.39–5.36 (m, 1H), 5.23 (d, J = 12.8 Hz, 1H), 5.10 (d, J = 12.8 Hz, 1H), 3.92–3.86 (m, 1H), 3.83 (d, J = 3.5 Hz, 9H), 3.36 (d, J = 9.6 Hz, 1H), 2.89 (td, J = 13.2, 3.0 Hz, 1H), 2.28–2.21 (m, 1H), 2.08 (qd, J = 11.0, 3.4 Hz, 1H), 1.86 (t, J = 13.8 Hz, 1H), 1.72–1.52 (m, 4H), 1.42 (dt, J = 12.9, 4.0 Hz, 1H), 1.38–1.25 (m, 2H), 1.24–1.18 (m, 1H), 1.17–1.03 (m, 1H), 0.91 (qd, J = 12.5, 3.5 Hz, 1H), 0.77 (td, J = 12.3, 3.1 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.74, 171.05, 153.11, 137.96, 137.05, 133.59, 127.86, 126.81, 126.74, 106.15, 60.99, 56.47, 56.36, 55.28, 52.39, 43.79, 41.38, 32.99, 30.91, 26.97, 26.75, 26.41, 26.38, 25.65, 21.12. HPLC (40–60 % solvent B, 1.5 mL/min, 20 min): Rt = 15.54 min, purity (220 nm) = 99 %. HRMS (ESI+): m/z: 516.24144 calculated $[M+H]^+$, found 516.24136 $[M+H]^+$.

### Thiazol-5-Ylmethyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15 a)

The substrate **15 a** was synthesized following the general procedure B with precursor **7** (40 mg, 0.09 mmol, 1.00 equiv), the commercially available thiazol-5-yl metanol (**14 a**) (8.26 μL, 10.90 mg, 0.09 mmol, 1.00 equiv), DMAP (34.8 mg, 0.28 mmol, 3.00 equiv) and DIC (16.30 μL, 13.3 mg, 0.10 mmol, 1.10 equiv) in DCM (1 mL). **15 a** (18 mg, 37 %) was obtained after purification by flash column chromatography (CH/EA = 2 : 1, v/v). TLC (DCM/MeOH = 50 : 1 v/v): $R_f$ = 0.15; Diastereomer ratio: 14 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.75 (t, J = 0.9 Hz, 1H), 6.46 (d, J = 0.9 Hz, 2H), 5.37–5.34 (m, 1H), 5.27 (dd, J = 12.9, 0.9 Hz, 1H), 5.15 (dd, J = 13.0, 0.9 Hz, 1H), 3.89–3.86 (m, 1H), 3.85 (d, J = 1.0 Hz, 3H), 3.83 (d, J = 1.0 Hz, 6H), 3.35 (d, J = 9.6 Hz, 1H), 2.84 (td, J = 13.2, 3.0 Hz, 1H), 2.23–2.17 (m, 1H), 2.13–2.01 (m, 1H), 1.85 (d, J = 12.6 Hz, 1H), 1.72–1.53 (m, 7H), 1.42 (dddd, J = 17.2, 12.9, 8.3, 4.0 Hz, 1H), 1.37–1.05 (m, 4H), 0.96–0.85 (m, 1H), 0.75 (td, J = 12.2, 9.0 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.83, 171.02, 154.77, 153.16, 143.62, 137.11, 133.51, 132.62, 106.13, 61.00, 58.22, 56.39, 55.28, 52.37, 43.82, 41.35, 32.95, 30.86, 26.82, 26.71, 26.36, 26.35, 25.54, 21.08. HPLC (50–55 % solvent B, 1.5 mL/min, 20 min): Rt = 8.97 min, purity (220 nm) = 99 %. HRMS (ESI+): m/z: 517.23668 calculated $[M+H]^+$, found 517.23702 $[M+H]^+$.

### Thiazol-2-Ylmethyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 b)

The substrate **11 b** was synthesized following the general procedure C with precursor **7** (20 mg, 0.05 mmol, 1.00 equiv), the commercially available thiazol-2-yl methanol **10 b** (5.7 mg, 0.05 mmol, 1.00 equiv), DMAP (17.5 mg, 0.14 mmol, 3.00 equiv) and EDC-HCl (10.1 mg, 0.05 mmol, 1.10 equiv) in DCM (1 mL). **11 b** (18 mg, 73 %) was obtained after purification by flash column chromatography (CH/EA = 3 : 1, v/v). TLC (CH/EA = 2 : 1 v/v): $R_f$ = 0.23; Diastereomer ratio: 12 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, J = 3.2, 1.2 Hz, 1H), 7.31 (dd, J = 3.3, 1.3 Hz, 1H), 6.50 (d, J = 1.2 Hz, 2H), 5.49–5.46 (m, 1H), 5.39–5.35 (m, 1H), 5.33 (dd, J = 13.7, 1.2 Hz, 1H), 4.01–3.95 (m, 1H), 3.85 (d, J = 1.2 Hz, 3H), 3.83 (d, J = 1.2 Hz, 6H), 3.40 (d, J = 9.6 Hz, 1H), 3.04–2.98 (m, 1H), 2.35–2.28 (m, 1H), 2.16–2.06 (m, 1H), 1.89 (d, J = 12.5 Hz, 1H), 1.79–1.58 (m, 6H), 1.48 (qt, J = 12.8, 3.8 Hz, 1H), 1.43–1.30 (m, 2H), 1.29–1.20 (m, 2H), 1.16 (dq, J = 13.0, 6.6 Hz, 1H), 0.99–0.89 (m, 1H), 0.78 (qd, J = 12.3, 3.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.87, 170.76, 164.79, 153.15, 142.77, 137.08, 133.56, 120.28, 106.13, 63.30, 60.97, 56.32, 55.25, 52.39, 43.88, 41.47, 32.95, 30.87, 26.95, 26.71, 26.37, 26.34, 25.61, 21.15. HPLC (40–60 % solvent B, 1.5 mL/min, 20 min): Rt = 10.97 min, purity (220 nm) = 99 %. HRMS (ESI+): m/z: 517.23668 calculated $[M+H]^+$, found 517.23744 $[M+H]^+$.

### Thiazol-4-Ylmethyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 c)

The substrate **11 c** was synthesized following the general procedure B with precursor **7** (15 mg, 0.04 mmol, 1.00 equiv), the commercially available thiazol-4-yl metanol **10 c** (4.2 mg, 0.037 mmol, 1.00 equiv), DMAP (13.4 mg, 0.11 mmol, 3.00 equiv) and DIC (6.3 μL, 5.1 mg, 0.04 mmol, 1.10 equiv) in DCM (1 mL). **11 c** (12 mg, 63 %) was obtained after purification by flash column chromatography (CH/EA = 2 : 1, v/v). TLC (CH/EA = 1 : 1 v/v): $R_f$ = 0.32; Diastereomer ratio: 16 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J = 2.0 Hz, 1H), 6.94 (dt, J = 1.9, 0.9 Hz, 1H), 6.49 (s, 2H), 5.43 (q, J = 2.3 Hz, 1H), 5.25 (dd, J = 13.4, 1.0 Hz, 1H), 5.20 (dd, J = 13.4, 1.0 Hz, 1H), 3.99–3.93 (m, 1H), 3.83 (s, 3H), 3.79 (s, 6H), 3.38 (d, J = 9.8 Hz, 1H), 3.01–2.94 (m, 1H), 2.31–2.26 (m, 1H), 2.09 (q, J = 10.3 Hz, 1H), 1.87 (d, J = 12.6 Hz, 1H), 1.74–1.53 (m, 7H), 1.45 (dtt, J = 16.7, 7.9, 3.9 Hz, 1H), 1.34 (tq, J = 13.1, 4.6 Hz, 2H), 1.23–1.08 (m, 2H), 0.97–0.88 (m, 1H), 0.75 (qd, J = 12.1, 3.3 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.87, 171.01, 153.31, 153.16, 152.19, 137.07, 133.64, 116.08, 106.05, 62.54, 61.00, 56.30, 55.19, 52.50, 43.92, 41.54, 32.93, 30.87, 26.93, 26.72, 26.36, 26.33, 25.65, 21.12. HPLC (50–80 % solvent B, 1.5 mL/min, 20 min): Rt = 10.7 min, purity (220 nm) = 96 %. HRMS (ESI+): m/z: 517.23668 calculated $[M+H]^+$, found 517.23671 $[M+H]^+$.

### Oxazol-5-Ylmethyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 d)

The substrate **11 d** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), the commercially available oxazol-5-yl methanol **10 d** (12 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **11 d** (24 mg, 40 %) was obtained after purification by flash column chromatography (CH/EA = 1 : 1 + 1 % HCOOH, v/v/v). TLC (CH/EA = 1 : 1 + 1 % HCOOH, v/v/v): $R_f$ = 0.34; Diastereomer ratio: 28 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.01 (s, 1H), 6.44 (s, 2H), 5.32 (dd, J = 5.9, 2.6 Hz, 1H), 5.07 (d, J = 13.4 Hz, 1H), 4.98 (d, J = 13.5 Hz, 1H), 3.89–3.85 (m, 1H), 3.82 (d, J = 3.9 Hz, 9H), 3.34 (d, J = 9.6 Hz, 1H), 2.86 (td, J = 13.1, 3.1 Hz, 1H), 2.23–2.13 (m, 1H), 2.06 (qt, J = 11.5, 3.2 Hz, 2H), 1.83 (t, J = 13.2 Hz, 1H), 1.72–1.52 (m, 6H), 1.41 (qt, J = 12.8, 4.1 Hz, 1H), 1.35–1.25 (m, 2H), 1.19–1.04 (m, 2H), 0.95–0.83

(m, 1H), 0.76–0.70 (m, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.84, 170.80, 153.08, 151.79, 146.87, 136.96, 133.40, 126.71, 106.00, 60.96, 56.30, 55.73, 55.32, 52.41, 43.76, 41.28, 32.94, 30.83, 26.84, 26.69, 26.34, 26.34, 25.50, 21.07. HPLC (30–100% solvent B, 3 min) Rt = 1.757 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 501.25953 calculated $[M+H]^+$, found 501.26074 $[M+H]^+$.

### Oxazol-4-Ylmethyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 e)

The substrate **11 e** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv) the commercially available oxazol-4-ylmethanol **10 e** (12 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **11 e** (28 mg, 46%) was obtained after purification by flash column chromatography (CH/EA = 1 : 1, v/v). TLC (CH/EA = 1 : 1 v/v): $R_f$ = 0.24; Diastereomer ratio: 38 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 1.0 Hz, 1H), 7.38 (t, J = 1.0 Hz, 1H), 6.45 (s, 2H), 5.37–5.33 (m, 1H), 5.01 (dd, J = 13.1, 1.0 Hz, 1H), 4.94 (dd, J = 13.1, 1.0 Hz, 1H), 3.95–3.89 (m, 1H), 3.82–3.81 (m, 3H), 3.80 (s, 6H), 3.36 (d, J = 9.7 Hz, 1H), 2.95 (td, J = 13.2, 2.9 Hz, 1H), 2.27–2.19 (m, 1H), 2.11–2.02 (m, 1H), 1.83 (t, J = 13.7 Hz, 1H), 1.71–1.52 (m, 8H), 1.43 (qt, J = 12.8, 3.9 Hz, 1H), 1.36–1.23 (m, 2H), 1.22–1.03 (m, 1H), 0.90 (dddd, J = 14.7, 12.4, 9.0, 3.3 Hz, 1H), 0.74 (qd, J = 12.4, 3.6 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.71, 170.88, 152.95, 151.19, 137.84, 136.97, 135.50, 133.39, 105.82, 60.82, 58.51, 56.14, 55.05, 52.31, 43.69, 41.27, 32.76, 30.70, 26.76, 26.56, 26.21, 26.19, 25.44, 20.95. HPLC (30–100% solvent B, 3 min) Rt = 1.775 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 501.25953 calculated $[M+H]^+$, found 501.26066 $[M+H]^+$.

### (1-Methyl-1H-Imidazol-5-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 f)

The substrate **11 f** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), **10 f** (12 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **11 f** (16 mg, 61%) was obtained after purification by flash column chromatography (CH/EA = 2 : 1, v/v). TLC (DCM/MeOH = 9 : 1, v/v): $R_f$ = 0.46; Diastereomer ratio: 11 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.54–8.51 (m, 1H), 7.62–7.58 (m, 1H), 6.46 (s, 2H), 5.36–5.33 (m, 1H), 5.09 (d, J = 13.2 Hz, 1H), 4.90 (d, J = 13.3 Hz, 1H), 3.93–3.88 (m, 1H), 3.91 (dt, J = 13.6, 3.5 Hz, 1H), 3.81 (s, 9H), 3.34 (d, J = 9.8 Hz, 1H), 3.29 (s, 3H), 2.84 (td, J = 13.3, 3.0 Hz, 1H), 2.20 (p, J = 7.6 Hz, 1H), 2.11–2.02 (m, 1H), 1.83 (d, J = 12.8 Hz, 1H), 1.72–1.54 (m, 7H), 1.42 (qt, J = 12.7, 3.9 Hz, 1H), 1.36–1.21 (m, 2H), 1.19–0.99 (m, 1H), 0.93–0.84 (m, 1H), 0.74 (qd, J = 12.2, 3.4 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.55, 170.75, 152.98, 150.49, 145.91, 136.72, 133.64, 112.84, 105.68, 60.86, 56.18, 55.53, 54.89, 52.24, 47.49, 43.77, 41.38, 32.73, 30.72, 26.77, 26.53, 26.19, 26.17, 25.49, 20.99. HPLC (5–100% solvent B, 3 min) Rt = 1.754 min, purity (220 nm): 98%. HRMS (ESI+): m/z: 514.29116 calculated $[M+H]^+$, found 514.29127 $[M+H]^+$.

### (1-Ethyl-1H-Imidazol-5-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 g)

The substrate **11 g** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv) and the corresponding alcohol **10 g** (20 mg, 0.16 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.1 equiv) in toluene (3 mL). **11 g** (19 mg, 30%) was obtained after purification by flash column chromatography (DCM/MeOH = 25 : 1, v/v). TLC (DCM/MeOH = 25 : 1, v/v): $R_f$ = 0.14; Diastereomer ratio: 19 : 1. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, J = 1.3 Hz, 1H), 6.88 (d, J = 1.3 Hz, 1H), 6.44 (s, 2H), 5.38–5.34 (m, 1H), 5.16 (d, J = 13.0 Hz, 1H), 5.07 (d, J = 13.1 Hz, 1H), 3.94 (d, J = 3.5 Hz, 1H), 3.81 (s, 9H), 3.75 (qd, J = 7.3, 5.8 Hz, 2H), 3.36 (d, J = 9.7 Hz, 1H), 3.07–2.95 (m, 1H), 2.21 (d, J = 13.5 Hz, 1H), 2.03 (t, J = 10.6 Hz, 1H), 1.82 (d, J = 12.2 Hz, 1H), 1.65 (dd, J = 15.8, 11.2 Hz, 8H), 1.28 (t, J = 7.3 Hz, 3H), 1.22–1.00 (m, 3H), 0.90 (qd, J = 12.1, 3.2 Hz, 1H), 0.73 (q, J = 11.7 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.92, 170.76, 153.03, 141.34, 136.86, 133.70, 128.06, 120.40, 105.87, 60.95, 58.22, 56.24, 54.93, 52.41, 43.85, 41.55, 41.04, 32.82, 30.88, 27.03, 26.65, 26.33, 25.58, 21.13, 16.23. HPLC (30–100% solvent B, 3 min) Rt = 1.884 min, purity (220 nm): 99%. HRMS (ESI+): m/z: 528.30681 calculated $[M+H]^+$, found 528.30730 $[M+H]^+$.

### Isothiazol-4-Ylmethyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 h)

The substrate **11 h** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv) the corresponding alcohol **10 h** (14 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **11 h** (27 mg, 43%) was obtained after purification by flash column chromatography (CH/EA = 3 : 1, v/v). TLC (CH/EA = 3 : 1, v/v): $R_f$ = 0.17; Diastereomer ratio: 21 : 1 (determined from the aromatic peaks of the isothiazole). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.35–8.32 (m, 2H), 6.50 (d, J = 1.4 Hz, 2H), 5.41–5.37 (m, 1H), 5.19 (d, J = 12.8 Hz, 1H), 5.03 (d, J = 12.8 Hz, 1H), 3.93 (d, J = 13.6 Hz, 1H), 3.86–3.82 (m, 9H), 3.38 (d, J = 9.7 Hz, 1H), 2.86–2.79 (m, 1H), 2.23 (d, J = 13.4 Hz, 1H), 2.16–2.04 (m, 1H), 1.88 (d, J = 12.8 Hz, 1H), 1.74–1.55 (m, 8H), 1.37–1.29 (m, 1H), 1.27–1.05 (m, 3H), 0.92 (qd, J = 12.3, 3.6 Hz, 1H), 0.77 (qd, J = 11.9, 3.0 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.68, 170.94, 156.97, 153.00, 146.68, 136.83, 133.99, 133.44, 105.86, 60.88, 58.82, 56.20, 55.08, 52.26, 43.74, 41.25, 32.79, 30.69, 26.62, 26.56, 26.20, 26.17, 25.40, 20.94. HPLC (5–100% solvent B, 3 min) Rt = 2.215 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 517.23668 calculated $[M+H]^+$, found 517.23683 $[M+H]^+$.

### Isoxazol-4-Ylmethyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 i)

The substrate **11 i** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), the corresponding alcohol **10 i** (12 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **11 i** (31 mg, 54%) was obtained after purification by flash column chromatography (CH/EA = 1 : 1, v/v). TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.37; Diastereomer ratio: 14 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.13 (s, 1H), 6.49 (s, 2H), 5.34 (dd, J = 6.1, 2.5 Hz, 1H), 4.99 (d, J = 12.8 Hz, 1H), 4.81 (d, J = 12.8 Hz, 1H), 3.92 (dt, J = 13.7, 3.7 Hz, 1H), 3.84 (d, J = 2.8 Hz, 9H), 3.37 (d, J = 9.7 Hz, 1H), 2.79 (td, J = 13.1, 3.1 Hz, 1H), 2.23–2.17 (m, 1H), 2.15–2.07 (m, 1H), 1.87 (dp, J = 12.6, 3.4 Hz, 1H), 1.73–1.55 (m, 7H), 1.44 (dt, J = 12.9, 4.0 Hz, 1H), 1.34 (dt, J = 12.4, 3.1 Hz, 1H), 1.23–1.08 (m, 3H), 0.91 (qd, J = 12.4, 3.4 Hz, 1H), 0.77 (qd, J = 12.1, 3.3 Hz, 1H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.72, 171.07, 156.94, 152.99, 149.51, 136.84, 133.36, 114.81, 105.91, 60.87, 56.23, 55.12, 55.07, 52.25, 43.74, 41.15, 32.78, 30.67, 26.55, 26.52, 26.20, 26.16, 25.35, 20.90.HPLC (5–100% solvent B, 3 min) Rt = 2.180 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 501.25953 calculated $[M+H]^+$, found 501.25983 $[M+H]^+$.

### (S)-Prop-2-Yn-1-yl 1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (34)

(S)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (**29**) (0.15 mL, 2.6 mmol, 1.00 equiv), prop-2-yn-1-ol (**32**) (0.65 g, 2.9 mmol, 1.10 equiv), EDC (0.55 g, 2.9 mmol, 1.10 equiv) and DMAP (63.0 mg, 0.52 mmol, 0.20 equiv) were stirred in DCM (10 mL) at room temperature for 16 h. After purification by flash column chromatography (EA/CH = 0-10 %) Boc deprotection was conducted in DCM/TFA (8 mL, 1 : 1 v/v) for 1 h at rt. The reaction mixture was quenched with saturated $NaHCO_3$ solution and the product extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under vacuo. The crude product was purified by flash chromatography (0-5 % MeOH in DCM) to give intermediate **33** as a yellow oil (226 mg, 52 %).

**7** (310 mg, 1.0 mmol, 1.00 equiv), **33** (202 mg, 1.21 mmol, 1.20 equiv), HATU (573 mg, 1.51 mmol, 1.50 equiv) and DIPEA (527 μL, 3.02 mmol, 3.00 equiv) were stirred in DMF (5 mL) at room temperature for 16 h. The orange-brown reaction mixture was then diluted with brine and the product extracted with $Et_2O$. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under vacuo. The crude product was purified by flash chromatography (0-10 % EtOAc in cyclohexane) and **34** was obtained as colorless solid (370 mg, 81 %). TLC (CH/EA = 4 : 1, v/v): $R_f$ = 0.16; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.43 (s, 2H), 5.36–5.28 (m, 1H), 4.53 (dd, J = 5.3, 2.5 Hz, 1H), 3.92–3.85 (m, 1H), 3.83–3.79 (m, 9H), 3.34 (d, J = 9.6 Hz, 1H), 2.96–2.85 (m, 1H), 2.36 (t, J = 2.5 Hz, 1H), 2.28–2.19 (m, 1H), 2.10–2.01 (m, 1H), 1.92–1.80 (m, 1H), 1.66–1.57 (m, 5H), 1.39 (s, 2H), 1.33–1.26 (m, 2H), 1.14–1.04 (m, 2H), 0.94–0.83 (m, 1H), 0.78–0.67 (m, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 172.63, 170.47, 152.88, 133.20, 105.81, 74.81, 60.77, 56.12, 52.22, 52.11, 43.59, 41.05, 32.80, 30.68, 26.87, 26.69, 26.54, 26.21, 26.18, 25.37, 20.90. HPLC (50-100 % Solvent B, 20 min): Rt = 14.6 min, purity (220 nm) = 93 %.

### (S)-(1H-1,2,3-Triazol-5-yl)methyl 1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 k)

A solution of **34** (100 mg, 0.22 mmol, 1.00 equiv), TMS-$N_3$ (43.5 μL, 0.33 mmol, 1.50 equiv) and CuI (2.08 mg, 10.9 μmol, 0.02 equiv) in DMF/MeOH (0.5 mL, 9 : 1 v/v) was stirred at 95 °C for 2 h. After purification by flash chromatography (0-100 % [EtOAc + 2 % MeOH + 1 % TEA] in cyclohexane) **11 k** was obtained as colorless solid (70 mg, 64 %). TLC (CH/EA 3 : 2 + 2 % MeOH + 1 % TEA, v/v/v/v): $R_f$ = 0.16. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.45–6.38 (m, 2H), 5.37–5.29 (m, 1H), 5.23–5.14 (m, 1H), 5.12–5.01 (m, 1H), 3.89 (d, J = 13.9 Hz, 1H), 3.82–3.71 (m, 9H), 3.34 (d, J = 9.7 Hz, 1H), 2.92–2.86 (m, 2H), 2.27–2.14 (m, 1H), 2.11–1.98 (m, 1H), 1.91–1.79 (m, 1H), 1.68–1.50 (m, 5H), 1.40 (dt, J = 12.9, 3.9 Hz, 1H), 1.30–1.19 (m, 2H), 1.14–1.04 (m, 2H), 0.90–0.82 (m, 1H), 0.77–0.69 (m, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 172.86, 170.87, 152.88, 136.57, 133.42, 128.95, 105.72, 60.84, 60.83, 56.24, 56.11, 55.03, 52.37, 43.72, 41.12, 36.51, 32.69, 31.47, 30.64, 26.65, 26.48, 26.12, 26.08, 25.35, 20.85. HPLC (0-100 % Solvent B, 20 min): Rt = 14.6 min, purity (220 nm) = 95 %. HRMS (ESI+): m/z: calculated 501.2713 $[M+H]^+$, found 501.2117 $[M+H]^+$.

### (S)-(1-Methyl-1H-1,2,3-Triazol-4-yl)methyl 1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 l)

A mixture of **34** (30.0 mg, 66 μmol, 1.00 equiv), $NaN_3$ (4.26 mg, 66 μmol, 1.00 equiv) and iodomethane (4.1 μL, 66 μmol, 1.00 equiv) and CuI (1.25 mg, 6.6 μmol, 0.10 equiv) in $H_2O$ (0.5 mL) was stirred at 80 °C for 3 h. After purification by flash chromatography (0-100 % [EtOAc + 2 % MeOH + 1 % TEA] in cyclohexane) **11 l** was obtained as a colorless solid (18 mg, 53 %). TLC (EtOAc + 2 % MeOH + 1 % TEA, v/v/v): $R_f$ = 0.41. $^1$H NMR (599 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.44 (s, 2H), 5.36–5.32 (m, 1H), 5.23–5.18 (m, 1H), 5.03–4.95 (m, 1H), 4.02 (s, 3H), 3.92–3.86 (m, 1H), 3.81–3.79 (m, 9H), 3.34 (d, J = 9.7 Hz, 1H), 2.94–2.85 (m, 1H), 2.26–2.18 (m, 1H), 2.08–2.04 (m, 1H), 1.83 (dt, J = 12.3, 3.1 Hz, 1H), 1.72–1.67 (m, 2H), 1.64–1.59 (m, 4H), 1.44–1.36 (m, 1H), 1.31–1.27 (m, 2H), 1.15–1.08 (m, 2H), 0.88 (qd, J = 12.5, 3.5 Hz, 1H), 0.73 (qd, J = 12.1, 3.3 Hz, 1H), 0.67–0.57 (m, 1H). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 172.57, 171.04, 152.83, 142.74, 136.55, 133.58, 123.97, 105.67, 60.80, 58.21, 56.26, 56.09, 54.93, 52.30, 43.68, 41.23, 36.60, 32.73, 30.68, 26.76, 26.51, 26.18, 26.13, 25.42, 20.93. HPLC [30-100 % Solvent B, 20 min]: Rt = 14.7 min, purity (220 nm) = 97 %. HRMS (ESI+): m/z: calculated 515.2870 $[M+H]^+$, found 515.2886 $[M+H]^+$.

### (4-Chloro-1-Methyl-1H-Pyrazol-3-Yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (11 j)

The substrate **11 j** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), **10 j** (12 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **11 j** (11 mg, 18 %) was obtained after purification by flash column chromatography (CH/EA = 1 : 1, v/v). TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.26; Diastereomer ratio: 18 : 1. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.42 (s, 2H), 5.42 (d, J = 5.5 Hz, 1H), 5.01 (d, J = 12.5 Hz, 1H), 4.96 (d, J = 12.5 Hz, 1H), 3.82 (d, J = 0.4 Hz, 4H), 3.81 (s, 9H), 3.33 (d, J = 9.7 Hz, 1H), 3.07–2.95 (m, 1H), 2.27 (d, J = 13.6 Hz, 1H), 2.13–1.99 (m, 1H), 1.85 (d, J = 13.2 Hz, 1H), 1.63 (q, J = 12.5 Hz, 5H), 1.49–1.34 (m, 4H), 1.21–1.03 (m, 3H), 0.96–0.77 (m, 1H), 0.77–0.58 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.45, 171.00, 152.90, 143.31, 137.01, 133.57, 129.07, 109.61, 105.78, 60.89, 58.02, 56.23, 55.11, 52.24, 43.74, 41.43, 39.68, 32.96, 30.87, 27.08, 26.74, 26.36, 25.76, 21.23. HPLC (30–100 % solvent B, 10 min) Rt = 7.902 min, purity (220 nm): 97 %.

### Methyl 2-Bromothiazole-5-Carboxylate (13 d)

The commercially available methyl 2-aminothiazole-5-carboxylate **12 d** (1.50 g, 9.48 mmol, 1.00 equiv) was dissolved in HBr (29 mL) at 0 °C and added dropwise to a cold aqueous solution of KBr (226 mg, 1.90 mmol, 0.20 equiv) and CuBr (1.4 g, 9.48 mmol, 1.00 equiv). Afterwards, a cooled solution of $NaNO_2$ (785 mg, 11.38 mmol, 1.20 equiv) in $H_2O$ (95 mL) was added dropwise. The reaction mixture was stirred for 3 hours at 60 °C. Upon completion, the reaction mixture was diluted with $H_2O$ and filtered. The crude residue was purified via flash column chromatography (CH/EA = 8 : 1, v/v) to yield **13 d** (855 mg, 40 %). TLC (CH/EA = 8 : 1, v/v): $R_f$ = 0.33; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 3.83 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 160.37, 147.96, 142.12, 132.75, 52.73.

### Methyl 2-Methoxythiazole-5-Carboxylate (13 e)

**13 d** (30 mg, 0.14 mmol, 1.00 equiv.) was added to a round-bottom flask under argon and dissolved in dry MeOH (1 mL) at rt. Afterwards, a 0.5 M solution of $NaOCH_3$ in MeOH (0.54 mL, 0.27 mmol, 2.00 equiv) was added and the reaction mixture was stirred at 50 °C for 4 days. Afterwards, the solvent was removed under reduced pressure and residue was redissolved in DCM (5 mL). The organic phase was washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to yield **13 e** (12 mg, 52 %). TLC (CH/EA = 3 : 1, v/v): $R_f$ = 0.53; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 4.05 (s, 3H), 3.79 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 178.82, 161.96, 144.43, 121.19, 58.82, 52.18.

### (2-Bromothiazol-5-Yl)methanol (14 d)

The substrate **13 d** (100 mg, 0.45 mmol, 1.00 equiv) was dissolved in EtOH (1.5 mL) and $H_2O$ (0.3 mL) and treated with $NaBH_4$ (51 mg, 1.35 mmol, 3.00 equiv) After 4 h, the reaction mixture was concentrated under reduced pressure and the residue was extracted with EA ( 3×5 mL), washed with brine (1×15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. **14 d** (58 mg, 67 %) was obtained without further purification. TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.42; $^1$H NMR (300 MHz, MeOD) δ 7.68–7.28 (m, 1H), 4.74 (d, J = 1.1 Hz, 2H). $^{13}$C NMR (75 MHz, MeOD) δ 144.71, 139.16, 135.78, 55.99.

### (2-Methoxythiazol-5-yl)methanol (14 e)

Substrate **13 e** (12 mg, 0.07 mmol, 1.00 equiv) was applied to general procedure E with $LiAlH_4$ (1.0 M in THF, 0.1 mL, 0.08 mmol, 1.10 equiv) in THF (2 mL), stirring for 4 h. **14 e** (8 mg, 80 %) was obtained without further purification. TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.27; $^1$H NMR (300 MHz, MeOD) δ 8.56 (t, J = 1.0 Hz, 1H), 6.20–6.13 (m, 2H), 5.59 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 178.82, 161.96, 144.43, 121.19, 58.82, 52.18.

### (2-Phenylthiazol-5-yl)methanol (14 g)

**14 g** was synthesized following the general procedure D starting from the commercially available 2-phenylthiazole-5-carbaldehyde **13 g** (100 mg, 0.53 mmol, 1.00 equiv) and $NaBH_4$ (40 mg, 1.06 mmol, 2.00 equiv) in THF (2.7 mL) and MeOH (5.30 mL). The crude product was used without further purification (75 mg, 74 %). TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.24; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.89–7.84 (m, 2H), 7.57 (s, 1H), 7.41 (q, J = 3.3 Hz, 3H), 4.81 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.15, 141.03, 139.09, 133.46, 130.28, 129.10, 126.51, 57.41.

### (2,4-Dichlorothiazol-5-yl)methanol (14 j)

**14 j** was synthesized following the general procedure D with the commercially available 2,4-dichlorothiazole-5-carbaldehyde **13 j** (198 mg, 1.08 mmol, 1.00 equiv) and $NaBH_4$ (84 mg, 2.22 mmol, 2.00 equiv) in THF (5.5 mL) and MeOH (11 mL). The crude product was purified with flash column chromatography (CH/EA = 4 : 1, v/v) to yield **14 j** (135 mg, 67 %). TLC (CH/EA = 4 : 1, v/v): $R_f$ = 0.23; $^1$H NMR (300 MHz, $CDCl_3$) δ 4.76 (d, J = 5.5 Hz, 1H).$^{13}$C NMR (75 MHz, $CDCl_3$) δ 151.04, 133.85, 133.32, 56.82. HPLC (5–100 % solvent B, 3 min) Rt = 1.172 min, purity (220 nm): > 99 %.

### (2,4-Dimethyl-1,3-Thiazol-5-yl)methanol (14 k)

**14 k** was synthesized following the general procedure D with the commercially available 2,4-dimethyl-1,3-thiazole-5-carbaldehyde **13 k** (204 mg, 1.42 mmol, 1.00 equiv) and $NaBH_4$ (214 mg, 5.66 mmol, 4.00 equiv) in MeOH (11 mL) and THF (3.8 mL). The crude product was purified by silica gel column chromatography (CH/EA = 3 : 1, v/v) to yield **14 k** (127 mg, 63 %). TLC (CH/EA = 1 : 3, v/v): $R_f$ = 0.18; $^1$H NMR (300 MHz, $CDCl_3$) δ 4.67 (s, 2H), 2.56 (s, 3H), 2.24 (s, 3H).$^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.44, 148.21, 131.02, 56.26, 19.02, 14.72.

### (2-Methylthiazol-5-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15 b)

The substrate **15 b** was synthesized following the general procedure B with precursor **7** (25 mg, 0.06 mmol, 1.00 equiv), the commercially available (2-methylthiazol-5-yl)metanol **14 b** (8.2 mg, 0.06 mmol, 1.00 equiv), DMAP (22 mg, 0.18 mmol, 3.00 equiv) and DIC (10.2 μL, 8.3 mg, 0.07 mmol, 1.10 equiv) in DCM (1 mL). **15 b** (10 mg, 31 %) was obtained after purification by flash column chromatography (CH/EA = 2 : 1, v/v). TLC (CH/EA = 1 : 1 v/v): $R_f$ = 0.23; Diastereomer ratio: 13 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 6.47 (s, 2H), 5.34 (q, J = 3.3 Hz,1H), 5.17 (dd, J = 12.9, 0.8 Hz, 1H), 5.06 (dd, J = 12.9, 0.8 Hz, 1H), 3.89 (dd, J = 14.6, 4.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 6H), 3.35 (d, J = 9.6 Hz, 1H), 2.89–2.83 (m, 1H), 2.65 (s, 3H), 2.23–2.17 (m, 1H), 2.07 (qd, J = 11.7, 6.1 Hz, 1H), 1.90–1.83 (m, 1H), 1.71–1.53 (m, 8H), 1.36–1.27 (m, 2H), 1.26–1.17 (m, 1H), 1.17–1.04 (m, 1H), 0.96–0.87 (m, 1H), 0.81–0.70 (m, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.56, 170.78, 168.01, 152.89, 142.43, 136.85, 133.24, 131.83, 105.91, 60.73, 58.28, 56.13, 55.06, 52.13, 43.54, 41.10, 32.73, 30.63, 26.63, 26.47, 26.13, 26.12, 25.30, 20.86, 19.16. HPLC (50–60 % solvent B, 1.5 mL/min, 20 min): Rt = 8.08 min, purity (220 nm) = 99 %. HRMS (ESI+): m/z: 531.25233 calculated $[M+H]^+$, found 531.25250 $[M+H]^+$.

### (2-Chlorothiazol-5-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15 c)

The substrate **15 c** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), the commercially available (2-chlorothiazol-5-yl)metanol **14 c** (18 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv), EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **15 c** (26 mg, 40 %) was obtained after purification by flash column chromatography (CH/EA = 3 : 1 + 1 % HCOOH, v/v/v). TLC (CH/EA = 3 : 1 + 1 % HCOOH, v/v/v): $R_f$ = 0.37; Diastereomer ratio: 30 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.46 (s, 2H), 5.37–5.24 (m, 1H), 5.13 (d, J = 13.1 Hz, 1H), 5.00 (d, J = 13.1 Hz, 1H), 3.91–3.86 (m, 1H), 3.85–3.80 (m, 9H), 3.35 (d, J = 9.7 Hz, 1H), 2.82 (td, J = 13.2, 3.1 Hz, 1H), 2.23–2.14 (m, 1H), 2.12–1.99 (m, 1H), 1.85 (d, J = 12.6 Hz, 1H), 1.71–1.51 (m, 7H), 1.43 (dddd, J = 16.8, 12.7, 8.3, 4.1 Hz, 1H), 1.38–1.05 (m, 4H), 0.96–0.60 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.79, 171.03, 153.59, 152.99, 141.49, 136.92, 134.68, 133.26, 105.98, 60.87, 58.07, 56.25, 55.19, 52.26, 43.72, 41.16, 32.81, 30.69, 26.61, 26.56, 26.23, 26.19, 25.32, 20.96. HPLC (50–100 % solvent B, 3 min) Rt = 1.567 min, purity (220 nm): 99 %. HRMS (ESI+): m/z: 551.19771calculated $[M+H]^+$, found 551.19784 $[M+H]^+$.

### (2-Bromothiazol-5-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15 d)

The substrate **15 d** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (127 mg, 0.86 mmol, 4.00 equiv), **14 d** (42 mg, 0.21 mmol, 1.00 equiv), precursor **7** (90 mg, 0.21 mmol, 1.00 equiv) EDC-HCl (45 mg, 0.24 mmol, 1.10 equiv) in toluene (4 mL). **15 d** (63 mg, 50 %) was obtained after purification by flash column chromatography (CH/EA = 3 : 1 + 1 % HCOOH, v/v/v). TLC (CH/EA = 3 : 1 + 1 % HCOOH, v/v/v): $R_f$ = 0.28; Diastereomer ratio: 18 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40–7.32 (m, 1H), 6.40 (d, J = 1.4 Hz, 2H), 5.27–5.25 (m, 1H), 5.09 (ddt, J = 13.1, 2.1, 0.8 Hz, 1H), 4.96 (ddt, J = 13.2, 2.1, 0.8 Hz, 1H), 3.86–3.80 (m, 1H), 3.77 (q, J = 2.3 Hz, 9H), 3.30 (d, J = 9.7 Hz, 1H), 2.82–2.72 (m, 1H), 2.15–2.09 (m, 1H), 2.05–1.95 (m, 2H), 1.78 (d, J = 12.6 Hz, 1H), 1.66–1.48 (m, 8H), 1.42–1.31 (m, 1H), 1.29–0.99 (m, 2H), 0.89–0–85 (m, 1H), 0.73–0.55 (m, 1H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.92, 171.06, 153.05, 142.89, 138.10, 136.99, 136.59, 133.30, 106.07, 60.93, 57.93, 56.33, 55.24, 52.36, 43.79, 41.21, 32.86, 30.75, 26.67, 26.62, 26.28, 26.26, 25.37, 21.01. HPLC (50–100 % solvent B, 3 min) Rt = 2.365 min, purity (220 nm): > 99 %. HRMS (ESI+): m/z: 595.14720 calculated $[M+H]^+$, found 595.14806 $[M+H]^+$.

### (2-Methoxythiazol-5-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15e)

The substrate **15e** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (28 mg, 0.19 mmol, 4.00 equiv), **14e** (7 mg, 0.05 mmol, 1.00 equiv), precursor **7** (20 mg, 0.05 mmol, 1.00 equiv) and EDC-HCl (10 mg, 0.05 mmol, 1.10 equiv) in dry toluene (1 mL). **15e** (12 mg, 46%) was obtained after purification by flash column chromatography (CH/EA = 1:1 + 1% HCOOH, v/v/v). TLC (CH/EA = 2:1 + 1% HCOOH, v/v/v): $R_f$ = 0.27; Diastereomer ratio: 27:1 (determined from the aromatic peak of the thiazole in $^1$H NMR). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.45 (d, J = 8.9 Hz, 2H), 5.34 (d, J = 5.5 Hz, 1H), 5.07 (d, J = 12.9 Hz, 1H), 4.94 (d, J = 12.9 Hz, 1H), 4.03 (s, 3H), 3.91–3.86 (m, 1H), 3.84 (s, 9H), 3.36 (d, J = 9.6 Hz, 1H), 2.87 (td, J = 13.2, 2.9 Hz, 1H), 2.20 (d, J = 13.7 Hz, 1H), 2.07 (q, J = 12.4 Hz, 2H), 1.86 (d, J = 12.9 Hz, 1H), 1.74–1.50 (m, 5H), 1.48–1.36 (m, 2H), 1.37–1.27 (m, 1H), 1.22–1.03 (m, 3H), 0.97–0.80 (m, 1H), 0.80–0.62 (m, 1H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.86, 171.20, 153.43, 153.10, 137.58, 136.97, 133.50, 124.55, 106.04, 61.00, 59.27, 58.35, 56.36, 55.31, 52.38, 43.81, 41.32, 32.98, 30.87, 26.89, 26.72, 26.36, 26.27, 25.55, 21.12. HPLC (50–100% solvent B, 3 min) Rt = 2.309 min, purity (220 nm): 87%.

10% of impurity is attributed to the presence of remaining starting material, which we were not able to remove. HRMS (ESI+): m/z: 547.24725 calculated $[M+H]^+$, found 547.24855 $[M+H]^+$.

### (2-(Trifluoromethyl)thiazol-5-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15f)

The substrate **15f** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), the commercially available (2-(trifluoromethyl)thiazol-5-yl)methanol **14f** (22 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **15f** (41 mg, 59%) was obtained after purification by flash column chromatography (CH/EA = 2:1 + 1% HCOOH, v/v/v). TLC (CH/EA = 2:1 + 1% HCOOH, v/v/v): $R_f$ = 0.53; Diastereomer ratio: 28:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.73 (q, J = 1.0 Hz, 1H), 6.40 (s, 2H), 5.26 (dd, J = 5.9, 2.8 Hz, 1H), 5.19 (d, J = 13.2 Hz, 1H), 5.09 (d, J = 13.3 Hz, 1H), 3.82 (dd, J = 12.8, 4.3 Hz, 1H), 3.78–3.75 (m, 9H), 3.30 (d, J = 9.6 Hz, 1H), 2.78 (td, J = 13.1, 3.1 Hz, 1H), 2.15–2.09 (m, 1H), 2.06–1.93 (m, 2H), 1.79 (d, J = 12.5 Hz, 1H), 1.66–1.48 (m, 8H), 1.30–1.01 (m, 3H), 0.89–0.79 (m, 1H), 0.69 (qd, J = 12.0, 3.1 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 173.02, 171.08, 153.49, 153.15, 143.95, 137.09, 136.95, 133.35, 118.54, 106.13, 60.98, 57.66, 56.37, 55.37, 52.46, 43.87, 41.29, 32.95, 30.82, 26.87, 26.70, 26.35, 26.34, 25.40, 21.08. HPLC (50–100% solvent B, 3 min) Rt = 1.736 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 585.22407 calculated $[M+H]^+$, found 585.22451 $[M+H]^+$.

### (2-Phenylthiazol-5-yl)methyl(S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15g)

The substrate **15g** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), **14g** (23 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.48 mmol, 1.00 equiv) EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (1 mL). **15g** (46 mg, 65%) was obtained after purification by flash column chromatography (CH/EA = 2:1 v/v). TLC (CH/EA = 2:1, v/v): $R_f$ = 0.50; Diastereomer ratio: 20:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.46 (tt, J = 6.5, 3.5 Hz, 5H), 6.49 (s, 2H), 5.38 (dd, J = 5.7, 2.5 Hz, 1H), 5.29 (d, J = 13.0 Hz, 1H), 5.14 (d, J = 13.0 Hz, 1H), 3.93–3.88 (m, 1H), 3.87 (s, 3H), 3.86 (s, 6H), 3.38 (d, J = 9.6 Hz, 1H), 2.92–2.84 (m, 1H), 2.27–2.20 (m, 1H), 2.15–2.06 (m, 2H), 1.88 (d, J = 12.0 Hz, 1H), 1.65 (tdd, J = 22.3, 16.9, 12.8 Hz, 6H), 1.44 (tt, J = 12.9, 3.9 Hz, 1H), 1.34 (tt, J = 13.7, 2.3 Hz, 1H), 1.27 (d, J = 3.1 Hz, 1H), 1.26–1.19 (m, 1H), 1.19–1.09 (m, 1H), 0.93 (qd, J = 12.5, 3.4 Hz, 1H), 0.78 (qd, J = 13.3, 12.7, 3.9 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.86, 171.11, 170.29, 153.11, 143.69, 136.96, 134.30 133.46, 132.44, 130.66, 129.16, 126.74, 106.03, 61.00, 58.35, 56.35, 55.32, 52.40, 43.83, 41.30, 32.97, 30.85, 26.84, 26.70, 26.37, 26.34, 25.49, 21.11. HPLC (30–100% solvent B, 3 min) Rt = 2.039 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 593.26798 calculated $[M+H]^+$, found 593.26883 $[M+H]^+$.

### (4-Methylthiazol-5-Yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15h)

The substrate **15h** was synthesized following the general procedure C with precursor **7** (25 mg, 0.06 mmol, 1.00 equiv), the commercially available (4-methylthiazol-5-yl)metanol **14h** (8.1 mg, 0.06 mmol, 1.00 equiv), DMAP (21.9 mg, 0.18 mmol, 3.00 equiv) and EDC-HCl (12.6 mg, 0.06 mmol, 1.10 equiv) in DCM (1 mL). **15h** (28 mg, 89%) was obtained after purification by flash column chromatography (CH/EA = 2:1, v/v). TLC (CH/EA = 2:1 v/v): $R_f$ = 0.17; Diastereomer ratio: 12:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 6.46 (s, 2H), 5.34 (dd, J = 6.4, 3.9 Hz, 1H), 5.21 (d, J = 13.1 Hz, 1H), 5.08 (d, J = 13.1 Hz, 1H), 3.91–3.87 (m, 1H), 3.83 (s, 3H), 3.83 (s, 6H), 3.35 (d, J = 9.7 Hz, 1H), 2.84 (td, J = 13.2, 3.0 Hz, 1H), 2.36 (s, 3H), 2.22–2.16 (m, 1H), 2.10–2.02 (m, 1H), 1.85 (d, J = 12.2 Hz, 1H), 1.72–1.52 (m, 7H), 1.42 (ddt, J = 12.8, 8.1, 3.9 Hz, 1H), 1.36–1.25 (m, 2H), 1.23–1.05 (m, 2H), 0.95–0.85 (m, 1H), 0.74 (qd, J = 12.0, 3.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.75, 170.94, 153.11, 152,64, 152.36, 136.99, 133.53, 125.41, 106.02, 60.97, 57.87, 56.32, 55.24, 52.32, 43.78, 41.40, 32.94, 30.84, 26.92, 26.69, 26.33, 26.26, 25.55, 21.10, 15.04. HPLC (40–50% solvent B, 1.5 mL/min, 20 min): Rt = 16.73 min, purity (220 nm) = 99%. HRMS (ESI+): m/z: 531.25233 calculated $[M+H]^+$, found 531.25356 $[M+H]^+$.

### (4-Chlorothiazol-5-Yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15i)

The substrate **15i** was synthesized following the general general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), the commercially available (4-chlorothiazol-5-yl)methanol **14i** (18 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **15i** (45 mg, 68%) was obtained after purification by flash column chromatography (CH/EA = 3:1 + 1% HCOOH, v/v/v). TLC (CH/EA = 3:1 + 1% HCOOH, v/v/v): $R_f$ = 0.17; Diastereomer ratio: 8:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 1.0 Hz, 1H), 6.45 (d, J = 1.3 Hz, 2H), 5.37–5.35 (m, 1H), 5.22 (dd, J = 13.3, 1.4 Hz, 1H), 5.11 (dd, J = 13.3, 1.3 Hz, 1H), 3.95–3.90 (m, 1H), 3.81 (d, J = 1.3 Hz, 9H), 3.35 (d, J = 9.7 Hz, 1H), 2.94–2.85 (m, 1H), 2.24–2.19 (m, 1H), 2.09–2.02 (m, 1H), 1.84 (d, J = 12.1 Hz, 1H), 1.70–1.53 (m, 6H), 1.36–1.26 (m, 4H), 1.21–1.00 (m, 2H), 0.94–0.80 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.87, 170.94, 153.17, 153.12, 139.74, 136.98, 133.53, 125.09, 105.99, 60.98, 57.75, 56.31, 55.18, 52.34, 43.86, 41.41, 32.89, 30.82, 26.87, 26.67, 26.31, 26.30, 25.53, 21.10. HPLC (50–100% solvent B, 3 min) Rt = 1.445 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 551.19771 calculated $[M+H]^+$, found 551.19818 $[M+H]^+$.

### (2,4-Dichlorothiazol-5-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15j)

The substrate **15j** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.05 mmol, 4.00 equiv), **14j** (52 mg, 0.28 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol,

1.00 equiv) and EDC-HCl (25 mg, 0.01 mmol, 1.10 equiv) in toluene (3 mL). **15 j** (34 mg, 49 %) was obtained after purification by flash column chromatography (CH/EA = 3 : 1 + 1 % HCOOH, v/v/v). TLC (CH/EA = 3 : 1 + 1 % HCOOH, v/v/v): $R_f$ = 0.36; Diastereomer ratio: 18 : 1. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.46 (s, 2H), 5.31 (dd, J = 6.0, 2.7 Hz, 1H), 5.13 (d, J = 13.4 Hz, 1H), 5.03 (d, J = 13.4 Hz, 1H), 3.94–3.87 (m, 1H), 3.84 (s, 9H), 3.35 (d, J = 9.6 Hz, 1H), 2.89 (ddd, J = 13.7, 12.3, 3.0 Hz, 1H), 2.23–2.13 (m, 1H), 2.06 (td, J = 12.3, 9.3 Hz, 1H), 1.84 (d, J = 12.5 Hz, 1H), 1.73–1.53 (m, 7H), 1.43 (dt, J = 12.7, 3.8 Hz, 1H), 1.32 (d, J = 12.5 Hz, 2H), 1.21–1.04 (m, 2H), 0.99–0.83 (m, 1H), 0.82–0.60 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.02, 171.18, 153.13, 152.67, 137.04, 133.35, 129.14, 128.33, 106.00, 60.98, 57.38, 56.34, 55.32, 52.43, 43.85, 41.40, 32.95, 30.83, 26.85, 26.68, 26.34, 25.43, 21.13. HPLC (5–100 % solvent B, 10 min) Rt = 8.612 min, purity (220 nm): 96 %. HRMS (ESI +): m/z: 585.15874calculated $[M+H]^+$, found 585.16001 $[M+H]^+$.

### (2,4-Dimethylthiazol-5-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (15 k)

The substrate **15 k** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.05 mmol, 4.00 equiv), **14 k** (40 mg, 0.28 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.01 mmol, 1.10 equiv) in toluene (3 mL). **15 k** (25 mg, 39 %) was obtained after purification by flash column chromatography (CH/EA = 2 : 1, v/v). TLC (CH/EA = 2 : 1, v/v): $R_f$ = 0.39; Diastereomer ratio: 16 : 1. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.47 (s, 2H), 5.34 (d, J = 5.4 Hz, 1H), 5.14 (d, J = 13.1 Hz, 1H), 5.00 (d, J = 13.1 Hz, 1H), 3.90 (dd, J = 4.1, 2.7 Hz, 1H), 3.83 (s, 9H), 3.35 (d, J = 9.6 Hz, 1H), 2.85 (td, J = 13.1, 2.9 Hz, 1H), 2.63 (s, 3H), 2.29 (s, 3H), 2.19 (d, J = 16.6 Hz, 1H), 2.10–1.99 (m, 1H), 1.84 (q, J = 5.2 Hz, 1H), 1.73–1.51 (m, 8H), 1.32 (d, J = 12.2 Hz, 2H), 1.20 (dt, J = 8.4, 3.9 Hz, 1H), 1.17–1.09 (m, 1H), 0.98–0.83 (m, 1H), 0.81–0.65 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.75, 170.99, 166.07, 153.11, 136.99, 133.54, 128.35, 124.96, 106.02, 60.97, 57.88, 56.33, 55.27, 52.36, 43.78, 41.41, 32.97, 30.86, 26.95, 26.71, 26.36, 25.56, 21.14, 19.03, 14.77. HPLC (50–100 % solvent B, 3 min) Rt = 1.487 min, purity (220 nm): > 99 %. HRMS (ESI +): m/z: 545.26798 calculated $[M+H]^+$, found 545.26881 $[M+H]^+$.

### Ethyl 1H-Pyrazole-4-Carboxylate (17)

The commercially available 1H-pyrazole-4-carboxylic acid **16** (1 g, 8.92 mmol, 1.00 equiv) was dissolved in EtOH (12 mL) and concentrated $H_2SO_4$ (1.5 mL, 26.77 mmol, 3.00 equiv) was added. The reaction mixture was heated at reflux for 24 hours. Upon completion, the solvent was removed under reduced pressure, the residue was neutralized with a saturated solution of $NaHCO_3$ and extracted with EA (3×10 mL). The organic phases were combined and dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **17** as a white solid (1.2 g, 96 %). TLC (CH/EA = 1 : 1 + 1 % HCOOH, v/v/v): $R_f$ = 0.33; $^1$H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.11 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 162.97, 136.54, 115.26, 60.51, 14.34. HPLC (5–100 % solvent B, 3 min) Rt = 1.237 min, purity (220 nm): 96 %.

### Ethyl 2-((Dimethylamino)methylene)-3-Oxobutanoate (19 k)

Ethylacetoacetate **18 k** (0.97 mL, 7.68 mmol, 1.00 equiv) and DMF-DMA (1.32 mL, 10 mmol, 1.30 equiv) were added to a 10 mL RBF and the reaction mixture was stirred overnight at room temperature. Upon completion, the mixture was concentrated under reduced pressure and the crude was purified by flash column chromatography (CH/EA = 2 : 1, v/v) to afford **19 k** (748 mg, 53 %). TLC (CH/EA = 1 : 2, v/v): $R_f$ = 0.13; $^1$H NMR (mixture of E and Z) $^1$H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.05 (q, J = 7.1 Hz, 2H), 3.25–2.67 (m, 6H), 2.26 (s, 3H), 1.98 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H). HPLC (5–100 % solvent B, 3 min) Rt = 1.270 min, purity (220 nm): 88 %.

### Ethyl 1-Methyl-1H-Pyrazole-4-Carboxylate (21 a)

**17** (100 mg, 0.71 mmol, 1.00 equiv) and $K_2CO_3$ (118 mg, 0.86 mmol, 1.20 equiv) were dissolved in DMF (7 mL). Afterwards, iodomethane (0.055 mL, 0.86 mmol, 1.00 equiv) was added and the reaction mixture was stirred at room temperature overnight. Upon completion, the reaction mixture was quenched with a 1 M solution of NaOH (10 mL) and extracted with EA (3×10 mL). The organic phases were combined and washed with brine (1×10 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (CH/EA = 1 : 1, v/v) to yield **21 a** (52 mg, 47 %). TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.33; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.89–7.87 (m, 1H), 7.85 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.08, 141.23, 133.39, 115.47, 60.26, 39.40, 14.51. HPLC (5–100 % solvent B, 3 min) Rt = 1.383 min, purity (220 nm): 98 %.

### Ethyl 1-Ethyl-1H-Pyrazole-4-Carboxylate (21 b)

**17** (200 mg, 1.43 mmol, 1.00 equiv) was applied to the general procedure F with $K_2CO_3$ (986 mg, 7.14 mmol, 5.00 equiv) and 1-bromoethane (0.12 mL, 1.43 mmol, 1.00 equiv) in acetone (8 mL). **21 b** (105 mg, 51 %) was obtained after purification by flash column chromatography (CH/EA = 3 : 1, v/v). TLC (CH/EA = 3 : 1, v/v): $R_f$ = 0.25; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 1.2 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.19 (q, J = 7.3 Hz, 2H), 1.51 (t, J = 7.4 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.05, 140.85, 131.64, 114.94, 60.09, 47.42, 15.24, 14.38. HPLC (5–100 % solvent B, 3 min) Rt = 1.492 min, purity (220 nm): > 99 %.

### Ethyl 1-Isopropyl-1H-Pyrazole-4-Carboxylate (21 c)

**17** (200 mg, 1.43 mmol, 1.0 equiv) was applied to the general procedure F with $K_2CO_3$ (986 mg, 7.14 mmol, 5.00 equiv) and 2-bromopropane (0.15 mL, 1.43 mmol, 1.00 equiv) in acetone (8 mL). **21 c** (192 mg, 74 %) was obtained after purification by flash column chromatography (CH/EA = 3 : 1, v/v). TLC (CH/EA = 3 : 1, v/v): $R_f$ = 0.33; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.89–7.87 (m, 1H), 4.48 (hept, J = 6.7 Hz, 1H), 4.26 (qd, J = 7.1, 0.9 Hz, 2H), 1.49 (dd, J = 6.7, 1.0 Hz, 6H), 1.31 (td, J = 7.1, 0.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.16, 140.52, 129.87, 114.54, 60.05, 54.33, 22.72, 14.39. HPLC (5–100 % solvent B, 3 min) Rt = 1.629 min, purity (220 nm): > 99 %.

### Ethyl 1-Propyl-1H-Pyrazole-4-Carboxylate (21 d)

**17** (50 mg, 0.36 mmol, 1.00 equiv) was applied to the general procedure F with $K_2CO_3$ (247 mg, 1.78 mmol, 5.00 equiv) and 1-bromopropane (0.070 mL, 0.71 mmol, 2.00 equiv) in acetone (2 mL). **21 d** (30 mg, 64 %) was obtained after purification by flash column chromatography (CH/EA = 3 : 1, v/v). TLC (CH/EA = 3 : 1, v/v): $R_f$ = 0.32; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 10.5 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.09 (t, J = 7.0 Hz, 2H), 1.90 (h, J = 7.3 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.07, 140.86, 132.40, 114.82, 60.09, 54.22, 23.40, 14.36, 10.98. HPLC (5–100 % solvent B, 3 min) Rt = 1.639 min, purity (220 nm): > 99 %.

### Ethyl 1-(2-((Tert-butyldimethylsilyl)oxy)ethyl)-1H-Pyrazole-4-Carboxylate (21 e)

**17** (300 mg, 2.14 mmol, 1.00 equiv) was applied to the general procedure G with $Cs_2CO_3$ (1046 mg, 3.21 mmol, 1.50 equiv) and (2-bromoethoxy)(tert-butyl)dimethylsilane (0.50 mL, 2.25 mmol, 1.05 equiv) in acetone (3 mL). **21 e** (630 mg, 98 %) was obtained without further purification. TLC (CH/EA = 2 : 1, v/v): $R_f$ = 0.53; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.91 (s, 1H), 4.28 (qd, J = 7.1, 1.2 Hz, 2H), 4.25–4.20 (m, 2H), 3.96–3.92 (m, 2H), 1.33 (td, J = 7.1, 1.2 Hz, 3H), 0.84 (d, J = 1.4 Hz, 9H), −0.07 (d, J = 1.4 Hz, 6H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.01, 141.08, 133.96, 114.76, 61.63, 60.01, 55.00, 25.71, 18.11, 14.35, −5.71. HPLC (30–100 % solvent B, 3 min) Rt = 2.020 min, purity (220 nm): 98 %.

### Ethyl 1-(3-((Tert-Butyldimethylsilyl)oxy)propyl)-1H-Pyrazole-4-Carboxylate (21 f)

**17** (150 mg, 1.07 mmol, 1.00 equiv) was applied to the general procedure F with $Cs_2CO_3$ (523 mg, 1.61 mmol, 1.50 equiv) and (3-bromopropoxy)(tert-butyl)dimethylsilane (0.27 mL, 1.61 mmol, 1.05 equiv) in acetone (1.5 mL). **21 f** (333 mg, 99 %) was obtained without further purification. TLC (CH/EA = 2 : 1, v/v): $R_f$ = 0.57; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.89 (s, 1H), 4.29 (q, J = 7.5 Hz, 2H), 4.25 (d, J = 6.9 Hz, 2H), 3.57 (t, J = 5.7 Hz, 2H), 2.06 (h, J = 6.6 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.91 (d, J = 1.0 Hz, 9H), 0.06–0.04 (m, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.06, 141.08, 132.97, 114.69, 60.05, 59.17, 49.20, 32.61, 25.88, 18.22, 14.38, −5.47. HPLC (5–100 % solvent B, 3 min) Rt = 2.405 min, purity (220 nm): 93 %.

### Ethyl 1-(2-Methoxyethyl)-1H-Pyrazole-4-Carboxylate (21 g)

**17** (200 mg, 1,43 mmol, 1 equiv) and $K_2CO_3$ (237 mg, 1.71 mmol, 1.20 equiv) were dissolved in DMSO (6 mL) and the reaction mixture was cooled at 0 °C. Afterwards, 1-bromo-2-methoxyethane (0.15 mL, 218 mg, 1.57 mmol, 1.20 equiv) was added and the reaction mixture was slowly warmed up to rt. **21 g** (218 mg, 77 %) was obtained after purification with flash column chromatography (CH/EA = 3 : 1, v/v). TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.43; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.89 (s, 1H), 4.29–4.24 (m, 4H), 3.75–3.70 (m, 2H), 3.31 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.05, 141.05, 133.52, 115.08, 70.60, 60.10, 58.96, 52.53, 14.35. HPLC (5–100 % solvent B, 3 min) Rt = 1.461 min, purity (220 nm): 90 %.

### 1,5-Dimethyl-1H-Pyrazole-4-Carbaldehyde (2 ij)

$POCl_3$ (1,20 mL, 12.48 mmol, 3.00 equiv) was added to DMF (3 mL, 16.64 mmol, 4.00 equiv) at 0 °C. The resulting solution was stirred for 30 minutes at 0 °C. Afterwards, the commercially available 1,5-dimethyl-1H-pyrazole **20 j** (400 mg, 4.16 mmol, 1.00 equiv) in DMF (1 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was cooled at 0 °C and neutralized with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with EA (3×10 mL), the organic phases combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield **21 j** (329 mg, 64 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.79 (s, 1H), 3.77 (d, J = 1.0 Hz, 3H), 2.50 (s, 3H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 184.66, 142.93, 141.26, 120.91, 35.94, 10.30. GCMS: (splitless, 10 minutes) Rt = 4.646, purity = 91 %.

### Ethyl 1-Ethyl-5-Methyl-1H-Pyrazole-4-Carboxylate (21 k)

**19 k** (300 mg, 1.62 mmol, 1.00 equiv) was dissolved in MeOH. Then, ethyl hydrazine oxalate (243 mg, 1.62 mmol, 1.00 equiv) and an aqueous solution of $Na_2CO_3$ (1 M, 3 mL) were added at room temperature. Afterwards, a solution of MeOH/HCl (10 : 1, v/v, 18 mL) was added and the reaction mixture was stirred at reflux overnight. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (CH/EA = 10 : 1, v/v) to yield **21 k** (81 mg, 27 %). TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.38; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 4.30–4.24 (m, 2H), 4.13–4.07 (m, 2H), 2.53 (d, J = 1.2 Hz, 1H), 1.43–1.38 (m, 3H), 1.36–1.31 (m, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.91, 142.04, 140.69, 111.74, 59.67, 44.08, 15.01, 14.40, 10.30. HPLC (5–100 % solvent B, 3 min) Rt = 1.591 min, purity (220 nm): 98 %.

### (1-Methyl-1H-Pyrazol-4-Yl)methanol (22 a)

**22 a** was synthesized following general procedure E starting from **21 a** (50 mg, 0.32 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 0.32 mL, 0.32 mmol, 1.00 equiv) in THF (3 mL), stirring for 3 h. **22 a** (33 mg, 92 %) was obtained without further purification. TLC (DCM/MeOH = 9 : 1, v/v): $R_f$ = 0.42; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.39 (s, 1H), 4.60 (s, 2H), 3.90 (d, J = 1.0 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.55, 129.08, 121.68, 56.05, 38.90. GCMS: (splitless, 10 min) Rt = 4.232 minutes, purity = 94 %.

### (1-Ethyl-1H-Pyrazol-4-yl)methanol (22 b)

**22 b** was synthesized following general procedure E starting from **21 b** (50 mg, 0.30 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 0.45 mL, 0.45 mmol, 1.00 equiv) in THF (5 mL), stirring overnight. **22 b** (35 mg, 92 %) was obtained without further purification. TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.13; $^1$H NMR (500 MHz, MeOD) δ 7.61 (s, 1H), 7.47 (s, 1H), 4.51 (s, 2H), 4.20–4.12 (m, 2H), 1.47–1.42 (m, 3H).$^{13}$C NMR (126 MHz, MeOD) δ 137.91, 128.14, 121.63, 54.50, 46.30, 14.65. HPLC (5–100 % solvent B, 3 min) Rt = 0.868 min, purity (220 nm): 93 %.

### (1-Isopropyl-1H-Pyrazol-4-Yl)metanol (22 c)

**22 c** was synthesized following the general procedure E starting from **21 c** (140 mg, 0.77 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 1.2 mL, 1.2 mmol, 1.00 equiv) in THF (5 mL), stirring for 4 h. **22 c** (82 mg, 76 %) was used without any further purification. TLC (CH/EA = 3 : 1, v/v): $R_f$ = 0.25; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 3.7 Hz, 2H), 4.54 (d, J = 2.3 Hz, 2H), 4.45 (p, J = 6.7 Hz, 1H), 1.47 (d, J = 6.7 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 137.88, 125.53, 121.07, 55.86, 53.69, 22.90.

### (1-Propyl-1H-Pyrazol-4-Yl)methanol (22 d)

**22 d** was synthesized following general procedure E starting from **21 d** (30 mg, 0.16 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 0.25 mL, 0.25 mmol, 1.00 equiv) in THF (3 mL), stirring overnight. **22 d** (17 mg, 74 %) was obtained without further purification. TLC (CH/EA = 3 : 1, v/v): $R_f$ = 0.23; $^1$H NMR (500 MHz, MeOD) δ 7.61–7.54 (m, 1H), 7.44 (s, 1H), 4.48 (s, 2H), 4.04 (td, J = 7.0, 1.1 Hz, 2H), 1.82 (h, J = 7.3 Hz, 2H), 0.86 (td, J = 7.4, 1.2 Hz, 3H). $^{13}$C NMR (126 MHz, MeOD) δ 139.11, 130.10, 122.74, 55.71, 54.26, 24.63, 11.15.

### (1-(2-((Tert-Butyldimethylsilyl)oxy)ethyl)-1H-Pyrazol-4-yl)metanol (22 e)

**22 e** was synthesized was synthesized following the general procedure E starting from **21 e** (150 mg, 0.5 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 0.50 mL, 0.50 mmol, 1.00 equiv) in THF (1.5 mL), stirring for 4 h. **22 e** (97 mg, 75 %) was obtained after purification by

flash column chromatography (CH/EA = 2:1 to 1:1, v/v). TLC (CH/EA = 1:2, v/v): $R_f$ = 0.17; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.48 (s, 1H), 4.58 (s, 2H), 4.21 (t, J = 5.3 Hz, 2H), 3.94 (t, J = 5.3 Hz, 2H), 0.85 (s, 9H), −0.04 (s, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.57, 129.68, 121.19, 62.17, 56.01, 54.63, 25.76, 18.18, −5.63. HPLC (5–100% solvent B, 3 min) Rt = 1.859 min, purity (220 nm): 95%.

### (1-(3-((Tert-butyldimethylsilyl)oxy)propyl)-1H-Pyrazol-4-yl)metanol (22 f)

**22 f** was synthesized following general procedure E starting from **21 f** (150 mg, 1.07 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 1.1 mL, 1.10 mmol, 1.00 equiv) in THF (5 mL), stirring overnight. **22 f** (99 mg, 34%) was obtained without further purification. TLC (CH/EA = 2:1, v/v): $R_f$ = 0.53; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.41 (s, 1H), 4.58 (s, 2H), 4.21 (t, J = 6.9 Hz, 2H), 3.59 (t, J = 5.8 Hz, 2H), 2.05 (p, J = 6.4 Hz, 2H), 0.92 (s, 9H), 0.06 (s, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.68, 128.73, 121.21, 59.66, 56.18, 48.94, 33.19, 26.03, 18.38, −5.27. HPLC (5–100% solvent B, 3 min) Rt = 1.979 min, purity (220 nm): 95%.

### (1-(2-Methoxyethyl)-1H-Pyrazol-4-yl)methanol (22 g)

**22 g** was synthesized following the general procedure E starting from **21 g** (100 mg, 0.50 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 0.50 mL, 0.50 mmol, 1.00 equiv) in THF (5 mL), stirring overnight. **22 g** (50 mg, 63%) was obtained without further purification. TLC (DCM/MeOH = 9:1, v/v): $R_f$ = 0.58; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.49 (s, 1H), 4.59 (s, 2H), 4.27 (t, J = 5.2 Hz, 2H), 3.76–3.72 (m, 2H), 3.34 (d, J = 0.7 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.71, 129.16, 121.46, 71.16, 58.95, 56.05, 52.09. HPLC (5–100% solvent B, 3 min) Rt = 0.782 min, purity (220 nm): 94%.

### (1,3-Dimethyl-1H-Pyrazol-4-yl)methanol (22 h)

**22 h** (160 mg, 54%) was synthesized following the general procedure D starting from the commercially available 1,3-dimethyl-1H-pyrazole-4-carbaldehyde **21 h** (250 mg, 2.01 mmol, 1.00 equiv) and $NaBH_4$ (152 mg, 4.03 mmol, 2.00 equiv) in THF (5.4 mL) and MeOH (7.2 mL). **22 h** (160 mg, 54%) was obtained after purification by flash column chromatography (DCM/MeOH = 25:1 v/v). TLC (DCM/MeOH 19:1, v/v): $R_f$ = 0.40; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.20 (s, 1H), 4.43 (s, 2H), 3.71 (s, 3H), 2.17 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 147.04, 130.07, 119.07, 54.97, 38.34, 11.38.

### (3-Methyl-1-Propyl-1H-Pyrazol-4-yl)methanol (22 i)

**22 i** was synthesized following the general procedure D starting from the commercially available 3-methyl-1-propyl-1H-pyrazole-4-carbaldehyde **21 i** (154 mg, 0.99 mmol, 1.00 equiv) and $NaBH_4$ (115 mg, 2.96 mmol, 2.00 equiv) in THF (2.7 mL) and MeOH (5.30 mL). The crude product was purified by flash column chromatography (CH/EA = 1:1, v/v) to give **22 i** (129 mg, 85%). TLC (CH/EA = 1:1 v/v): $R_f$ = 0.17; $^1$H NMR (300 MHz, MeOD) δ 7.48 (s, 1H), 4.84 (s, 2H), 3.98 (t, J = 7.0 Hz, 2H), 2.23 (s, 3H), 1.81 (h, J = 7.3 Hz, 2H), 0.88 (t, J = 7.4 Hz, 3H).$^{13}$C NMR (75 MHz, MeOD) δ 146.78, 130.01, 118.53, 53.84, 52.73, 23.40, 9.98, 9.90.

### (1,5-Dimethyl-1H-Pyrazol-4-yl)methanol (22 j)

**22 j** was synthesized following the general procedure D with **21 j** (290 mg, 2.34 mmol, 1.00 equiv) and $NaBH_4$ (177 mg, 4.67 mmol, 2.00 equiv) in THF (6 mL) and MeOH (8.5 mL). The crude product was used without further purification (160 mg, 54%). TLC (DCM/MeOH = 9:1, v/v): $R_f$ = 0.41; $^1$H NMR (500 MHz, MeOD) δ 7.36 (s, 1H), 4.43 (s, 2H), 3.75 (d, J = 1.6 Hz, 3H), 2.27 (s, 3H). $^{13}$C NMR (126 MHz, MeOD) δ 137.67, 137.55, 118.44, 54.03, 34.76, 7.76.

### (1-Ethyl-5-Methyl-1H-Pyrazol-4-yl)methanol (22 k)

**22 k** was synthesized following the general procedure E starting from **21 k** (70 mg, 0.38 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 0.40 mL, 0.40 mmol, 1.00 equiv) in THF (3 mL), stirring for 2 h. The crude product was filtered through a silica plough to afford **22 k** (36 mg, 67%). TLC (DCM/MeOH = 9:1, v/v): $R_f$ = 0.30; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 4.51 (s, 2H), 4.09 (q, J = 7.3 Hz, 2H), 2.29 (s, 3H), 1.39 (t, J = 7.3 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.04, 136.63, 118.52, 55.78, 44.11, 15.42, 9.31. GCMS: (splitless, 10 min) Rt = 4.981 minutes, purity = 97%.

### (4,5,6,7-Tetrahydropyrazolo[1,5-a]pyridin-3-Yl)methanol (22 l)

**22 l** was synthesized following the general procedure E starting from the commercially available 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-carboxylic acid **21 l** (70 mg, 0.39 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 0.80 mL, 0.78 mmol, 1.00 equiv) in THF (3 mL), stirring overnight. **22 l** (59 mg, 92%) was obtained after purification by flash column chromatography (DCM/MeOH = 9:1, v/v). TLC (DCM/MeOH = 9:1, v/v): $R_f$ = 0.55; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 4.53 (s, 2H), 4.15 (t, J = 6.1 Hz, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.08–2.01 (m, 2H), 1.92–1.86 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.34, 137.69, 116.59, 55.34, 47.85, 23.28, 21.32, 20.16. HPLC (5–100% solvent B, 3 min) Rt = 1.065 min, purity (220 nm): 97%.

### (5,6-Dihydro-4H-Pyrrolo[1,2-b]pyrazol-3-yl)methanol (22 m)

**22 m** was synthesized following the general procedure E starting from the commercially available 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole-3-carboxylic acid **21 m** (50 mg, 0.33 mmol, 1.00 equiv) and $LiAlH_4$ (1 M in THF, 0.70 mL, 0.66 mmol, 1.00 equiv) in THF (3 mL), stirring overnight. **22 m** (30 mg, 67%) was obtained without any further purification. TLC (DCM/MeOH = 9:1, v/v): $R_f$ = 0.45; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 4.53 (d, J = 1.5 Hz, 2H), 4.12 (t, J = 7.3 Hz, 2H), 2.90 (t, J = 7.3 Hz, 2H), 2.65–2.58 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 144.49, 142.93, 113.83, 56.13, 47.71, 26.40, 22.27. HPLC (5–100% solvent B, 3 min) Rt = 0.832 min, purity (220 nm): 97%.

### (1-Methyl-1H-Pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 a)

The substrate **23 a** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (113 mg, 0.76 mmol, 4.00 equiv), **22 a** (21 mg, 0.19 mmol, 1.00 equiv), precursor **7** (80 mg, 0.19 mmol, 1.00 equiv) and EDC-HCl (40 mg, 0.21 mmol, 1.10 equiv) in toluene (4 mL). **23 a** (63 mg, 64%) was obtained after purification by flash column chromatography (CH/EA = 1:1, v/v). TLC (CH/EA = 1:1, v/v): $R_f$ = 0.17; Diastereomer ratio: 12:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.17 (s, 1H), 6.47 (s, 2H), 5.32 (q, J = 2.5 Hz, 1H), 4.97 (d, J = 12.4 Hz, 1H), 4.76 (d, J = 12.4 Hz, 1H), 3.88 (d, J = 7.2 Hz, 1H), 3.84 (s, 3H), 3.83–3.81 (m, 9H), 3.35 (d, J = 9.6 Hz, 1H), 2.79 (td, J = 13.2, 3.0 Hz, 1H), 2.23–2.17 (m, 1H), 2.10–2.04 (m, 1H), 1.90–1.83 (m, 1H), 1.71–1.51 (m, 7H), 1.42–1.37 (m, 1H), 1.32 (dt, J = 12.4, 3.1 Hz, 2H), 1.22–1.16 (m, 1H), 1.16–1.06 (m, 1H), 0.80–0.62 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.50, 171.18, 152.95, 139.45, 136.72, 133.58, 130.45, 116.18, 105.90, 60.89, 57.57, 56.21, 55.17, 52.30, 43.68, 41.21, 38.91, 32.88, 30.77, 26.78, 26.63, 26.30, 26.26, 25.52, 21.01. HPLC (5–

100% solvent B, 3 min) Rt = 2.144 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 514.29116 calculated $[M+H]^+$, found 514.29162 $[M+H]^+$.

### (1-Ethyl-1H-pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 b)

The substrate **23 b** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (163 mg, 1.10 mmol, 4.00 equiv), **22 b** (35 mg, 0.27 mmol, 1.00 equiv), precursor **7** (115 mg, 0.27 mmol, 1.00 equiv) and EDC-HCl (58 mg, 0.30 mmol, 1.10 equiv) in toluene (5 mL). **23 b** (118 mg, 81%) was obtained after purification by flash column chromatography (DCM/MeOH = 20:1, v/v). TLC (DCM/MeOH = 50:1, v/v): $R_f$ = 0.23; Diastereomer ratio: 15:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.35 (s, 2H), 5.22–5.18 (m, 1H), 4.87 (d, J = 12.4 Hz, 1H), 4.65 (d, J = 12.4 Hz, 1H), 4.01 (q, J = 7.4 Hz, 2H), 3.75 (m, 1H), 3.72 (s, 6H), 3.70 (s, 3H), 3.23 (d, J = 9.6 Hz, 1H), 2.67 (td, J = 13.2, 3.0 Hz, 1H), 2.08 (dp, J = 13.9, 2.8 Hz, 1H), 2.02–1.88 (m, 1H), 1.75 (d, J = 12.6 Hz, 1H), 1.60–1.40 (m, 8H), 1.33 (t, J = 7.3 Hz, 3H), 1.20 (tt, J = 9.3, 4.8 Hz, 2H), 1.12–0.91 (m, 3H), 0.84–0.73 (m, 1H), 0.69–0.58 (m, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.51, 171.15, 152.89, 138.83, 136.67, 133.49, 129.08, 116.17, 105.87, 60.85, 57.45, 56.18, 52.26, 46.99, 43.62, 41.13, 32.84, 30.72, 26.72, 26.58, 26.24, 26.21, 25.44, 20.93, 15.42. HPLC (30–100% solvent B, 3 min) Rt = 1.868 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 528.30681 calculated $[M+H]^+$, found 528.30738 $[M+H]^+$.

### (1-Isopropyl-1H-Pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 c)

The substrate **23 c** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (42 mg, 0.29 mmol, 4.00 equiv), **22 c** (10 mg, 0.07 mmol, 1.00 equiv), precursor **7** (30 mg, 0.07 mmol, 1.00 equiv) and EDC-HCl (15 mg, 0.08 mmol, 1.1 equiv) in toluene (3 mL). **23 c** (20 mg, 51%) was obtained after purification by flash column chromatography (DCM/MeOH = 50:1, v/v). TLC (DCM/MeOH = 50:1, v/v): $R_f$ = 0.17; Diastereomer ratio: 14:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.35 (s, 1H), 6.49 (s, 2H), 5.35–5.32 (m, 1H), 5.01 (d, J = 12.4 Hz, 1H), 4.81 (d, J = 12.4 Hz, 1H), 4.54–4.43 (m, 1H), 3.89 (d, J = 1.1 Hz, 1H), 3.86 (d, J = 1.9 Hz, 9H), 3.37 (d, J = 9.6 Hz, 1H), 2.83 (td, J = 13.2, 3.0 Hz, 1H), 2.24–2.19 (m, 1H), 2.14–2.04 (m, 1H), 1.89 (d, J = 12.9 Hz, 1H), 1.74–1.55 (m, 7H), 1.48 (d, J = 6.7 Hz, 6H), 1.45–1.36 (m, 2H), 1.25–1.05 (m, 3H), 0.98–0.87 (m, 1H), 0.83–0.63 (m, 1H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.21, 171.31, 153.05, 138.93, 136.84, 133.60, 127.40, 115.93, 106.04, 60.99, 58.52, 57.74, 56.32, 55.33, 52.42, 43.73, 41.28, 33.00, 30.88, 26.91, 26.71, 26.39, 26.36, 25.58, 22.96, 21.05. HPLC (30–100% solvent B, 3 min) Rt = 1.958 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 542.32246 calculated $[M+H]^+$, found 542.32361 $[M+H]^+$.

### (1-Propyl-1H-Pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 d)

The substrate **23 d** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (42 mg, 0.29 mmol, 4.00 equiv), **22 d** (10 mg, 0.07 mmol, 1.00 equiv), precursor **7** (30 mg, 0.07 mmol, 1.00 equiv) and EDC-HCl (15 mg, 0.08 mmol, 1.10 equiv) in toluene (1.5 mL). **23 d** (39 mg, 60%) was obtained after purification by flash column chromatography (DCM/MeOH = 20:1, v/v). TLC (DCM/MeOH = 50:1, v/v): $R_f$ = 0.20; Diastereomer ratio: 18:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.28 (s, 1H), 6.49 (s, 2H), 5.35–5.32 (m, 1H), 5.01 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 12.7 Hz, 1H), 4.08–4.03 (m, 2H), 3.86 (s, 1H), 3.86 (s, 6H), 3.84 (s, 3H), 3.37 (d, J = 9.6 Hz, 1H), 2.80 (td, J = 13.2, 3.0 Hz, 1H), 2.21 (d, J = 13.4 Hz, 1H), 2.14–2.01 (m, 2H), 1.96–1.80 (m, 2H), 1.74–1.51 (m, 6H), 1.48–1.39 (m, 1H), 1.38–1.31 (m, 2H), 1.23–1.16 (m, 3H), 0.90–0.86 (m, 3H), 0.77 (qd, J = 12.3, 3.1 Hz, 1H), 0.72–0.65 (m, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.62, 171.26, 153.02, 139.06, 136.81, 133.60, 129.95, 116.16, 106.02, 60.97, 57.55, 56.30, 55.29, 53.91, 52.36, 43.73, 41.25, 32.98, 30.85, 26.91, 26.85, 26.70, 26.34, 25.57, 23.72, 21.04, 11.13. HPLC (30–100% solvent B, 3 min) Rt = 1.968 min, purity (220 nm): 97%. HRMS (ESI+): m/z: 542.32246 calculated $[M+H]^+$, found 542.32320 $[M+H]^+$.

### (1-(2-Hydroxyethyl)-1H-Pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (24 e)

The intermediate **23 e** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), **22 e** (31 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **23 e** (33 mg, 42%) was obtained after purification by flash column chromatography (CH/EA = 5:1 to 3:1, v/v). TLC (CH/EA = 1:1 + 1% HCOOH, v/v/v): $R_f$ = 0.38; HPLC (5–100% solvent B, 3 min) Rt = 2.610 min, purity (220 nm): >99%.

**23 e** (33 mg, 0.05 mmol, 1.00 equiv) was applied to the general procedure H with TBAF (1 M in THF, 0.05 mL, 0.05 mmol, 1.00 equiv) in THF (1.5 mL). **24 e** (16 mg, 59%) was obtained after purification by flash column chromatography (DCM/MeOH = 9:1, v/v). TLC (DCM/MeOH = 9:1, v/v): $R_f$ = 0.31; Diastereomer ratio: 14:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.25 (s, 1H), 6.49 (s, 2H), 5.33–5.28 (m, 1H), 5.06 (d, J = 12.5 Hz, 1H), 4.77 (d, J = 12.5 Hz, 1H), 4.21 (d, J = 4.9 Hz, 2H), 3.95 (t, J = 4.7 Hz, 2H), 3.91–3.89 (m, 1H), 3.86 (s, 3H), 3.85 (s, 6H), 3.36 (d, J = 9.7 Hz, 1H), 2.81 (t, J = 13.3 Hz, 1H), 2.26–2.19 (m, 1H), 2.09 (qd, J = 13.6, 5.6 Hz, 1H), 1.88 (d, J = 12.3 Hz, 1H), 1.74–1.53 (m, 6H), 1.48–1.38 (m, 1H), 1.38–1.29 (m, 3H), 1.24–1.06 (m, 2H), 0.96–0.85 (m, 1H), 0.77 (qd, J = 12.2, 3.3 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.62, 171.30, 153.04, 139.17, 136.64, 133.77, 130.79, 116.40, 105.96, 61.78, 61.04, 57.66, 56.35, 55.31, 54.11, 52.58, 43.94, 41.27, 32.96, 30.83, 26.77, 26.69, 26.35, 26.30, 25.58, 21.11. HPLC (5–100% solvent B, 3 min) Rt = 1.997 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 544.30173 calculated $[M+H]^+$, found 544.30173 $[M+H]^+$.

### (1-(3-Hydroxypropyl)-1H-Pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (24 f)

The intermediate **23 f** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (141 mg, 0.95 mmol, 4.00 equiv), **22 f** (64 mg, 0.24 mmol, 1.0 equiv), precursor **7** (100 mg, 0.24 mmol, 1.00 equiv) and EDC-HCl (50 mg, 0.26 mmol, 1.10 equiv) in toluene (6 mL). **23 f** (80 mg, 50%) was obtained after purification by flash column chromatography (CH/EA = 2:1, v/v). TLC (CH/EA = 2:1, v/v): $R_f$ = 0.17; HPLC (50–100% solvent B, 3 min) Rt = 2.296 min, purity (220 nm): 72%.

**23 f** (50 mg, 0.07 mmol, 1.00 equiv) was applied to the general procedure H with TBAF (1 M in THF, 0.07 mL, 0.07 mmol, 1.00 equiv) in THF (1.5 mL). **24 f** (36 mg, 88%) was obtained after purification by flash column chromatography (DCM/MeOH = 20:1, v/v). TLC (DCM/MeOH = 9:1, v/v): $R_f$ = 0.50; Diastereomer ratio: 11:1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.23 (s, 1H), 6.48 (s, 2H), 5.31 (t, J = 3.5 Hz, 1H), 5.06 (d, J = 12.4 Hz, 1H), 4.75 (d, J = 12.4 Hz, 1H), 4.21 (t, J = 6.5 Hz, 2H), 3.89 (d, J = 3.7 Hz, 1H), 3.85 (s, 9H), 3.55 (tt, J = 11.7, 5.6 Hz, 2H), 3.37 (d, J = 9.7 Hz, 1H), 2.78 (td, J = 13.3, 3.0 Hz, 1H), 2.22 (d, J = 14.2 Hz, 1H), 2.07 (ddt, J = 17.7, 11.8, 7.0 Hz, 1H), 1.99 (p, J =

6.0 Hz, 2H), 1.88 (d, J = 12.8 Hz, 1H), 1.72–1.56 (m, 7H), 1.37–1.29 (m, 3H), 1.21 (dt, J = 12.6, 3.7 Hz, 1H), 1.16 (dd, J = 11.8, 5.5 Hz, 1H), 0.81–0.66 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.73, 171.22, 153.00, 139.50, 136.73, 133.61, 130.36, 116.29, 105.99, 60.98, 59.21, 57.67, 56.29, 55.30, 52.47, 49.05, 43.76, 41.20, 32.95, 32.72, 30.83, 26.75, 26.68, 26.34, 26.29, 25.52, 21.01. HPLC (5–100% solvent B, 3 min) Rt = 1.999 min, purity (220 nm): 98%. HRMS (ESI+): m/z: 558.31788 calculated $[M+H]^+$, found 558.31803 $[M+H]^+$.

### (1-(2-Methoxyethyl)-1H-Pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 g)

The substrate **23 g** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), **22 g** (19 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.1 equiv) in toluene (3 mL). **23 g** (24 mg, 36%) was obtained after purification by flash column chromatography (CH/EA = 1 : 1, v/v). TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.22; Diastereomer ratio: 14 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.35 (s, 1H), 6.48 (s, 2H), 5.33 (dd, J = 6.0, 2.5 Hz, 1H), 4.99 (d, J = 12.3 Hz, 1H), 4.81 (d, J = 12.3 Hz, 1H), 4.22 (td, J = 5.1, 1.3 Hz, 2H), 3.89 (d, J = 3.7 Hz, 1H), 3.85 (d, J = 1.3 Hz, 6H), 3.83 (s, 3H), 3.70 (t, J = 5.3 Hz, 2H), 3.37 (d, J = 9.7 Hz, 1H), 3.30 (s,3H), 2.84 (td, J = 13.3, 3.0 Hz, 1H), 2.23–2.18 (m, 1H), 2.13–2.06 (m, 2H), 1.88 (d, J = 12.6 Hz, 1H), 1.72–1.54 (m, 7H), 1.47–1.26 (m, 1H), 1.26–1.05 (m, 3H), 0.92 (qd, J = 12.3, 3.5 Hz, 1H), 0.73 (dqd, J = 34.6, 12.1, 3.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.62, 171.20, 153.00 139.74, 136.80, 133.57 130.55, 116.26, 105.98, 71.16, 60.94, 59.01, 57.70, 56.27, 55.26, 52.35, 52.18, 43.69, 41.27, 32.96, 30.84, 26.89, 26.69, 26.37, 26.34, 25.58, 21.04. HPLC (30–100% solvent B, 3 min) Rt = 1.803 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 558.31738 calculated $[M+H]^+$, found 558.31759 $[M+H]^+$.

### (1,3-Dimethyl-1H-Pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 h)

The substrate **23 h** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), **22 h** (15 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **23 h** (56 mg, 89%) was obtained after purification by flash column chromatography (DCM/MeOH = 50 : 1, v/v). TLC (CH/EA = 1 : 1 + 1% HCOOH, v/v/v): $R_f$ = 0.17; Diastereomer ratio: 16 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.47 (s, 2H), 5.35–5.31 (m, 1H), 4.97 (d, J = 12.4 Hz, 1H), 4.73 (d, J = 12.7 Hz, 1H), 3.88 (d, J = 14.1 Hz, 1H), 3.85–3.81 (m, 9H), 3.76 (s, 3H), 3.35 (d, J = 9.7 Hz, 1H), 2.81 (td, J = 13.2, 2.8 Hz, 1H), 2.23–2.17 (m, 1H), 2.10 (s, 3H), 2.08–2.01 (m, 1H), 1.86 (d, J = 12.2 Hz, 1H), 1.71–1.49 (m, 7H), 1.46–1.02 (m, 5H), 0.79–0.61 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.51, 171.16, 152.98, 147.64, 136.73, 133.61, 131.59, 113.89, 105.84, 60.89, 57.18, 56.20, 55.17, 52.32, 43.66, 41.33, 38.58, 32.91, 30.79, 26.92, 26.64, 26.31, 26.28, 25.55, 21.08, 11.36. HPLC (5–100% solvent B, 3 min) Rt = 2.124 min, purity (220 nm): 99%. HRMS (ESI+): m/z: 528.30681 calculated $[M+H]^+$, found 528.30751 $[M+H]^+$.

### (3-Methyl-1-Propyl-1H-Pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 i)

The substrate **23 i** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (141 mg, 0.95 mmol, 4.00 equiv), **22 i** (37 mg, 0.24 mmol, 1.00 equiv), precursor **7** (100 mg, 0.24 mmol, 1.00 equiv) and EDC-HCl (50 mg, 0.26 mmol, 1.10 equiv) in toluene (5 mL). **23 i** (77 mg, 78%) was obtained after purification by flash column chromatography (DCM/MeOH = 20 : 1, v/v). TLC (CH/EA = 1 : 1, v/v): $R_f$ = 0.50; Diastereomer ratio: 23 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.45 (s, 2H), 5.32–5.27 (m, 1H), 4.95 (d, J = 12.4 Hz, 1H), 4.72 (d, J = 12.4 Hz, 1H), 3.90 (t, J = 7.1 Hz, 2H), 3.86–3.81 (m, 1H), 3.81 (s, 9H), 3.32 (d, J = 9.6 Hz, 1H), 2.78 (td, J = 13.3, 3.0 Hz, 1H), 2.18–2.13 (m, 1H), 2.08 (s, 3H), 2.06–2.00 (m, 1H), 1.86–1.73 (m, 3H), 1.68–1.47 (m, 7H), 1.40–1.24 (m, 3H), 1.20–0.99 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H), 0.77–0.59 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.54, 171.13, 152.99, 147.47, 136.82, 133.54, 130.74, 113.51, 105.94, 60.86, 57.24, 56.21, 55.20, 53.58, 52.31, 43.61, 41.32, 32.92, 30.79, 26.95, 26.64, 26.31, 26.30, 25.53, 23.68, 21.02, 11.41, 11.09. HPLC (30–100% solvent B, 3 min) Rt = 2.296 min, purity (220 nm): >99%. HRMS (ESI+): m/z: 556.33811calculated $[M+H]^+$, found 556.33850 $[M+H]^+$.

### (1,5-Dimethyl-1H-Pyrazol-4-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 j)

The substrate **23 j** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (42 mg, 0.43 mmol, 4.00 equiv), **22 j** (9 mg, 0.07 mmol, 1.00 equiv), precursor **7** (30 mg, 0.07 mmol, 1.00 equiv) and EDC-HCl (15 mg, 0.08 mmol, 1.10 equiv) in toluene (3 mL). **23 j** (28 mg, 74%) was obtained after purification by flash column chromatography (CH/EA = 1 : 1 + 1% HCOOH, v/v/v). TLC (CH/EA = 1 : 1 + 1% HCOOH, v/v/v): $R_f$ = 0.17; Diastereomer ratio: 17 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.48 (s, 2H), 5.36–5.33 (m, 1H), 4.94 (d, J = 12.5 Hz, 1H), 4.80 (d, J = 12.5 Hz, 1H), 3.93–3.91 (m, 1H), 3.85 (s, 3H), 3.84 (d, J = 2.3 Hz, 6H), 3.79 (s, 3H), 3.37 (d, J = 9.7 Hz, 1H), 2.87 (td, J = 13.3, 3.0 Hz, 1H), 2.24–2.18 (m, 1H), 2.09 (s, 3H), 2.08–2.02 (m, 1H), 1.90–1.82 (m, 1H), 1.75–1.56 (m, 8H), 1.41 (t, J = 4.0 Hz, 1H), 1.22 (ddd, J = 16.2, 8.2, 3.6 Hz, 1H), 1.16 (dd, J = 13.0, 3.5 Hz, 1H), 1.08 (dt, J = 9.1, 3.6 Hz,1H), 0.97–0.87 (m, 1H), 0.76 (qd, J = 11.9, 3.1 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.60, 171.19, 153.04, 139.09, 138.26, 136.80, 133.71, 113.79, 105.90, 60.98, 57.50, 56.30, 55.18, 52.39, 43.79, 41.39, 36.32, 32.95, 30.87, 26.97, 26.70, 26.36, 26.34, 25.64, 21.16, 9.16. HPLC (30–100% solvent B, 3 min) Rt = 1.804 min, purity (220 nm): 95%. HRMS (ESI+): m/z: 528.30681 calculated $[M+H]^+$, found 528.30711 $[M+H]^+$.

### (1-Ethyl-5-Methyl-1H-Pyrazol-4-Yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 k)

The substrate **23 k** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), **22 k** (17 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **23 k** (37 mg, 57%) was obtained after purification by flash column chromatography (CH/EA = 1 : 1, v/v). TLC (CH/EA = 1 : 1 + 1% HCOOH, v/v/v): $R_f$ = 0.23; Diastereomer ratio: 13 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.48 (s, 2H), 5.35–5.31 (m, 1H), 4.95 (d, J = 12.4 Hz, 1H), 4.80 (d, J = 12.5 Hz, 1H), 4.05 (q, J = 7.3 Hz, 2H), 3.90–3.86 (m,1H), 3.85 (d, J = 1.2 Hz, 9H), 3.36 (d, J = 9.6 Hz, 1H), 2.88 (td, J = 13.3, 3.0 Hz, 1H), 2.22–2.16 (m, 1H), 2.11 (s, 3H), 1.86 (td, J = 12.1, 5.8 Hz, 1H), 1.72–1.51 (m, 7H), 1.36 (t, J = 7.3 Hz, 3H), 1.33–1.26 (m, 3H), 1.25–1.04 (m, 3H), 0.91 (qd, J = 12.4, 3.5 Hz, 1H), 0.80–0.63 (m, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.58, 171.14, 153.01, 139.38, 139.09, 136.79, 133.65, 113.50, 105.90, 60.93, 57.66, 56.26, 55.18, 52.36, 44.14, 41.37, 39.54, 32.94, 30.85, 27.01, 26.67, 26.35, 26.33, 25.61, 20.10, 15.30, 9.01. HPLC (5–100% solvent B, 3 min) Rt = 2.180 min, purity (220 nm): 98%. HRMS (ESI+): m/z: 542.32246 calculated $[M+H]^+$, found 542.32316 $[M+H]^+$.

**(4,5,6,7-Tetrahydropyrazolo[1,5-A]pyridin-3-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 l)**

The substrate **23 l** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), **22 l** (18 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **23 l** (43 mg, 65 %) was obtained after purification by flash column chromatography (CH/EA = 1 : 1, v/v). TLC (CH/EA = 1 : 2, v/v): $R_f$ = 0.27; Diastereomer ratio: 9 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.49 (s, 2H), 5.34–5.31 (m, 1H), 4.95 (d, J = 12.4 Hz, 1H), 4.78 (d, J = 12.3 Hz, 1H), 4.09 (t, J = 6.1 Hz, 2H), 3.89 (d, J = 3.2 Hz, 1H), 3.85 (s, 6H), 3.84 (s, 3H), 3.37 (d, J = 9.5 Hz, 1H), 2.88 (td, J = 13.3, 3.0 Hz, 1H), 2.67 (dt, J = 16.7, 6.4 Hz, 1H), 2.57 (dt, J = 16.8, 6.5 Hz, 1H), 2.22–2.17 (m, 1H), 2.12–2.01 (m, 3H), 1.98 (qd, J = 5.9, 4.5 Hz, 2H), 1.88 (ddq, J = 15.3, 9.1, 2.7 Hz, 1H), 1.72–1.52 (m, 7H), 1.41 (dt, J = 12.9, 3.9 Hz, 1H), 1.38–1.03 (m, 4H), 0.97–0.86 (m, 1H), 0.76 (td, J = 12.2, 9.1 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.58, 171.11, 152.99, 139.35, 138.59, 136.79, 133.61, 111.75, 105.90, 60.92, 57.13, 56.25, 55.18, 52.36, 47.89, 43.67, 41.36, 32.94, 30.84, 26.99, 26.66, 26.32, 25.58, 24.49, 23.25, 21.38, 21.17, 20.09. HPLC (5–100 % solvent B, 3 min) Rt = 2.234 min, purity (220 nm): > 99 %. HRMS (ESI+): m/z: 554.32264 calculated $[M+H]^+$, found 554.32265 $[M+H]^+$.

**(5,6-Dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)methyl (S)-1-((S)-2-Cyclohexyl-2-(3,4,5-Trimethoxyphenyl)acetyl)piperidine-2-Carboxylate (23 m)**

The substrate **23 m** was synthesized following the general procedure A with 4-(pyrrolidin-1-yl)pyridine (71 mg, 0.48 mmol, 4.00 equiv), **22 m** (16 mg, 0.12 mmol, 1.00 equiv), precursor **7** (50 mg, 0.12 mmol, 1.00 equiv) and EDC-HCl (25 mg, 0.13 mmol, 1.10 equiv) in toluene (3 mL). **23 m** (41 mg, 64 %) was obtained after purification by flash column chromatography (CH/EA = 1 : 1, v/v). TLC (CH/EA = 1 : 2, v/v): $R_f$ = 0.25; Diastereomer ratio: 10 : 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.49 (s, 2H), 5.36–5.33 (m, 1H), 4.94 (d, J = 12.3 Hz, 1H), 4.80 (d, J = 12.3 Hz, 1H), 4.11–4.06 (m, 2H), 3.92–3.87 (m, 1H), 3.85 (d, J = 1.7 Hz, 9H), 3.37 (d, J = 9.7 Hz, 1H), 2.95–2.84 (m, 2H), 2.72 (q, J = 7.3 Hz, 2H), 2.58–2.51 (m, 1H), 2.25–2.19 (m, 1H), 1.86 (ddt, J = 13.3, 7.2, 3.2 Hz, 1H), 1.73–1.51 (m, 6H), 1.37–1.04 (m, 6H), 0.97–0.83 (m, 1H), 0.81–0.70 (m, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.59, 171.16, 153.00, 143.90, 136.81, 134.42, 133.65, 129.45, 108.96, 105.93, 60.95, 57.88, 56.27, 55.18, 52.37, 47.93, 43.73, 41.25, 32.95, 30.85, 26.98, 26.68, 26.35, 26.34, 25.62, 24.50, 22.36, 21.15. HPLC (5–100 % solvent B, 3 min) Rt = 2.198 min, purity (220 nm): > 99 %. HRMS (ESI+): m/z: 540.30681 calculated $[M+H]^+$, found 540.30748 $[M+H]^+$.

## Supporting Information

Additional information regarding crystallography, chemical synthesis and biological data can be found in the supplementary material of this article.

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## *Conflict of Interests*

The authors declare no conflict of interest.

## *Data Availability Statement*

The data that support the findings of this study are available in the supplementary material of this article.

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