Illuminating N-acylethanolamine biosynthesis with new chemical tools
Mock, E.D.

Citation

Version: Publisher's Version
License: Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from: https://hdl.handle.net/1887/80154

Note: To cite this publication please use the final published version (if applicable).
Chapter 3

Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401

3.1 Introduction

N-acylphosphatidylethanolamine phospholipase D (NAPE-PLD) is considered to be the principal enzyme in the brain that produces N-acylethanolamines (NAEs), a family of signaling lipids.\(^1\) NAPE-PLD catalyzes the hydrolysis of N-acylphosphatidylethanolamines (NAPEs) to NAEs, which includes the endocannabinoid anandamide.\(^2\) Through activation of the cannabinoid receptors 1 and 2 (CB\(_1\) and CB\(_2\)), as well as the ion channel transient receptor potential vanilloid 1 (TRPV1), anandamide regulates various physiological processes such as appetite, pain, fertility, stress and anxiety.\(^3\)

Decreased levels of saturated, mono- and poly-unsaturated NAEs have been observed in the brains of various strains of NAPE-PLD knock-out mice, although anandamide levels were not affected in all genetic mouse models.\(^4-7\) This suggested the existence of compensatory mechanisms in animals with long-term ablation of NAPE-PLD activity and has spurred the discovery of alternative NAE biosynthetic pathways.\(^1,8\) These genetic models highlight the necessity of a complementary approach to modulate anandamide
biosynthesis in an acute manner. Thus, there is a need for pharmacological tools that inhibit the function of NAPE-PLD. Previously, several NAPE-PLD inhibitors have been described, but they lack the potency, selectivity or physicochemical properties to function as in situ or in vivo active NAPE-PLD inhibitors.\textsuperscript{9-11}

In Chapter 2, pyrimidine-4-carboxamides were identified as a novel chemotype of NAPE-PLD inhibitors in a high-throughput screening (HTS) campaign. Here, the structure-activity relationship (SAR) of a library of NAPE-PLD inhibitors is described. Starting from HTS hit 1 (Figure 1) a hit optimization program led to the discovery of LEI-401. Modification of the N-methylphenethylamine and morpholine substituents of compound 1, provided LEI-401 as a NAPE-PLD inhibitor with nanomolar activity and good physicochemical properties.

3.2 Results

To study the SAR of hit 1, different synthetic routes were employed that allowed systematic variation of the amide, morpholine and phenethylamine substituents as well as the pyrimidine scaffold. This led to the synthesis of compounds 2-105.

The influence of the nitrogen atoms in the pyrimidyl ring was investigated with pyridyl analogues 2 and 3 (Scheme 1). The synthesis of compound 2 commenced with the regioselective nucleophilic aromatic substitution (\textit{S}\textsubscript{N}Ar) of dichloride 106 with N-methylphenethylamine, which gave 107 (confirmed by \textsuperscript{1}H,\textsuperscript{13}C-HMBC and \textsuperscript{1}H-NOESY 2D NMR). Subsequent ester hydrolysis and amide coupling afforded 109, which was converted to 2 with morpholine using Buchwald-Hartwig amination conditions.\textsuperscript{12} Isomer 3 was synthesized in four steps from symmetric dichloride 110: \textit{S}\textsubscript{N}Ar with morpholine, ester hydrolysis and amide coupling giving 113, followed by similar Pd-catalyzed amination with N-methylphenethylamine.

Next, the systematic synthesis of amide, morpholine and phenethylamine analogues of 1 was performed. Amide derivatives were made via two general four-step sequences, which either produced the amide in the second or final step (Scheme 2A,B). The primary route depicted in Scheme 2A started with orotic acid (114), which was converted to acyl chloride 115 using phosphorous oxychloride. Cold addition (-78 °C to 0 °C) of various primary amines gave amides 116a-k. The more electrophilic 4-chloro substituent of the
dichloropyrimidine was regioselectively substituted with morpholine analogues to afford 117a-af (confirmed by 1H-NOESY 2D NMR). Finally, high temperature and/or microwave irradiation was used to couple different phenethylamine derivatives to the 2-chloropyrimidine scaffold, which provided the desired products. Non-commercially available N-methylphenethylamines were synthesized from benzyl halides 118a-b, that were converted to the corresponding nitrile (119a-b) followed by hydrogenation affording the primary amine (120a-b). Mono-N-methylation was achieved by carbamoylation and subsequent LiAlH₄ reduction, giving the N-methylphenethylamines 121a-o. Alternatively, phenethylamine was converted to the N-phenyl analogue 122 via Chan-Lam coupling or to N-alkyl derivatives 123a-e by reductive amination with aldehydes or ketones. The secondary route for introduction of the amide in the final step consisted of regioselective substitution of dichloropyrimidine 124 to give 125 (Scheme 2B). Then, ester hydrolysis followed by coupling with N-methylphenethylamine gave carboxylic acid 17, which was condensed with various amines. Molecules (2, 5, 18-21, 27, 28, 65, 66, 74-77) not listed in Scheme 1 or 2 were synthesized according to the routes described in the Supplementary Information (Supplementary Scheme 1-8).

Scheme 2. A) General synthetic route for compound 1 analogues. B) Alternative synthetic route for amide analogues. Reagents and conditions: a) POCl₃, DMF, reflux, 60%; b) R₁NH₂, Et₃N, DCM, -78 °C to 0 °C, 78% – 99%; c) (cyclo)alkylNH, DiPEA, MeOH, 0 °C, 32% – 99%, or (hetero)arylNH or heteroarylOH or heteroarylNH, K₂CO₃, DMF, rt, 51% – 76%; d) 121a-o or 122 or 123a-e, DiPEA, n-BuOH, μW, 160 °C or oil bath, 120 °C, 21% – 97%; e) KCN, EtOH, dioxane, H₂O, reflux, 84% – 99%; f) H₂, Pd/C, HCl, EtOH, rt, 98% – 99%; g) methyl chloroformate, DiPEA, DCM, 0 °C to rt; h) LiAlH₄, THF, 0 °C to reflux, 40% – 94% over 2 steps; i) phenylboronic acid, Cu(OAc)₂·H₂O, 4 Å MS, O₂, DCE, rt, 32%; j) aldehyde or ketone, NaB(OAc)₃·H, AcOH, DCM, rt, 18% – 63%. k) NaOH, THF, MeOH, H₂O, rt, 99%; l) N-methylphenethylamine, DiPEA, n-BuOH, 120 °C, 51%; m) R₁NH₂, PyBOP, DiPEA, DMF, 0 °C to rt, 43% – 55%.

A fluorescent NAPE-PLD activity assay was performed to measure the half maximum inhibitory concentration (IC₅₀) of inhibitors (2-105), as described previously (Chapter 2). The data are reported in Tables 1-7 as the pIC₅₀ ± SEM (N = 2, n = 2). First, to identify the essential pharmacophore of the scaffold, pyridyl analogues 2 and 3 and pyrimidyl regioisomer 4 were evaluated (Table 1). The removal of the X₂-nitrogen (compound 2),
but not $X_1$ (compound 3), resulted in a ten-fold drop in potency. This suggested that the $X_2$-nitrogen may form an important $H$-bond interaction with the protein, while the electron withdrawing effect seems less important. A significant decrease in potency was also observed for regioisomer 4, indicating that the scaffold of the hit was most optimal.

### Table 1. Activity data for hit 1 and scaffold analogues 2-4.

<table>
<thead>
<tr>
<th>ID</th>
<th>$X_1$</th>
<th>$X_2$</th>
<th>$X_3$</th>
<th>pIC$_{50}$ ± SEM</th>
<th>cLogP$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>N</td>
<td>CH</td>
<td>6.09 ± 0.04</td>
<td>3.84</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>CH</td>
<td>CH</td>
<td>4.98 ± 0.03</td>
<td>4.25</td>
</tr>
<tr>
<td>3</td>
<td>CH</td>
<td>N</td>
<td>CH</td>
<td>5.84 ± 0.03</td>
<td>3.90</td>
</tr>
<tr>
<td>4</td>
<td>CH</td>
<td>N</td>
<td>N</td>
<td>5.39 ± 0.11</td>
<td>3.84</td>
</tr>
</tbody>
</table>

$^a$ cLogP was calculated using Chemdraw 15.

Next, the influence of the amide $R_1$-substituent was investigated. Methylation of the amide in compound 1 resulted in complete loss of potency (compound 5, Table 2), suggesting that the amide may form another hydrogen bond, or, alternatively that the methyl group has a steric clash with the enzyme. Removal of the methylene group (6) reduced the activity, whereas linear alkylamides 7-12 showed optimal inhibition with a propyl chain. Branching of the alkyl substituent, introduction of heteroatoms or larger aromatic groups were less favorable (compounds 13, 14, 16, 24-26). The ten-fold drop in potency for isobutylamide 13 may be attributed to the increased size of the isobutyl group or lack of $\pi$-character compared to the cyclopropyl moiety. Of note, propargylamide 15 was equally active compared to the hit. Substituting the lipophilic amide for more polar analogues did not result in increased activities (compounds 17-23), although glycine methyl ester 19 showed to be equipotent to 1. The amide bioisostere imidazole 27 displayed a substantial decrease in potency. In conclusion, the cyclopropylmethylamide of 1 is the most optimal $R_1$-substituent and the SAR suggests that it occupies a small lipophilic pocket in NAPE-PLD.

To assess the influence of the $N$-methylphenethylamine moiety on the inhibitory activity, a large number of structural analogues (28-67) were evaluated (Tables 3-5).
Chapter 3

Analogues 28-50 demonstrated that the N-methylphenethylamine is important for inhibitory activity as its complete removal resulted in inactive compounds (28 and 29) (Table 3). N-Methyl was found to be preferred over the hydrogen of 30. A similar trend

Table 2. Structure-activity relationship analysis of amide analogues 5-27.

<table>
<thead>
<tr>
<th>ID</th>
<th>R₁:</th>
<th>pIC₅₀ ± SEM</th>
<th>cLogPᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>6.09 ± 0.04</td>
<td>3.84</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>&lt;4.3</td>
<td>2.71</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>5.43 ± 0.07</td>
<td>3.45</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>4.75 ± 0.08</td>
<td>2.52</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>4.87 ± 0.07</td>
<td>2.87</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>5.34 ± 0.11</td>
<td>3.40</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>5.74 ± 0.09</td>
<td>3.93</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>5.17 ± 0.08</td>
<td>4.45</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>4.46 ± 0.10</td>
<td>5.51</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>5.15 ± 0.09</td>
<td>4.32</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>4.67 ± 0.08</td>
<td>4.72</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>6.04 ± 0.06</td>
<td>3.29</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>4.48 ± 0.07</td>
<td>3.66</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>&lt;4.3</td>
<td>3.29</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>&lt;4.3</td>
<td>2.66</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>6.08 ± 0.03</td>
<td>2.87</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>4.77 ± 0.06</td>
<td>2.01</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>5.30 ± 0.04</td>
<td>2.31</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>4.96 ± 0.03</td>
<td>3.07</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>4.51 ± 0.02</td>
<td>2.27</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>4.49 ± 0.03</td>
<td>3.18</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>4.63 ± 0.07</td>
<td>4.84</td>
</tr>
<tr>
<td>26</td>
<td></td>
<td>&lt;4.3</td>
<td>6.72</td>
</tr>
<tr>
<td>27</td>
<td></td>
<td>4.39 ± 0.05</td>
<td>3.94</td>
</tr>
</tbody>
</table>

ᵃ cLogP was calculated using Chemdraw 15.
was apparent for benzylic amines 31 and 32. Reducing (31) or increasing the alkyl chain length (33, 34) decreased the potency, indicating that the two methylene chain length is optimal. Various large substituents (e.g. phenyl) on the phenyl group were tolerated, but

<table>
<thead>
<tr>
<th>ID</th>
<th>R₂:</th>
<th>pIC₅₀ ± SEM</th>
<th>cLogP⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>6.09 ± 0.04</td>
<td>3.84</td>
</tr>
<tr>
<td>28</td>
<td>Cl</td>
<td>&lt;4.3</td>
<td>1.58</td>
</tr>
<tr>
<td>29</td>
<td>H</td>
<td>&lt;4.3</td>
<td>0.84</td>
</tr>
<tr>
<td>30</td>
<td><img src="image2" alt="Image" /></td>
<td>5.56 ± 0.06</td>
<td>3.76</td>
</tr>
<tr>
<td>31</td>
<td><img src="image3" alt="Image" /></td>
<td>5.04 ± 0.08</td>
<td>3.51</td>
</tr>
<tr>
<td>32</td>
<td><img src="image4" alt="Image" /></td>
<td>4.64 ± 0.10</td>
<td>3.11</td>
</tr>
<tr>
<td>33</td>
<td><img src="image5" alt="Image" /></td>
<td>5.50 ± 0.07</td>
<td>4.22</td>
</tr>
<tr>
<td>34</td>
<td><img src="image6" alt="Image" /></td>
<td>5.00 ± 0.04</td>
<td>4.75</td>
</tr>
<tr>
<td>35</td>
<td><img src="image7" alt="Image" /></td>
<td>5.20 ± 0.08</td>
<td>4.55</td>
</tr>
<tr>
<td>36</td>
<td><img src="image8" alt="Image" /></td>
<td>5.61 ± 0.14</td>
<td>4.55</td>
</tr>
<tr>
<td>37</td>
<td><img src="image9" alt="Image" /></td>
<td>6.01 ± 0.07</td>
<td>4.55</td>
</tr>
<tr>
<td>38</td>
<td><img src="image10" alt="Image" /></td>
<td>5.74 ± 0.07</td>
<td>4.34</td>
</tr>
<tr>
<td>39</td>
<td><img src="image11" alt="Image" /></td>
<td>6.05 ± 0.07</td>
<td>4.29</td>
</tr>
<tr>
<td>40</td>
<td><img src="image12" alt="Image" /></td>
<td>5.46 ± 0.07</td>
<td>3.76</td>
</tr>
<tr>
<td>41</td>
<td><img src="image13" alt="Image" /></td>
<td>6.11 ± 0.04</td>
<td>3.76</td>
</tr>
<tr>
<td>42</td>
<td><img src="image14" alt="Image" /></td>
<td>5.21 ± 0.08</td>
<td>4.72</td>
</tr>
<tr>
<td>43</td>
<td><img src="image15" alt="Image" /></td>
<td>5.52 ± 0.10</td>
<td>5.94</td>
</tr>
<tr>
<td>44</td>
<td><img src="image16" alt="Image" /></td>
<td>5.46 ± 0.08</td>
<td>5.94</td>
</tr>
<tr>
<td>45</td>
<td><img src="image17" alt="Image" /></td>
<td>6.22 ± 0.06</td>
<td>5.94</td>
</tr>
<tr>
<td>46</td>
<td><img src="image18" alt="Image" /></td>
<td>6.31 ± 0.10</td>
<td>5.43</td>
</tr>
<tr>
<td>47</td>
<td><img src="image19" alt="Image" /></td>
<td>4.94 ± 0.07</td>
<td>2.34</td>
</tr>
<tr>
<td>48</td>
<td><img src="image20" alt="Image" /></td>
<td>4.97 ± 0.10</td>
<td>2.34</td>
</tr>
<tr>
<td>49</td>
<td><img src="image21" alt="Image" /></td>
<td>4.89 ± 0.04</td>
<td>2.34</td>
</tr>
<tr>
<td>50</td>
<td><img src="image22" alt="Image" /></td>
<td>5.97 ± 0.03</td>
<td>3.49</td>
</tr>
</tbody>
</table>

* cLogP was calculated using Chemdraw 15.
only at the ortho position, (compounds 35-46), suggesting that there is space in the binding pocket. Heteroatoms in the phenyl ring were not favorable (47-50), while the thiophene isostere 50 displayed similar potency compared to 1. N-Alkyl analogues 51-56 demonstrated that larger groups than methyl are allowed (Table 4). In particular, isopropyl derivative 52 displayed a two-fold increase in activity, albeit with a significant lipophilicity penalty. Next, several cyclic phenethylamine derivatives were evaluated (compounds 57-67), to study the effect of conformational restriction by reducing the number of rotatable bonds (Table 5). A two-fold activity improvement was observed for both 3-phenylpiperidine 59 and 2-benzylpyrrolidine 60. Introduction of heteroatoms in the piperidine ring was not favored as witnessed by morpholine 64 and piperazine 65, but the activity could be recovered by introducing a N-benzyl-group in the piperazine analogue 66.

Table 4. Structure-activity relationship analysis of N-methylphenethylamine analogues 51-56.

<table>
<thead>
<tr>
<th>ID</th>
<th>R₂:</th>
<th>pIC₅₀ ± SEM</th>
<th>cLogP&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>6.09 ± 0.04</td>
<td>3.84</td>
</tr>
<tr>
<td>51</td>
<td></td>
<td>6.19 ± 0.08</td>
<td>4.37</td>
</tr>
<tr>
<td>52</td>
<td></td>
<td>6.55 ± 0.07</td>
<td>4.68</td>
</tr>
<tr>
<td>53</td>
<td></td>
<td>5.96 ± 0.07</td>
<td>4.42</td>
</tr>
<tr>
<td>54</td>
<td></td>
<td>5.95 ± 0.09</td>
<td>5.61</td>
</tr>
<tr>
<td>55</td>
<td></td>
<td>6.13 ± 0.06</td>
<td>4.50</td>
</tr>
<tr>
<td>56</td>
<td></td>
<td>6.28 ± 0.16</td>
<td>5.79</td>
</tr>
</tbody>
</table>

<sup>a</sup>cLogP was calculated using Chemdraw 15.
Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401


<table>
<thead>
<tr>
<th>ID</th>
<th>R₂:</th>
<th>pIC₅₀ ± SEM</th>
<th>cLogP⁺</th>
<th>ID</th>
<th>R₂:</th>
<th>pIC₅₀ ± SEM</th>
<th>cLogP⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>6.09 ± 0.04</td>
<td>3.84</td>
<td>62</td>
<td></td>
<td>4.60 ± 0.10</td>
<td>5.59</td>
</tr>
<tr>
<td>57</td>
<td></td>
<td>5.65 ± 0.09</td>
<td>3.08</td>
<td>63</td>
<td></td>
<td>5.59 ± 0.09</td>
<td>3.76</td>
</tr>
<tr>
<td>58</td>
<td></td>
<td>5.66 ± 0.10</td>
<td>3.42</td>
<td>64</td>
<td></td>
<td>5.91 ± 0.03</td>
<td>2.59</td>
</tr>
<tr>
<td>59</td>
<td></td>
<td>6.42 ± 0.11</td>
<td>3.97</td>
<td>65</td>
<td></td>
<td>5.11 ± 0.06</td>
<td>2.58</td>
</tr>
<tr>
<td>60</td>
<td></td>
<td>6.42 ± 0.09</td>
<td>3.94</td>
<td>66</td>
<td>Bn</td>
<td>6.00 ± 0.12</td>
<td>5.02</td>
</tr>
<tr>
<td>61</td>
<td></td>
<td>6.13 ± 0.06</td>
<td>4.50</td>
<td>67</td>
<td>Chx</td>
<td>5.49 ± 0.11</td>
<td>5.49</td>
</tr>
</tbody>
</table>

⁺ cLogP was calculated using Chemdraw 15.

To study the SAR of the R₃-substituent, inhibitors 68-97 were evaluated (Table 6). Substitution of the morpholine for a more hydrophobic piperidine (68) was allowed, while the 3,3-difluoropiperidine 69 increased the potency two-fold. The 4-position of the morpholine ring was less favorable for substitution (compounds 70-77). Replacing the morpholine with a dimethylamine 78 increased the activity two-fold, suggesting that the morpholine is too polar or may experience steric hindrance in the pocket. Several other small alkylamines were tested (79-84). Pyrrolidine 84 was the most effective with almost a four-fold increase in potency. Substitutions on the pyrrolidine ring were investigated (compounds 85-91), revealing that hydroxylation on the 3-position (86) resulted in similar potency as pyrrolidine 84, while decreasing the cLogP with more than one log unit. Both enantiomers of the 3-hydroxytetrahydrofuran (87 and 88) were equally active. Of note, introduction of aromatic substituents was allowed (91-97), but did not improve the potency of the inhibitors.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>ID</th>
<th>R₃:</th>
<th>pIC₅₀ ± SEM</th>
<th>cLogP&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ID</th>
<th>R₃:</th>
<th>pIC₅₀ ± SEM</th>
<th>cLogP&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>6.09 ± 0.04</td>
<td>3.84</td>
<td>83</td>
<td></td>
<td>5.78 ± 0.03</td>
<td>3.68</td>
</tr>
<tr>
<td>68</td>
<td></td>
<td>6.19 ± 0.08</td>
<td>5.22</td>
<td>84</td>
<td></td>
<td>6.65 ± 0.09</td>
<td>4.66</td>
</tr>
<tr>
<td>69</td>
<td>F</td>
<td>6.41 ± 0.12</td>
<td>5.51</td>
<td>85</td>
<td>F</td>
<td>5.93 ± 0.10</td>
<td>4.95</td>
</tr>
<tr>
<td>70</td>
<td>F</td>
<td>5.05 ± 0.08</td>
<td>4.61</td>
<td>86</td>
<td>OH</td>
<td>6.65 ± 0.04</td>
<td>3.33</td>
</tr>
<tr>
<td>71</td>
<td>S</td>
<td>5.58 ± 0.08</td>
<td>4.67</td>
<td>87</td>
<td>OH</td>
<td>6.52 ± 0.03</td>
<td>3.33</td>
</tr>
<tr>
<td>72</td>
<td>SO₂</td>
<td>&lt;4.3</td>
<td>2.87</td>
<td>88</td>
<td>OH</td>
<td>6.63 ± 0.05</td>
<td>3.33</td>
</tr>
<tr>
<td>73</td>
<td>N</td>
<td>5.80 ± 0.04</td>
<td>4.40</td>
<td>89</td>
<td>O</td>
<td>6.15 ± 0.11</td>
<td>4.09</td>
</tr>
<tr>
<td>74</td>
<td>NH</td>
<td>5.27 ± 0.07</td>
<td>3.83</td>
<td>90</td>
<td>N</td>
<td>5.02 ± 0.03</td>
<td>4.28</td>
</tr>
<tr>
<td>75</td>
<td>NaC</td>
<td>5.92 ± 0.05</td>
<td>4.55</td>
<td>91</td>
<td></td>
<td>5.85 ± 0.08</td>
<td>6.22</td>
</tr>
<tr>
<td>76</td>
<td>NBz</td>
<td>5.11 ± 0.09</td>
<td>5.01</td>
<td>92</td>
<td></td>
<td>5.96 ± 0.05</td>
<td>6.32</td>
</tr>
<tr>
<td>77</td>
<td>NCbz</td>
<td>4.89 ± 0.09</td>
<td>6.74</td>
<td>93</td>
<td></td>
<td>6.81 ± 0.06</td>
<td>6.65</td>
</tr>
<tr>
<td>78</td>
<td></td>
<td>6.54 ± 0.05</td>
<td>4.55</td>
<td>94</td>
<td></td>
<td>5.92 ± 0.08</td>
<td>4.09</td>
</tr>
<tr>
<td>79</td>
<td></td>
<td>6.07 ± 0.06</td>
<td>4.47</td>
<td>95</td>
<td></td>
<td>5.65 ± 0.04</td>
<td>3.64</td>
</tr>
<tr>
<td>80</td>
<td>OH</td>
<td>6.00 ± 0.03</td>
<td>3.81</td>
<td>96</td>
<td></td>
<td>4.95 ± 0.11</td>
<td>5.74</td>
</tr>
<tr>
<td>81</td>
<td></td>
<td>6.30 ± 0.10</td>
<td>5.61</td>
<td>97</td>
<td></td>
<td>5.28 ± 0.05</td>
<td>4.25</td>
</tr>
<tr>
<td>82</td>
<td></td>
<td>6.37 ± 0.05</td>
<td>4.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> cLogP was calculated using Chemdraw 15.
Table 7. Structure-activity relationship analysis of optimized analogues 98-105.

<table>
<thead>
<tr>
<th>ID</th>
<th>R₁:</th>
<th>R₂:</th>
<th>R₃:</th>
<th>pIC₅₀ ± SEM</th>
<th>cLogPᵃ</th>
<th>LipEᵇ (hNAPE-PLD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hNAPE-PLD</td>
<td>mNAPE-PLD</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>6.09 ± 0.04</td>
<td>5.48 ± 0.04</td>
<td>3.84</td>
</tr>
<tr>
<td>78</td>
<td></td>
<td></td>
<td></td>
<td>6.54 ± 0.05</td>
<td>n.d.</td>
<td>4.55</td>
</tr>
<tr>
<td>98</td>
<td></td>
<td></td>
<td></td>
<td>6.95 ± 0.10</td>
<td>6.41 ± 0.10</td>
<td>4.68</td>
</tr>
<tr>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td>6.39 ± 0.11</td>
<td>n.d.</td>
<td>4.68</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td>6.68 ± 0.09</td>
<td>6.24 ± 0.09</td>
<td>3.97</td>
</tr>
<tr>
<td>101</td>
<td></td>
<td></td>
<td></td>
<td>4.76 ± 0.08</td>
<td>5.02 ± 0.08</td>
<td>3.01</td>
</tr>
<tr>
<td>102</td>
<td></td>
<td></td>
<td></td>
<td>7.14 ± 0.04</td>
<td>6.35 ± 0.04</td>
<td>3.46</td>
</tr>
<tr>
<td>(LEI-401)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>103</td>
<td></td>
<td></td>
<td></td>
<td>6.96 ± 0.04</td>
<td>6.42 ± 0.04</td>
<td>3.46</td>
</tr>
<tr>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td>6.60 ± 0.05</td>
<td>5.74 ± 0.05</td>
<td>3.46</td>
</tr>
<tr>
<td>105</td>
<td></td>
<td></td>
<td></td>
<td>6.49 ± 0.04</td>
<td>5.90 ± 0.04</td>
<td>3.46</td>
</tr>
</tbody>
</table>

ᵃ cLogP was calculated using Chemdraw 15;ᵇ Lipophilic efficiency (LipE) = pIC₅₀ − cLogP.

Combination of the optimal R₁ (cyclopropylmethylamide), R₂ ((R/S)-3-phenylpiperidine) and various R₃ substituents (dimethylamine, morpholine or (R/S)-3-hydroxypyrrolidine)
resulted in compounds 98-105 (Table 7). It was found that the combination of (S)-3-phenylpiperidine with (S)-3-hydroxyoxypyrrolidine afforded the most potent compound (102, pIC$_{50}$ = 7.14 ± 0.04), having a ten-fold increase in activity compared to 1. Interestingly, its (R,R)-enantiomer (compound 107) showed a three-fold reduced activity. In addition, the significant reduction of the cLogP for 102 resulted in the highest lipophilic efficiency (LipE = 3.68). In view of the inhibitory activity and optimal LipE it was decided to select compound 102 (termed LEI-401) as the lead compound for further biological profiling (Chapters 4-5).

Since the biological profiling of NAPE-PLD inhibitors is mostly performed in mouse models, it was assessed whether LEI-401 showed any species difference using recombinant mouse NAPE-PLD expressed in HEK293T cells. Despite high homology between human and mouse NAPE-PLD (89%), it was found that LEI-401 showed somewhat lower potency (pIC$_{50}$ = 6.35 ± 0.04) for mouse NAPE-PLD, although optimal activity compared to other inhibitors was retained (Table 7).

Table 8. hNAPE-PLD activity data and physicochemical parameters of 1 and 103 (LEI-401).

<table>
<thead>
<tr>
<th>Compound</th>
<th>pIC$_{50}$ ± SEM</th>
<th>K$_i$ (μM) 95% CI</th>
<th>cLogP$^b$</th>
<th>LipE$^c$</th>
<th>MW$^d$ (Da)</th>
<th>tPSA$^b$ (Å$^2$)</th>
<th>HBD$^e$</th>
<th>HBA$^f$</th>
<th>RB$^g$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structural formula" /></td>
<td>6.09 ± 0.04</td>
<td>0.30</td>
<td>3.84</td>
<td>2.31</td>
<td>396</td>
<td>69.5</td>
<td>1</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td><img src="image" alt="Structural formula" /></td>
<td>7.14 ± 0.04</td>
<td>0.027</td>
<td>0.021-0.033</td>
<td>3.46</td>
<td>3.68</td>
<td>422</td>
<td>80.5</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

$^a$ CI: Confidence interval; $^b$ cLogP and topological polar surface area (tPSA) were calculated using Chemdraw 15; $^c$ Lipophilic efficiency (LipE) = pIC$_{50}$ – cLogP; $^d$ MW: molecular weight; $^e$ HBD: H-bond donors; $^f$ HBA: H-bond acceptors; $^g$ RB: rotatable bonds.

A summary of the activity data and the physicochemical parameters of 1 and LEI-401 is shown in Table 8. Using the Cheng-Prusoff equation, the $K_i$ of LEI-401 was determined ($K_i = 27$ nM), making LEI-401 the first nanomolar potent inhibitor for NAPE-PLD.
Furthermore, LEI-401 shows promise as a lead candidate since its properties fall within the Rule of Five for drug-like molecules (MW $<$ 500, HBD $<$ 5, HBA $<$ 10, cLogP $<$ 5) as well as the Veber rules (tPSA $<$ 140 Å$^2$; RB $<$ 10). Due to a polar surface area below 90 Å$^2$, LEI-401 is expected to cross the blood-brain barrier (BBB), which will allow targeting of NAPE-PLD in the central nervous system.

3.3 Conclusion

In this chapter, the optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors is described. A map displaying an overview of the SAR is presented in Figure 2. Conformational restriction of the N-methylphenethylamine of hit compound 1 by introduction of a (S)-3-phenylpiperidine afforded a three-fold potency increase. Exchange of the morpholine for the smaller and more polar (S)-3-hydroxypyrrolidine gave a synergistic ten-fold increase in activity. This provided the nanomolar potent NAPE-PLD inhibitor LEI-401 ($K_i = 27$ nM), possessing favorable drug-like properties.

![Figure 2. Structure activity map for the pyrimidine-4-carboxamide NAPE-PLD inhibitor library.](image)

Acknowledgements

Ioli Kotsogianni, Jelle Vooijs and Carmen Fonseca are kindly acknowledged for their contributions with regard to compound synthesis and biochemical testing. Hans den Dulk is kindly thanked for generating NAPE-PLD plasmids. Hans van den Elst, Sebastian Grimm and Rian van den Nieuwendijk are kindly acknowledged for HPLC purification and optical rotation measurements.
3.4 Experimental section

A. Biological Procedures

NAPE-PLD surrogate substrate activity assay
The NAPE-PLD activity assay was performed as described in Chapter 2.

B. Synthetic Procedures

General
All chemicals (Sigma-Aldrich, Fluka, Acros, Merck, Combi-Blocks, Fluorochem, TCI) were used as received. All solvents used for reactions were of analytical grade. THF, Et₂O, DMF, CH₃CN and DCM were dried over activated 4 Å molecular sieves, MeOH over 3 Å molecular sieves. Flash chromatography was performed on silica gel (Screening Devices BV, 40-63 μm, 60 Å). The eluent EtOAc was of technical grade and distilled before use. Reactions were monitored by thin layer chromatography (TLC) analysis using Merck aluminium sheets (Silica gel 60, F₂₅₄). Compounds were visualized by UV-absorption (254 nm) and spraying for general compounds: KMnO₄ (20 g/L) and K₂CO₃ (10 g/L) in water, or for amines: ninhydrin (0.75 g/L) and acetic acid (12.5 mL/L) in ethanol, followed by charring at ~150 °C. ¹H and ¹³C NMR experiments were recorded on a Bruker AV-300 (300/75 MHz), Bruker AV-400 (400/101 MHz), Bruker DMX-400 (400/101 MHz), Bruker AV-500 (500/126 MHz) and Bruker AV-600 (600/151 MHz). Chemical shifts are given in ppm (δ) relative to tetramethylsilane or CDCl₃ as internal standards. Multiplicity: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, p = pentet, m = multiplet. Coupling constants (J) are given in Hz. LC-MS measurements were performed on a Thermo Finnigan LCQ Advantage MAX ion-trap mass spectrometer (ESI⁺) coupled to a Surveyor HPLC system (Thermo Finnigan) equipped with a standard C18 (Gemini, 4.6 mm D x 50 mm L, 5 μm particle size, Phenomenex) analytical column and buffers A: H₂O, B: CH₃CN, C: 0.1%aq. TFA. High resolution mass spectra were recorded on a LTQ Orbitrap (Thermo Finnigan) mass spectrometer or a Synapt G2-Si high definition mass spectrometer (Waters) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000) and dioctylphthalate (m/z = 391.28428) as a lock mass. Preparative HPLC was performed on a Waters Acquity Ultra Performance LC with a C18 column (Gemini, 150 x 21.2 mm, Phenomenex). All final compounds were determined to be > 95% pure by integrating UV intensity recorded via HPLC.

General procedure A:

A microwave tube with a magnetic stir bar was charged with the appropriate 2-chloropyrimidine (1 eq), n-BuOH (0.2 M), the appropriate amine (1.5 eq) and DiPEA (3-4 eq). The tube was capped, flushed with N₂ and heated to 160 °C in a microwave reactor (75 W) for 4-36 h or heated to 120 °C in an oil bath for 1-6 days. When the reaction was completed as judged by LC-MS, it was transferred to a round-bottom flask, concentrated under reduced pressure and coevaporated with toluene (2x). The residue was purified by silica
Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401.

gel column chromatography affording the product, or alternatively by HPLC-MS purification yielding the TFA salt. The free base was generated by dissolving the TFA salt in EtOAc, followed by washing with sat. aq. NaHCO₃ (2x). The organic layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure, affording the pure product.

**General procedure B:**

![Reaction Scheme](attachment:image1.png)

A round-bottom flask was charged with carboxylic acid (1 eq) and dissolved in dry DMF (0.2 M). PyBOP (1.2-1.5 eq), DiPEA (3-5 eq) and the appropriate amine (1.2-5 eq) were added and the mixture was stirred overnight at rt. Work-up involved dilution with EtOAc, washing with H₂O (1x) and brine (2x), drying (Na₂SO₄), filtering and concentration under reduced pressure. The residue was purified by silica gel column chromatography affording the pure product.

**General procedure C:**

![Reaction Scheme](attachment:image2.png)

A microwave vial was charged with the dichloropyrimidine (1 eq) and dry MeOH (0.1 M) and cooled to 0 °C. DiPEA (1.5-2.5 eq) and the appropriate amine (1.05 eq) were added and the mixture was stirred for 1-2 h at 0 °C. The solvents were evaporated under reduced pressure. The vial was charged with n-BuOH (0.2 M), N-methylphenethylamine (1.5 eq) and DiPEA (3-4 eq). The tube was capped, flushed with N₂ and heated to 160 °C in a microwave reactor (75 W) for 4 h. When the reaction was completed as judged by LC-MS, it was transferred to a round-bottom flask, concentrated under reduced pressure and co-evaporated with toluene (2x). The residue was purified by silica gel column chromatography affording the product, or alternatively by HPLC-MS purification yielding the TFA salt. The free base was generated by dissolving the TFA salt in EtOAc, followed by washing with sat. aq. NaHCO₃ (2x). The organic layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure, affording the pure product.

**General procedure D:**

![Reaction Scheme](attachment:image3.png)

A round-bottom flask with dry DCM (0.1 M) was charged via syringe with 2,6-dichloropyrimidine-4-carbonyl chloride (1 eq) and cooled to -78 °C. Et₃N (1.3-2.3 eq) and the appropriate amine (1.025 eq) were added and the mixture was stirred, while letting the acetone bath warm up to 0 °C (3-4 h). The mixture was transferred to a separatory funnel and the organic layer was washed with H₂O (2x) and brine (1x), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Silica gel column chromatography afforded the pure amide.

**General procedure E:**
A round-bottom flask was charged with the dichloropyrimidine (1 eq) and dry MeOH (0.1 M) and cooled to 0 °C. DiPEA (1.5-2.5 eq) and the appropriate amine (1.05 eq) were added and the mixture was stirred for 1-2 h at 0 °C. The solvents were evaporated under reduced pressure and the crude material was purified by silica gel column chromatography, affording the pure product.

General procedure F:

A round-bottom flask was charged with the dichloropyrimidine (1 eq) and dry DMF (0.1 M). K$_2$CO$_3$ (1.5 eq) and the appropriate phenol or heteroaryl (1.05 eq) were added and the mixture was stirred overnight at rt. H$_2$O was added and the mixture was extracted with EtOAc (3x). The organic layers were combined and washed with brine (2x), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, affording the pure product.

General procedure G:

Carbamoylation: a round-bottom flask was charged with the primary amine (1 eq) and dry DCM (0.2 M). The solution was cooled to 0 °C and DiPEA (2 eq) and methylchloroformate (1.5 eq) were added. The reaction was stirred and allowed to warm up to room temperature over 1-2 h. Then the mixture was diluted with DCM and washed with sat. aq. NaHCO$_3$ (2x), brine (1x), dried (MgSO$_4$), filtered and concentrated under reduced pressure. The resulting crude material was purified by silica gel column chromatography affording the methyl carbamate. Carbamate reduction: a round-bottom flask was charged with the methyl carbamate (1 eq) and dry THF (0.15 M). The solution was cooled to 0 °C and LiAlH$_4$ (2 M in THF solution, 1.6 eq) was added dropwise. The reaction was then stirred at reflux for 1-2 h. Fieser workup involved dilution of the reaction mixture with Et$_2$O (3x) and cooling to 0 °C, followed by the sequential addition of water (1 μL for every 1 mg of LiAlH$_4$), NaOH (aq) 15% (1 μL for every 1 mg of LiAlH$_4$) and water (3 μL for every 1 mg of LiAlH$_4$). The mixture was allowed to warm to room temperature and stirred for 15 min. Then it was dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the product as a clear oil, which was used without further purification or purified by silica gel chromatography.
**N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-morpholino-pyrimidine-4-carboxamide (1).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (59 mg, 0.20 mmol, 1 eq), N-methylphenethylamine HBr salt (66 mg, 0.30 mmol, 1.5 eq) and DIPEA (140 μL, 0.80 mmol, 4 eq). Total heating time: 8 h at 160 °C with μW irradiation. Column chromatography (40% → 60% EtOAc/pentane) afforded the product (40 mg, 0.10 mmol, 50%). TLC: Rf = 0.3 (40% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.03 (br s, 1H), 7.34 – 7.25 (m, 2H), 7.25 – 7.12 (m, 3H), 6.72 (s, 1H), 3.88 – 3.72 (m, 6H), 3.72 – 3.55 (m, 4H), 3.30 (t, J = 6.5 Hz, 2H), 3.13 (s, 3H), 2.90 (t, J = 7.7 Hz, 2H), 1.14 – 0.99 (m, 1H), 0.64 – 0.44 (m, 2H), 0.38 – 0.19 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.66, 163.97, 160.86, 156.78, 139.92, 128.95, 128.58, 126.29, 90.08, 66.74, 51.68, 44.50, 44.11, 33.55, 11.08, 3.57. HRMS [C22H20N3O2 + H]⁺: 396.2394 calculated, 396.2387 found.

**N-(Cyclopropylmethyl)-6-(methyl(phenethyl)amino)-4-morpholino-picolinamide (2).** A microwave vial with a magnetic stir bar under N2 was charged with 4-chloropyridine 109 (30 mg, 87 μmol, 1 eq), morpholine (9 μL, 0.10 mmol, 1.2 eq) and dry toluene (87 μL). The vial was capped and the solution purged with N2. This was followed by the addition of RuPhosPd G3 (0.01 M THF solution, 100 μL, 0.027 eq) and NaOtBu (2 M THF solution, 97 μL, 0.19 mmol, 2.2 eq) and the mixture was purged again with N2 and stirred in a preheated oil bath at 110 °C for 44 h. The mixture was filtered through a plug of Celite and the filtrate concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (30% - 60% EtOAc/pentane) affording the product (5 mg, 13 μmol, 15%). TLC: Rf = 0.2 (30% EtOAc/pentane) and recovered starting material (11 mg, 32 μmol, 37%). 1H NMR (500 MHz, CDCl3) δ 8.03 (t, J = 5.7 Hz, 1H), 7.29 (t, J = 7.3 Hz, 2H), 7.24 – 7.13 (m, 4H), 5.77 (d, J = 2.0 Hz, 1H), 3.91 – 3.81 (m, 4H), 3.63 (t, J = 7.4 Hz, 2H), 3.51 – 3.40 (m, 4H), 3.34 – 3.29 (m, 2H), 2.92 – 2.83 (m, 5H), 1.11 – 1.05 (m, 1H), 0.58 – 0.50 (m, 2H), 0.29 (q, J = 4.7 Hz, 2H). 13C NMR (126 MHz, CDCl3) δ 165.54, 160.20, 156.01, 148.69, 139.16, 129.00, 128.80, 126.61, 99.04, 90.28, 66.98, 54.09, 46.37, 44.16, 38.55, 33.55, 11.08, 3.57. HRMS [C23H20N2O2 + H]⁺: 395.2442 calculated, 395.2438 found.

**N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-morpholino-isonicotinamide (3).** A microwave vial with a magnetic stir bar under N2 was charged with 2-chloropyridine 113 (31 mg, 0.10 mmol, 1 eq), N-methylphenethylamine HBr salt (28 mg, 0.13 mmol, 1.3 eq) and dry toluene (0.1 mL). The vial was capped and the solution purged with N2. This was followed by the addition of RuPhosPd G3 (0.01 M THF solution, 100 μL, 1 μmol, 0.01 eq) and NaOtBu (2 M THF solution, 120 μL, 0.24 mmol, 2.4 eq) and the mixture was purged again with N2 and stirred in a preheated oil bath at 110 °C. After 24 h the reaction was complete as judged by LC-MS. The mixture was filtered through a plug of Celite and the filtrate concentrated under reduced pressure to provide the crude material. Purification by HPLC (C18 reverse phase, 45% → 55% CH3CN/H2O + 0.2% TFA, RT 12.3 min) afforded the product (16 mg, 40 μmol, 41%). TLC: Rf = 0.5 (60% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.35 – 7.24 (m, 2H), 7.25 – 7.14 (m, 3H), 6.24 – 6.13 (m, 2H), 6.10 (s, 1H), 3.87 – 3.78 (m, 4H), 3.78 – 3.67 (m, 2H), 3.59 – 3.47 (m, 4H), 3.28 (dd, J = 7.2, 5.4 Hz, 2H), 2.98 (s, 3H), 2.93 – 2.82 (m, 2H), 1.15 – 0.95 (m, 1H), 0.64 – 0.48 (m, 2H), 0.35 – 0.19 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 168.07, 159.06, 157.76, 145.86, 140.05, 128.98, 128.60, 126.26, 92.90, 91.48, 66.94, 52.51, 45.80, 44.97, 36.87, 33.92, 10.82, 3.68. HRMS [C22H20N2O2 + H]⁺: 395.2442 calculated, 395.2434 found.
**N-(Cyclopentylmethyl)-6-(methyl(phenethyl)amino)-2-morpholinopyrimidine-4-carboxamide (4).** The title compound was prepared according to general procedure A using 4-chloropyrimidine 127 (21 mg, 70 μmol, 1.0 eq), N-methylphenethylamine HBr salt (16 mg, 70 μmol, 1 eq) and DiPEA (36.6 μL, 0.21 mmol, 3 eq) in MeOH. Total heating time: 6 h at 70 °C. Column chromatography (30% -> 60% EtOAc/pentane) afforded the product (20 mg, 50 μmol, 71%). TLC: Rf = 0.3 (60% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.44 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.13 (m, 3H), 6.84 (s, 1H), 3.79 (br s, 1H), 3.38 – 3.22 (m, 2H), 3.02 (s, 3H), 2.90 (t, J = 7.4 Hz, 2H), 1.14 – 1.00 (m, 1H), 0.62 – 0.46 (m, 2H), 0.36 – 0.21 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 162.97, 159.05, 128.91, 128.82, 126.75, 93.22, 66.81, 44.92, 44.69, 10.71, 3.65. HRMS [C23H29N5O2 + H]+: 396.2394 calculated, 396.2385 found.

**N-(Cyclopentylmethyl)-N-methyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (5).** A round-bottom flask was charged with amide 1 (36 mg, 90 μmol, 1 eq), dry DMF (1.5 mL) and cooled to 0 °C. NaH (60% in mineral oil, 4 mg, 0.10 mmol, 1.1 eq) was added and the mixture was stirred for 30 min followed by addition of methyl iodide (11 μL, 0.18 mmol, 2 eq). The reaction was allowed to warm to rt while stirring overnight. The reaction was quenched with H2O (20 mL) followed by extraction with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 50 mL), dried (MgSO4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50 -> 80% EtOAc/pentane) affording the product (18 mg, 40 μmol, 44%). TLC: Rf = 0.3 (60% EtOAc/pentane). 1H NMR analysis showed two rotamers in 6:4 ratio in CDCl3 at 298 K, which was confirmed by high temperature 1H NMR experiments. 1H NMR (400 MHz, CDCl3) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.16 (m, 3H), 6.07 – 6.02 (m, 1H), 3.83 – 3.71 (m, 6H), 3.62 – 3.55 (m, 4H), 3.43 – 3.23 (m, 2H), 3.16 – 3.10 (m, 3H), 3.10 – 3.02 (m, 3H), 2.92 – 2.83 (m, 2H), 1.14 – 1.01 (m, 1H), 0.60 – 0.43 (m, 2H), 0.36 – 0.12 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 163.34, 162.35, 160.82, 156.31, 140.05, 128.91, 128.52, 126.20, 90.43, 66.76, 55.26, 51.57, 44.33, 35.80, 33.94, 33.10, 10.33, 3.66. HRMS [C23H27N5O2 + H]+: 410.2551 calculated, 410.2545 found.

**N-Cyclopentyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (6).** The title compound was prepared according to general procedure B using carboxylic acid 17 (34 mg, 0.10 mmol, 1 eq), DiPEA (52 μL, 0.30 mmol, 3 eq), PyBOP (78 mg, 0.12 mmol, 1.2 eq) and cyclopentylamine (8.3 μL, 0.12 mmol, 1.2 eq). Column chromatography (50% -> 80% EtOAc/pentane) afforded the product (8 mg, 21 μmol, 21%). TLC: Rf = 0.3 (60% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.92 (br s, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.15 (m, 3H), 6.70 (s, 1H), 3.84 – 3.72 (m, 6H), 3.66 (br s, 4H), 3.09 (s, 3H), 2.94 – 2.82 (m, 3H), 1.36 – 1.21 (m, 1H), 0.92 – 0.82 (m, 2H), 0.67 – 0.58 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 166.25, 163.97, 160.84, 156.51, 139.98, 128.84, 128.64, 126.34, 89.86, 66.78, 51.67, 44.52, 35.72, 33.98, 22.53, 6.78. HRMS [C23H27N5O2 + H]+: 382.2238 calculated, 382.2241 found.

**2-(Methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (7).** The title compound was prepared according to general procedure B using carboxylic acid 17 (27 mg, 79 μmol, 1 eq), DiPEA (56 μL, 0.32 mmol, 4 eq), PyBOP (62 mg, 0.12 mmol, 1.5 eq), HOBt (16 mg, 0.12 mmol, 1.5 eq) and ammonium chloride (15 mg, 0.32 mmol, 3.5 eq). Column chromatography (80% -> 100% EtOAc/pentane) afforded the product (20 mg, 59 μmol, 75%). TLC: Rf = 0.5 (80% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.74 (br s, 1H), 7.34 – 7.25 (m, 2H), 7.25 – 7.16 (m, 3H), 6.71 (br s, 1H), 5.83 (s, 1H), 3.86 – 3.72 (m, 6H), 3.66 (br s, 4H), 3.09 (s, 3H), 2.90 (t, J = 7.1 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 167.46, 163.96,
Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401

161.04, 156.27, 139.93, 128.86, 128.62, 126.31, 90.17, 66.74, 51.60, 44.50, 35.77, 33.97. HRMS [C₁₈H₂₃N₅O₂ + H]⁺: 342.1925 calculated, 342.1934 found.

**N-Methyl-2-(methylphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide TFA salt (8).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 117a (8:5:1 mixture of regioisomers) (51 mg, 0.20 mmol, 1 eq), DIPEA (139 μL, 0.80 mmol, 4 eq) and N-methylphenethylamine HBr salt (65 mg, 0.30 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Purification by preparative HPLC (C18 reverse phase, 25% to 35% CH₂CN/H₂O + 0.2% TFA, RT = 8.77) afforded the product as the TFA salt (83 mg, 0.18 mmol, 88%) TLC: Rₜ = 0.3 (50% EtOAc/pentane). ¹H NMR (400 MHz, MeOD) δ 7.30 – 7.12 (m, 5H), 6.90 (s, 1H), 3.92 (t, J = 7.0 Hz, 2H), 3.85 – 3.69 (m, 8H), 3.18 (s, 3H), 3.00 – 2.88 (m, 5H). ¹³C NMR (101 MHz, MeOD) δ 162.45, 162.16 (q, J = 35.8 Hz), 154.95, 147.48, 139.88, 129.99, 129.67, 127.62, 117.79 (q, J = 291.3 Hz), 94.22, 67.37, 53.01, 46.62, 36.22, 34.27, 26.90. HRMS [C₁₈H₂₃N₅O₂ + H]⁺: 356.2081 calculated, 356.2079 found.

**N-Ethyl-2-(methylphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (9).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 117b (54 mg, 0.20 mmol, 1 eq), DIPEA (139 μL, 0.80 mmol, 4 eq) and N-methylphenethylamine HBr salt (65 mg, 0.30 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (50% → 70% EtOAc/pentane) afforded the product (64 mg, 0.17 mmol, 86%). TLC: Rₜ = 0.3 (50% EtOAc/pentane). ¹H NMR (500 MHz, CDCl₃) δ 7.88 (s, 1H), 7.32 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 6.71 (s, 1H), 3.84 – 3.77 (m, 2H), 3.77 – 3.73 (m, 4H), 3.69 – 3.62 (m, 4H), 3.50 – 3.42 (m, 2H), 3.11 (s, 3H), 2.94 – 2.84 (m, 2H), 1.25 (t, J = 7.3 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 164.65, 163.98, 160.88, 156.82, 139.99, 128.83, 128.59, 126.29, 90.02, 66.74, 51.63, 44.51, 35.71, 34.26, 33.98, 14.94. HRMS [C₁₈H₂₇N₅O₂ + H]⁺: 370.2238 calculated, 370.2236 found.

**N-Propyl-2-(methylphenethyl)amino)-6-morpholino-pyrimidine-4-carboxamide (10).** The title compound was prepared according to general procedure B using carboxylic acid 17 (23 mg, 67 μmol, 1 eq), DIPEA (60 μL, 0.34 mmol, 3 eq), PyBOP (52 mg, 0.10 mmol, 1.5 eq) and propylamine HCl salt (8 mg, 0.80 mmol, 1.2 eq). Column chromatography (40% → 60% EtOAc/pentane) afforded the product (17 mg, 44 μmol, 66%). TLC: Rₜ = 0.3 (50% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 7.99 (br s, 1H), 7.37 – 7.28 (m, 2H), 7.28 – 7.19 (m, 3H), 6.74 (s, 1H), 3.90 – 3.75 (m, 6H), 3.69 (br s, 4H), 3.42 (q, J = 6.7 Hz, 2H), 3.13 (s, 3H), 2.92 (t, J = 7.5 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.80, 164.01, 160.86, 156.82, 139.98, 128.85, 128.61, 126.31, 90.06, 66.77, 51.65, 44.52, 41.08, 35.73, 33.98, 23.01, 11.61. HRMS [C₁₉H₂₉N₅O₂ + H]⁺: 384.2394 calculated, 384.2394 found.

**N-Butyl-2-(methylphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (11).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 117c (30 mg, 0.10 mmol, 1 eq), DIPEA (70 μL, 0.40 mmol, 4 eq) and N-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 45 h at 120 °C. Column chromatography (40% → 60% EtOAc/pentane) afforded the product (29 mg, 73 μmol, 73%). TLC: Rₜ = 0.6 (50% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 7.94 (br s, 1H), 7.33 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 6.72 (s, 1H), 3.84 – 3.72 (m, 6H), 3.66 (br s, 4H), 3.42 (q, J = 6.6 Hz, 2H), 3.11 (s, 3H), 2.95 – 2.84 (m, 2H), 1.60 (p, J = 7.1 Hz, 2H), 1.42 (h, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.74, 164.00, 160.86, 156.83, 139.97, 128.84, 128.60, 126.31, 90.05, 66.76, 51.64, 44.52, 39.12, 35.72, 33.97, 31.81, 20.30, 13.94. HRMS [C₂₀H₃₅N₅O₂ + H]⁺: 398.2551 calculated, 398.2560 found.
**N-Hexyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (12).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 117d (33 mg, 0.10 mmol, 1 eq), DiPEA (70 µL, 0.40 mmol, 4 eq) and N-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 3 d at 120 °C. Column chromatography (40% -> 50% EtOAc/ pentane) afforded the product (36 mg, 85 µmol, 85%). TLC: Rf = 0.6 (50% EtOAc/pentane). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.94 (s, 1H), 7.33 – 7.25 (m, 2H), 7.25 – 7.17 (m, 3H), 6.72 (s, 1H), 3.83 – 3.73 (m, 6H), 3.71 – 3.62 (m, 4H), 3.41 (q, \(J = 6.9\) Hz, 2H), 3.10 (s, 3H), 2.95 – 2.85 (m, 2H), 1.61 (p, \(J = 7.6, 7.2\) Hz, 2H), 1.44 – 1.27 (m, 6H), 0.94 – 0.84 (m, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.71, 164.01, 160.86, 156.85, 139.97, 128.84, 128.60, 126.30, 90.05, 66.76, 51.65, 44.53, 39.43, 35.73, 33.98, 31.63, 29.68, 26.78, 22.67, 14.14. HRMS [C\(_{24}\)H\(_{33}\)N\(_2\)O\(_2\) + H\(^+\)]: 426.2864 calculated, 426.2857 found.

**N-Isobutyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (13).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 117e (30 mg, 0.10 mmol, 1 eq), DiPEA (70 µL, 0.40 mmol, 4 eq) and N-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 3 d at 120 °C. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (29 mg, 73 µmol, 73%). TLC: Rf = 0.7 (50% EtOAc/pentane). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.04 (br s, 1H), 7.33 – 7.25 (m, 2H), 7.25 – 7.16 (m, 3H), 6.72 (s, 1H), 3.88 – 3.73 (m, 6H), 3.73 – 3.62 (m, 4H), 3.26 (t, \(J = 6.5\) Hz, 2H), 3.10 (s, 3H), 2.96 – 2.85 (m, 2H), 1.97 – 1.82 (m, 1H), 0.98 (d, \(J = 6.7\) Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.77, 164.01, 160.84, 156.84, 139.94, 128.84, 128.58, 126.29, 90.07, 66.75, 51.63, 46.65, 44.52, 35.72, 33.98, 28.80, 20.28. HRMS [C\(_{24}\)H\(_{34}\)N\(_2\)O\(_2\) + H\(^+\)]: 398.2551 calculated, 398.2552 found.

**N-Neopentyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (14).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 117f (31 mg, 0.10 mmol, 1 eq), DiPEA (70 µL, 0.40 mmol, 4 eq) and N-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 3 d at 120 °C. Column chromatography (20% -> 50% EtOAc/pentane) afforded the product (30 mg, 73 µmol, 73%). TLC: Rf = 0.6 (40% EtOAc/pentane). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.14 (br s, 1H), 7.32 – 7.25 (m, 2H), 7.24 – 7.17 (m, 3H), 6.73 (s, 1H), 3.85 – 3.78 (m, 2H), 3.78 – 3.73 (m, 4H), 3.71 – 3.61 (m, 4H), 3.23 (d, \(J = 6.6\) Hz, 2H), 3.10 (s, 3H), 2.95 – 2.86 (m, 2H), 0.97 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.82, 164.03, 160.82, 156.82, 139.89, 128.85, 128.59, 126.30, 90.15, 66.76, 51.62, 50.57, 44.53, 35.72, 33.99, 32.28, 27.38. HRMS [C\(_{25}\)H\(_{35}\)N\(_2\)O\(_2\) + H\(^+\)]: 412.2707 calculated, 412.2710 found.

**2-(Methyl(phenethyl)amino)-6-morpholino-N-(prop-2-yn-1-yl)pyrimidine-4-carboxamide (15).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 117g (42 mg, 0.15 mmol, 1 eq), DiPEA (105 µL, 0.60 mmol, 4 eq) and N-methylphenethylamine HBr salt (49 mg, 0.225 mmol, 1.5 eq). Total heating time: 45 h at 120 °C. Column chromatography (30% -> 50% EtOAc/pentane) afforded the product (43 mg, 0.11 mmol, 73%). TLC: Rf = 0.7 (50% EtOAc/pentane). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.03 (br s, 1H), 7.33 – 7.25 (m, 2H), 7.25 – 7.17 (m, 3H), 6.69 (s, 1H), 4.22 (dd, \(J = 5.6, 2.5\) Hz, 2H), 3.86 – 3.72 (m, 6H), 3.72 – 3.60 (m, 4H), 3.11 (s, 3H), 2.96 – 2.85 (m, 2H), 2.29 (t, \(J = 2.4\) Hz, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.60, 163.89, 160.88, 156.03, 139.91, 128.90, 128.60, 126.30, 90.15, 79.57, 71.67, 66.72, 51.70, 44.50, 35.75, 33.98, 29.21. HRMS [C\(_{25}\)H\(_{35}\)N\(_2\)O\(_2\) + H\(^+\)]: 380.2081 calculated, 380.2089 found.
N-(2,2,2-Trifluoroethyl)-2-(methyl(phenethyl)amino)-6-morpholinoypyrimidine-4-carboxamide (16). The title compound was prepared according to general procedure B using carboxylic acid 17 (25 mg, 73 μmol, 1 eq), DiPEA (51 μL, 0.29 mmol, 4 eq), PyBOP (57 mg, 0.11 mmol, 1.5 eq) and 2,2,2-trifluoroethylamine HCl salt (12 mg, 88 μmol, 1.2 eq). Column chromatography (30% -> 40% EtOAc/pentane) afforded the product (17 mg, 40 μmol, 55%). TLC: R_f = 0.8 (50% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) δ 8.20 (br s, 1H), 7.32 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 6.70 (s, 1H), 4.12 – 4.02 (m, 2H), 3.83 – 3.78 (m, 2H), 3.78 – 3.74 (m, 4H), 3.71 – 3.59 (m, 4H), 3.11 (s, 3H), 2.92 – 2.86 (m, 2H). ^13C NMR (126 MHz, CDCl_3) δ 165.31, 163.88, 160.92, 155.42, 150.89, 138.95, 128.86, 128.65, 126.37, 124.31 (q, J = 278.4 Hz), 90.45, 66.75, 51.70, 44.58, 40.89 (q, J = 34.8 Hz), 35.77, 34.04. HRMS [C_{10}H_{22}F_{2}N_{2}O_{2} + H]^+: 424.1955 calculated, 424.1958 found.

2-(Methyl(phenethyl)amino)-6-morpholinoypyrimidine-4-carboxylic acid (17). Ester hydrolysis: a round-bottom flask was charged with methyl ester 125 (680 mg, 2.64 mmol, 1 eq) in 12.5 mL THF/MeOH (4:1). A 1.5 M aqueous NaOH solution (1.76 mL, 2.64 mmol, 1 eq) was added to the solution 110 mL, with stirring at room temperature. The reaction was stirred for 3 days at 120 °C. Column chromatography (2.5% → 15% MeOH/DCM) afforded the product (175 mg, 0.51 mmol, 51%). TLC: R_f = 0.5 (100% EtOAc with 3 drops of AcOH). ^1H NMR (400 MHz, MeOD + CDCl_3) δ 7.35 – 7.26 (m, 2H), 7.26 – 7.15 (m, 3H), 6.87 (s, 1H), 3.91 (t, J = 7.0 Hz, 2H), 3.81 (br s, 8H), 3.17 (s, 3H), 2.97 (t, J = 7.0 Hz, 2H). ^13C NMR (101 MHz, MeOD + CDCl_3) δ 161.70, 152.17, 148.40, 137.57, 133.96, 128.50, 128.38, 126.57, 93.89, 66.02, 51.86, 45.10, 33.13. HRMS [C_{18}H_{23}N_{2}O_{3} + H]^+: 343.1765 calculated, 343.1772 found.

(2-(Methyl(phenethyl)amino)-6-morpholinoypyrimidine-4-carbonyl)glycine (18). The title compound was prepared according to general procedure A using 2-chloropyrimidine 126 (244 mg, 1.0 mmol, 1 eq), DiPEA (0.52 mL, 3.0 mmol, 3 eq) and N-methylphenethylamine (189 μL, 1.3 mmol, 1.3 eq). Total heating time: 6 d at 120 °C. Column chromatography (2.5% → 15% MeOH/DCM) afforded the product (175 mg, 0.51 mmol, 51%). TLC: R_f = 0.5 (100% EtOAc with 3 drops of AcOH). ^1H NMR (500 MHz, MeOD + CDCl_3) δ 8.20 (br s, 2H), 7.32 – 7.26 (m, 2H), 7.26 – 7.15 (m, 3H), 6.87 (s, 1H), 3.91 (t, J = 7.0 Hz, 2H), 3.81 (br s, 8H), 3.17 (s, 3H), 2.97 (t, J = 7.0 Hz, 2H). ^13C NMR (126 MHz, MeOD + CDCl_3) δ 173.63, 164.96, 163.55, 160.59, 155.89, 139.54, 128.50, 128.38, 126.57, 93.89, 66.02, 51.86, 45.10, 33.13. HRMS [C_{18}H_{23}N_{2}O_{3} + H]^+: 343.1765 calculated, 343.1772 found.

Methyl (2-(methyl(phenethyl)amino)-6-morpholinoypyrimidine-4-carbonyl)glycinate (19). A round-bottom flask was charged with carboxylic acid 18 (28 mg, 70 μmol, 1 eq) in dry DCM (1.5 mL). This was followed by addition of HOBt (15 mg, 0.11 mmol, 1.5 eq), EDC·HCl (20 mg, 0.11 mmol, 1.5 eq). The reaction was stirred for 1 h at rt after which MeOH (11 μL, 0.28 mmol, 4 eq) was added and then stirred overnight at rt. The reaction was diluted with EtOAc (25 mL), washed with sat. aq. NaHCO_3 (2 x 25 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified using silica gel column chromatography (60% -> 80% EtOAc/pentane) affording the product (18 mg, 44 μmol, 62%). TLC: R_f = 0.3 (70% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 8.40 (br s, 1H), 7.39 – 7.13 (m, 5H), 6.69 (s, 1H), 4.22 (d, J = 5.5 Hz, 2H), 3.86 – 3.71 (m, 9H), 3.71 – 3.59 (m, 4H), 3.11 (s, 2H), 2.86 (t, J = 7.3 Hz, 2H), 2.92 (t, J = 7.3 Hz, 2H), 3.59 (m, 4H), 3.11 (s, 3H), 2.92 (t, J = 7.3 Hz, 2H).
3H), 2.96 – 2.85 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.25, 165.14, 163.91, 160.92, 155.99, 139.96, 128.98, 128.58, 126.27, 90.13, 66.75, 52.52, 51.68, 44.51, 41.37, 35.79, 34.01. HRMS [C$_2$H$_2$N$_2$O$_4$ + H]$^+$: 414.2136 calculated, 414.2144 found.

$N$-(2-(Methylamino)-2-oxoethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (20). The title compound was prepared according to general procedure B using carboxylic acid 18 (12 mg, 30 µmol, 1 eq), DIPEA (21 µL, 120 µmol, 4 eq), PyBOP (19 mg, 45 µmol, 1.5 eq) and methylamine HCl salt (3 mg, 36 µmol, 1.2 eq). Column chromatography (2.5% -> 10% MeOH/DCM) afforded the product (6 mg, 15 µmol, 50%). TLC: R$_f$ = 0.4 (5% MeOH/DCM). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.43 (br s, 1H), 7.32 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 6.69 (br s, 1H), 6.22 (br s, 1H), 4.08 (d, J = 6.1 Hz, 2H), 3.86 – 3.79 (m, 2H), 3.79 – 3.73 (m, 4H), 3.67 (br s, 4H), 3.10 (s, 3H), 2.93 – 2.86 (m, 2H), 2.84 (d, J = 4.9 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 169.58, 165.74, 163.84, 160.90, 155.66, 139.91, 128.93, 128.65, 126.36, 90.21, 66.75, 51.65, 44.60, 43.84, 35.86, 34.06, 26.41. HRMS [C$_2$H$_2$N$_2$O$_4$ + H]$^+$: 414.2226 calculated, 414.2224 found.

$N$-(2-Hydroxyethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (21). The title compound was prepared according to general procedure B using carboxylic acid 17 (39 mg, 0.11 mmol, 1 eq), DIPEA (60 µL, 0.34 mmol, 3 eq), PyBOP (89 mg, 0.17 mmol, 1.5 eq) and ethanolamine (34 µL, 0.57 mmol, 5 eq). Column chromatography (70% -> 100% EtOAc/pentane to 5% MeOH/EtOAc) afforded the product (25 mg, 65 µmol, 59%). TLC: R$_f$ = 0.3 (80% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.29 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 6.70 (s, 1H), 3.87 – 3.78 (m, 4H), 3.78 – 3.74 (m, 4H), 3.70 – 3.62 (m, 4H), 3.62 – 3.55 (m, 2H), 3.10 (s, 3H), 2.98 – 2.80 (m, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.19, 163.93, 160.87, 156.29, 139.96, 128.89, 128.61, 126.32, 90.14, 66.74, 62.71, 51.61, 44.51, 42.71, 35.77, 33.98. HRMS [C$_2$H$_2$N$_2$O$_4$ + H]$^+$: 386.2187 calculated, 386.2191 found.

$N$-(2-Methoxyethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (22). A round-bottom flask was charged with alcohol 21 (17 mg, 44 µmol, 1 eq) in dry DMF (1 mL) and cooled to 0°C. NaOtBu (2 M in THF, 33 µL, 66 µmol, 1.5 eq) and methyl iodide (3.1 µL, 49 µmol, 1.1 eq) were added. The reaction was allowed to warm to rt while stirring overnight. EtOAc (25 mL) was added followed by washing with H$_2$O (1 x 25 mL) and brine (2 x 25 mL), drying (Na$_2$SO$_4$), filtering and concentration under reduced pressure. The residue was purified by silica gel column chromatography (70 -> 80% EtOAc/pentane) affording the product (5 mg, 13 µmol, 30%). TLC: R$_f$ = 0.4 (80% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.26 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 6.71 (s, 1H), 3.85 – 3.71 (m, 6H), 3.72 – 3.59 (m, 6H), 3.59 – 3.51 (m, 2H), 3.38 (s, 3H), 3.11 (s, 3H), 2.95 – 2.83 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.96, 163.98, 160.89, 156.67, 139.95, 128.93, 128.62, 126.29, 90.08, 71.38, 66.78, 59.02, 51.72, 44.53, 39.25, 35.77, 33.96. HRMS [C$_2$H$_2$N$_2$O$_4$ + H]$^+$: 400.2343 calculated, 400.2345 found.

$N$-(Cyanomethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (23). The title compound was prepared according to general procedure B using carboxylic acid 17 (21 mg, 61 µmol, 1 eq), DIPEA (53 µL, 0.31 mmol, 5 eq), PyBOP (48 mg, 92 µmol, 1.5 eq) and aminooacetanitriile bisulfate (11 mg, 73 µmol, 1.2 eq). Column chromatography (50% -> 70% EtOAc/pentane) afforded the product (10 mg, 26 µmol, 43%). TLC: R$_f$ = 0.6 (60% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.12 (br s, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.14 (m, 3H), 6.67 (s, 1H), 4.34 (d, J =
6.1 Hz, 2H), 3.86 – 3.79 (m, 2H), 3.79 – 3.74 (m, 4H), 3.66 (br s, 4H), 3.10 (s, 3H), 2.95 – 2.84 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 165.12, 163.72, 160.92, 154.96, 139.94, 128.88, 128.68, 126.41, 115.95, 90.37, 66.71, 51.58, 44.50, 35.86, 34.05, 27.52. HRMS [C\(_{20}\)H\(_{15}\)O\(_2\)N\(_2\) + H]\(^+\): 381.2034 calculated, 381.2042 found.

**N-(Thiazol-2-ylmethyl)-2-(methyl(phenethyl)amino)-6-morpholino-pyrimidine-4-carboxamide (24).** The title compound was prepared according to general procedure B using carboxylic acid 17 (27 mg, 0.79 \(\mu\)mol, 1 eq), DIPEA (82 \(\mu\)L, 0.47 mmol, 6 eq), PyBOP (62 \(\mu\)L, 0.12 mmol, 1.5 eq) and 2-aminomethylthiazole double HCl salt (19 mg, 0.10 mmol, 1.3 eq). Purification by preparative HPLC (C18 reverse phase, 34% to 37% CH\(_3\)CN/H\(_2\)O + 0.2% TFA) afforded the product (11 mg, 25 \(\mu\)mol, 32%). TLC: \(R_f\) = 0.3 (80% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.61 (br s, 1H), 7.73 (d, \(J = 3.3\) Hz, 1H), 7.29 (d, \(J = 3.3\) Hz, 1H), 7.28 – 7.22 (m, 2H), 7.21 – 7.14 (m, 3H), 6.74 (s, 1H), 4.94 (d, \(J = 6.2\) Hz, 2H), 3.85 – 3.71 (m, 6H), 3.71 – 3.59 (m, 4H), 3.09 (s, 3H), 2.93 – 2.81 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.81, 165.12, 163.72, 160.92, 154.96, 139.94, 128.88, 128.68, 126.41, 115.95, 90.37, 66.71, 51.58, 44.50, 43.18, 36.13, 34.31. HRMS [C\(_{21}\)H\(_{19}\)O\(_2\)N\(_2\) + H]\(^+\): 439.1911 calculated, 439.1913 found.

**N-Benzyl-2-(methylphenethylamino)-6-morpholino-pyrimidine-4-carboxamide (25).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 117i (67 mg, 0.20 mmol, 1 eq), DIPEA (139 \(\mu\)L, 0.80 mmol, 4 eq) and N-methylphenethylamine HBr salt (65 mg, 0.30 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with \(\mu\)W irradiation. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (75 mg, 0.17 mmol, 87%). TLC: \(R_f\) = 0.8 (60% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.25 (br s, 1H), 7.39 – 7.33 (m, 4H), 7.33 – 7.26 (m, 1H), 7.24 – 7.14 (m, 3H), 7.14 – 7.04 (m, 2H), 6.76 (s, 1H), 4.63 (d, \(J = 6.1\) Hz, 2H), 3.80 – 3.71 (m, 6H), 3.71 – 3.62 (m, 4H), 3.08 (s, 3H), 2.89 – 2.80 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.83, 163.90, 160.82, 156.52, 139.79, 138.35, 128.80, 128.77, 128.54, 127.69, 127.51, 126.20, 90.17, 66.70, 51.63, 44.46, 43.37, 35.68, 33.88. HRMS [C\(_{25}\)H\(_{24}\)N\(_2\)O\(_2\)S+ H]\(^+\): 432.2394 calculated, 432.2390 found.

**N-[[1,1'-Biphenyl]-4-ylmethyl]-2-(methylphenethylamino)-6-morpholino-pyrimidine-4-carboxamide (26).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 117j (41 mg, 0.10 mmol, 1 eq), DIPEA (70 \(\mu\)L, 0.40 mmol, 4 eq) and N-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with \(\mu\)W irradiation. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (40 mg, 79 \(\mu\)mol, 79%). TLC: \(R_f\) = 0.5 (50% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.29 (br s, 1H), 7.57 (d, \(J = 7.9\) Hz, 4H), 7.47 – 7.39 (m, 4H), 7.38 – 7.30 (m, 1H), 7.23 – 7.07 (m, 5H), 6.77 (s, 1H), 4.68 (d, \(J = 6.1\) Hz, 2H), 3.81 – 3.72 (m, 6H), 3.71 – 3.61 (m, 4H), 3.08 (s, 3H), 2.90 – 2.81 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.92, 163.94, 160.86, 156.54, 140.84, 140.51, 139.82, 137.43, 128.88, 128.79, 128.56, 128.17, 127.56, 127.42, 127.17, 126.24, 90.22, 66.73, 51.65, 44.50, 43.12, 35.73, 33.91. HRMS [C\(_{25}\)H\(_{25}\)N\(_2\)O\(_2\)H] +: 508.2707 calculated, 508.2704 found.

**4-(5-Cyclopropyl-1H-imidazol-2-yl)-N-methyl-6-morpholino-N-phenethylpyrimidin-2-amine (27).** Acyloxyimethylketone synthesis: a round-bottom flask was charged with carboxylic acid 17 (53 mg, 0.15 mmol, 1 eq) in dry DMF (1 mL). Cs\(_2\)CO\(_3\) (91 mg, 0.28 mmol, 1.8 eq) and 2-bromocyclopropylethane (16 \(\mu\)L, 0.16 mmol, 1.05 eq) were added and the mixture was stirred for 1.5 h. The reaction was diluted with EtOAc (25 mL) and the mixture was washed with H\(_2\)O (1 x 25 mL) and brine (2 x 25 mL), dried (Na\(_2\)SO\(_4\)), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% -> 50% EtOAc/pentane) affording the
acyloxybenzylketone 131 (34 mg, 80 μmol, 53%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36 – 7.12 (5H, 6H), 6.63 (s, 1H), 5.04 (s, 2H), 3.87 – 3.78 (m, 2H), 3.78 – 3.72 (m, 4H), 3.71 – 3.53 (m, 4H), 3.14 (s, 3H), 2.97 – 2.80 (m, 2H), 2.16 – 2.00 (m, 1H), 1.22 – 1.08 (m, 2H), 1.04 – 0.88 (m, 2H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 203,64, 165,50, 163,61, 161,85, 154,67, 139,97, 128,93, 128,50, 126,17, 93,17, 69,31, 66,69, 51,54, 44,41, 35,64, 33,77, 17,38, 11,70. **Imidazolide synthesis**: a microwave vial was charged with acyloxybenzylketone 131 (34 mg, 80 μmol, 1 eq) and NH\(_2\)OAc (31 mg, 0.40 mmol, 5 eq) in xylene (0.7 mL). The vial was capped and stirred at 140 °C for 2 h. Purification by preparative HPLC (C18 reverse phase, 35% to 40% CH\(_3\)CN/H\(_2\)O + 0.2% TFA) afforded the product (2 mg, 5 μmol, 6%). TLC: R\(_f\) = 0.7 (40% EtOAc/pentane).

\(^1\)H NMR (850 MHz, CDCl\(_3\)) \(\delta\) 9.89 (s, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 6.98 – 6.49 (m, 2H), 3.84 (s, 2H), 3.80 – 3.73 (m, 4H), 3.68 (br s, 4H), 3.14 (s, 3H), 2.97 – 2.83 (m, 2H), 1.91 (br s, 1H), 0.92 (br s, 2H), 0.74 (br s, 2H). \(^13\)C NMR (214 MHz, CDCl\(_3\)) \(\delta\) 163.48, 161.12, 154.40, 145.32, 140.18, 128.91, 128.66, 126.35, 111.74, 87.19, 66.84, 51.62, 44.66, 35.84, 34.08, 9.44, 7.18, 6.01. HRMS [C\(_{23}\)H\(_{28}\)N\(_2\)O + H\(^+\)]: 405.2397 calculated, 405.2403 found.

**2-Chloro-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (28)**.

The title compound was prepared according to general procedure E using dichloropyrimidine 116a (1.7 g, 7.1 mmol, 1 eq), DIPEA (1.9 mL, 10.6 mmol, 1.5 eq) and morpholine (0.64 mL, 7.4 mmol, 1.05 eq). Column chromatography (30% → 60% EtOAc/pentane) afforded the product (1.7 g, 6.3 mmol, 89%). TLC: R\(_f\) = 0.5 in 40% EtOAc/pentane. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.94 (t, J = 5.9 Hz, 1H), 7.28 (s, 1H), 3.87 – 3.63 (m, 8H), 3.33 – 3.25 (m, 2H), 1.12 – 1.00 (m, 1H), 0.61 – 0.52 (m, 2H), 0.32 – 0.24 (m, 2H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 163.83, 162.21, 159.84, 157.90, 99.36, 66.35, 44.45, 10.65, 3.64. Regioselectivity was confirmed by \(^1\)H-NOESY NMR analysis. HRMS [C\(_{21}\)H\(_{17}\)ClN\(_2\)O\(_2\) + H\(^+\)]: 297.1113 calculated, 297.1116 found. Regioisomer 6-chloro-N-(cyclopropylmethyl)-2-morpholinopyrimidine-4-carboxamide (127) was also obtained (99 mg, 0.33 mmol, 5%). R\(_f\) = 0.6 in 40% EtOAc/pentane. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.80 – 7.65 (m, 1H), 7.32 (s, 1H), 3.90 – 3.72 (m, 8H), 3.30 (t, J = 6.5 Hz, 1H), 1.14 – 0.98 (m, 1H), 0.69 – 0.46 (m, 2H), 0.39 – 0.17 (m, 2H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 163.48, 162.31, 160.58, 158.86, 107.51, 66.64, 44.42, 44.30, 10.80, 3.55.

**N-(Cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (29)**.

A round-bottom flask was charged with 2-chloropyrimidine 28 (24 mg, 80 μmol, 1 eq), NaHCO\(_3\) (8 mg, 0.10 mmol, 1.2 eq) and MeOH (0.5 mL). The solution was purged with N\(_2\) followed by addition of Pd/C (10% w/w, 40 mg, 50 mol%, 5 mol%), purged again with N\(_2\) and then stirred overnight under an H\(_2\) atmosphere (balloon). The mixture was filtered through a plug of Celite, which was washed with MeOH and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40% -> 70% EtOAc/pentane) to afford the product (20 mg, 76 μmol, 95%). TLC: R\(_f\) = 0.2 (40% EtOAc/pentane).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.57 (s, 1H), 8.09 (t, J = 5.7 Hz, 1H), 7.36 (s, 1H), 3.80 – 3.77 (m, 4H), 3.76 – 3.67 (m, 4H), 3.33 – 3.28 (m, 2H), 3.08 – 3.01 (m, 1H), 0.59 – 0.54 (m, 2H), 0.32 – 0.26 (m, 2H). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 163.56, 163.02, 157.44, 155.78, 100.60, 66.59, 44.44, 44.37, 10.79, 3.65. HRMS [C\(_{23}\)H\(_{28}\)N\(_2\)O\(_2\) + H\(^+\)]: 263.1503 calculated, 263.1502 found.

**N-(Cyclopropylmethyl)-6-morpholino-2-(phenethylamino)pyrimidine-4-carboxamide (30)**.

The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (59 mg, 0.20 mmol, 1 eq), 2-phenethylamine (30 μL, 0.24 mmol, 1.2 eq) and DIPEA (70 μL, 0.40 mmol, 2 eq). Total heating time: 8 h at 160 °C with μW irradiation. Column chromatography (2% - 5% MeOH/DCM) afforded the product (40 mg, 0.10 mmol, 50%). TLC: R\(_f\) = 0.4 (4% MeOH/DCM).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.02 (br s, 1H), 7.39 – 7.28 (m, 2H), 7.28 – 7.15 (m, 3H), 6.78 (s, 1H), 4.96 (br s, 1H), 3.84 – 3.71 (m, 4H), 3.71 – 3.49 (m, 6H), 3.27 (t, J = 6.4 Hz, 2H), 2.92 (t, J = 7.2 Hz, 2H), 1.13 – 0.95 (m, 1H), 0.64 – 0.41 (m, 2H), 0.37 – 0.18 (m, 2H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.46, 163.98,
The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (59 mg, 0.20 mmol, 1 eq), N-methylbenzylamine (38 μL, 0.30 mmol, 1.5 eq) and DIPEA (140 μL, 0.80 mmol, 4 eq). Total heating time: 8 h at 160 °C with μW irradiation. Column chromatography (2% -> 5% MeOH/DCM) afforded the product (40 mg, 0.10 mmol, 50%). TLC: Rf = 0.5 (4% MeOH/DCM). 1H NMR (500 MHz, CDCl3) δ 7.94 (br s, 1H), 7.32 – 6.90 (m, 7H), 6.78 (s, 1H), 5.24 (br s, 1H), 4.60 (d, J = 5.9 Hz, 2H), 3.76 – 3.69 (m, 4H), 3.69 – 3.60 (m, 4H), 3.25 (t, J = 7.1, 5.8 Hz, 2H), 1.09 – 0.95 (m, 1H), 0.57 – 0.48 (m, 2H), 0.29 – 0.22 (m, 2H). 13C NMR (126 MHz, CDCl3) δ 164.20, 164.03, 164.00, 161.41, 156.91, 139.73, 128.65, 127.53, 127.27, 91.86, 66.67, 44.41, 44.25, 10.78, 3.59. HRMS [C21H27N3O2 + H]+: 382.2238 calculated, 382.2241 found.

2-{(Benzyl(methyl)amino)-N-(cyclopropylmethyl)-6-morpholino.pyrimidine-4-carboxamide (31). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (59 mg, 0.20 mmol, 1 eq), 1 H NMR (400 MHz, CDCl3) δ 7.94 (br s, 1H), 7.41 – 7.19 (m, 5H), 6.78 (s, 1H), 5.24 (br s, 1H), 4.60 (d, J = 5.9 Hz, 2H), 3.76 – 3.69 (m, 4H), 3.69 – 3.60 (m, 4H), 3.25 (t, J = 7.1, 5.8 Hz, 2H), 1.09 – 0.95 (m, 1H), 0.57 – 0.48 (m, 2H), 0.29 – 0.22 (m, 2H). 13C NMR (126 MHz, CDCl3) δ 164.20, 164.03, 161.41, 159.71, 128.65, 127.53, 127.27, 91.86, 66.67, 44.41, 44.25, 10.78, 3.59. HRMS [C21H27N3O2 + H]+: 368.2081 calculated, 368.2081 found.
2-((4-Chlorophenethyl)(methyl)amino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (35). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine 121d (34 mg, 0.20 mmol, 2 eq) and DiPEA (70 µL, 0.40 mmol, 4 eq). Total heating time: 25 h at 120 °C. Column chromatography (30% → 70% EtOAc/pentane) afforded the product (10 mg, 30 µmol, 30%). TLC: Rf = 0.4 (50% EtOAc/pentane). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.98 (br s, 1H), 7.28 – 7.23 (m, 2H), 7.17 – 7.09 (m, 2H), 6.73 (s, 1H), 3.82 – 3.72 (m, 6H), 3.65 (t, \(J = 4.8\) Hz, 4H), 3.35 – 3.24 (m, 2H), 3.09 (s, 3H), 2.94 – 2.82 (m, 2H), 1.12 – 1.01 (m, 1H), 0.60 – 0.49 (m, 2H), 0.36 – 0.23 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.64, 163.98, 156.81, 138.45, 132.12, 130.22, 128.72, 90.28, 66.76, 51.50, 44.53, 44.15, 35.86, 33.39, 10.91, 3.51. HRMS [C\(_{22}\)H\(_{28}\)ClN\(_2\)O\(_2\) + H\(^+\)]: 430.2004 calculated, 430.2004 found.

2-((3-Chlorophenethyl)(methyl)amino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (36). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (20 mg, 0.12 mmol, 1 eq), amine 121e (20 mg, 0.12 mmol, 1.5 eq) and DiPEA (49 µL, 0.28 mmol, 4 eq). Total heating time: 5 d at 120 °C. Column chromatography (30% → 50% EtOAc/pentane) afforded the product (26 mg, 62 µmol, 89%). TLC: Rf = 0.6 (40% EtOAc/pentane). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.00 (t, \(J = 5.9\) Hz, 1H), 7.25 – 7.14 (m, 3H), 7.14 – 7.02 (m, 1H), 6.73 (s, 1H), 3.86 – 3.72 (m, 6H), 3.66 (t, \(J = 4.9\) Hz, 4H), 3.30 (dd, \(J = 7.1, 5.8\) Hz, 2H), 3.12 (s, 3H), 2.93 – 2.83 (m, 2H), 1.12 – 1.01 (m, 1H), 0.60 – 0.50 (m, 2H), 0.33 – 0.24 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.62, 163.98, 160.86, 156.78, 141.98, 134.32, 129.82, 128.99, 127.06, 126.50, 90.27, 66.74, 51.34, 44.51, 44.12, 35.72, 33.68, 10.90, 3.48. HRMS [C\(_{22}\)H\(_{28}\)ClN\(_2\)O\(_2\) + H\(^+\)]: 430.2004 calculated, 430.2004 found.

2-((2-Chlorophenethyl)(methyl)amino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (37). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine 121f (28 mg, 0.17 mmol, 1.7 eq) and DiPEA (70 µL, 0.40 mmol, 4 eq). Total heating time: 3 d at 120 °C. Purification by HPLC (C18 reverse phase, 35% → 45% CH\(_3\)CN/H\(_2\)O + 0.2% TFA, RT 10.8 min) afforded the product (31 mg, 70 µmol, 70%). TLC: Rf = 0.7 (50% EtOAc/pentane). \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.06 (br s, 1H), 7.37 – 7.32 (m, 1H), 7.21 – 7.12 (m, 3H), 6.70 (s, 1H), 3.89 – 3.83 (m, 2H), 3.78 – 3.74 (m, 4H), 3.69 – 3.62 (m, 4H), 3.29 (dd, \(J = 7.0, 5.9\) Hz, 2H), 3.14 (s, 3H), 3.06 – 3.02 (m, 2H), 1.13 – 1.01 (m, 1H), 0.59 – 0.51 (m, 2H), 0.31 – 0.27 (m, 2H), \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.70, 163.95, 160.97, 156.79, 137.46, 134.14, 131.17, 129.60, 127.93, 127.01, 90.11, 66.78, 49.36, 44.51, 44.14, 35.52, 31.93, 10.97, 3.59. HRMS [C\(_{22}\)H\(_{28}\)ClN\(_2\)O\(_2\) + H\(^+\)]: 430.2004 calculated, 430.2004 found.

N-(Cyclopropylmethyl)-2-(methyl(4-methylphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (38). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine 121g (23 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 µL, 0.40 mmol, 4 eq). Total heating time: 3 d at 120 °C. Column chromatography (30% → 50% EtOAc/pentane) afforded the product (16 mg, 40 µmol, 40%). TLC: Rf = 0.8 (50% EtOAc/pentane). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.04 (t, \(J = 5.8\) Hz, 1H), 7.11 (s, 4H), 6.72 (s, 1H), 3.82 – 3.72 (m, 6H), 3.66 (t, \(J = 4.8\) Hz, 4H), 3.30 (dd, \(J = 7.1, 5.8\) Hz, 2H), 3.13 (s, 3H), 2.90 – 2.82 (m, 2H), 2.33 (s, 3H), 1.14 – 0.99 (m, 1H), 0.61 – 0.49 (m, 2H), 0.33 – 0.25 (m, 2H), \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.72, 164.01, 160.89,
Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401

$N$-(Cyclopropylmethyl)-2-(methyl(2-methylphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (39). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine $121h$ (23 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 4 d at 120 °C. Column chromatography (30% → 60% EtOAc/pentane) afforded the product (39 mg, 95 μmol, 95%). TLC: $R_f = 0.4$ (40% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (t, $J = 5.9$ Hz, 1H), 7.23 - 7.06 (m, 4H), 6.73 (s, 1H), 3.85 - 3.71 (m, 6H), 3.66 (t, $J = 4.8$ Hz, 4H), 3.29 (dd, $J = 7.1$, 5.9 Hz, 2H), 3.15 (s, 3H), 2.97 - 2.83 (m, 2H), 2.39 (s, 3H), 1.15 - 0.98 (m, 1H), 0.62 - 0.47 (m, 2H), 0.34 - 0.22 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.69, 163.99, 160.91, 156.84, 137.97, 136.13, 130.38, 129.54, 126.51, 126.22, 90.12, 66.74, 50.23, 44.50, 44.12, 35.58, 31.31, 19.46, 10.91, 3.52. HRMS [C$_{23}$H$_{31}$N$_3$O$_2$ + H]$^+$: 410.2551 calculated, 410.2549 found.

$N$-(Cyclopropylmethyl)-2-([4-methoxyphenethyl](methyl)amino)-6-morpholinopyrimidine-4-carboxamide (40). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine $121i$ (36 mg, 0.20 mmol, 2 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 7 d at 120 °C. Column chromatography (30% → 70% EtOAc/pentane) afforded the product (38 mg, 90 μmol, 90%). TLC: $R_f = 0.4$ (30% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.04 (t, $J = 5.6$ Hz, 1H), 7.18 - 7.07 (m, 2H), 6.87 - 6.80 (m, 2H), 6.72 (s, 1H), 3.79 (s, 3H), 3.79 - 3.72 (m, 6H), 3.66 (t, $J = 4.8$ Hz, 4H), 3.50 (dd, $J = 7.1$, 5.8 Hz, 2H), 3.11 (s, 3H), 2.88 - 2.81 (m, 2H), 1.11 - 1.02 (m, 1H), 0.58 - 0.52 (m, 2H), 0.32 - 0.27 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.71, 164.00, 160.88, 158.16, 156.79, 131.97, 129.76, 114.01, 90.06, 66.76, 55.39, 51.86, 44.51, 44.11, 35.75, 33.01, 10.90, 3.49. HRMS [C$_{23}$H$_{31}$N$_3$O$_3$ + H]$^+$: 426.2500 calculated, 426.2497 found.

$N$-(Cyclopropylmethyl)-2-[(2-methoxynaphthenyl)(methyl)amino]-6-morpholinopyrimidine-4-carboxamide (41). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine $121j$ (24 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 8 h at 160 °C with μW irradiation. Column chromatography (30% → 70% EtOAc/pentane) afforded the product (42 mg, 0.10 mmol, 99%). TLC: $R_f = 0.3$ (30% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.08 (t, $J = 6.0$ Hz, 1H), 7.20 (td, $J = 7.8$, 1.8 Hz, 1H), 7.13 (dd, $J = 7.3$, 1.7 Hz, 1H), 6.94 - 6.82 (m, 2H), 6.71 (s, 1H), 3.83 (s, 3H), 3.81 - 3.72 (m, 6H), 3.66 (t, $J = 4.8$ Hz, 4H), 3.30 (dd, $J = 7.0$, 5.9 Hz, 2H), 3.12 (s, 3H), 3.03 - 2.84 (m, 2H), 1.13 - 0.97 (m, 1H), 0.65 - 0.44 (m, 2H), 0.35 - 0.20 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.81, 163.99, 160.95, 157.81, 156.77, 130.55, 128.37, 127.64, 120.64, 110.48, 89.88, 66.79, 55.47, 49.93, 44.49, 44.04, 35.65, 28.70, 10.94, 3.47. HRMS [C$_{23}$H$_{31}$N$_3$O$_4$ + H]$^+$: 426.2500 calculated, 426.2496 found.

$N$-(Cyclopropylmethyl)-2-[[4-(trifluoromethyl)phenethyl]amino]-6-morpholinopyrimidine-4-carboxamide (42). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (22 mg, 73 μmol, 1 eq), amine $121k$ (29 mg, 0.10 mmol, 1.5 eq) and DiPEA (51 μL, 0.29 mmol, 4 eq). Total heating time: 25 h at 120 °C. Purification by HPLC (C18 reverse phase, 47% → 55% CH$_3$CN/H$_2$O + 0.2% TFA, RT 12 min) afforded the product (9 mg, 20 μmol, 27%). TLC: $R_f = 0.4$ (50% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.98 (br s, 1H), 7.54 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 7.9$ Hz, 2H), 6.73 (s, 1H), 3.87 - 3.79 (m, 2H), 3.79 - 3.71 (m, 4H), 3.65 (t, $J = 4.8$ Hz, 4H), 3.35 - 3.24 (m, 2H), 3.10 (s, 3H), 3.02 - 2.93 (m, 2H), 1.12 - 0.99 (m, 1H), 0.65 - 0.48 (m, 2H), 0.39 - 0.22 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.61, 163.98, 160.88, 156.81, 144.18 (q, $J = 1.4$ Hz, 129.21, 128.89,
**N-(Cyclopropylmethyl)-2-(methyl(4-phenoxyphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (43).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine 121I (34 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 48 h at 120 °C. Column chromatography (30% → 70% EtOAc/pentane) afforded the product (26 mg, 50 μmol, 50%). TLC: Rf = 0.4 (50% EtOAc/pentane). ¹H NMR (600 MHz, CDCl₃) δ 8.00 (br s, 1H), 7.35 – 7.28 (m, 2H), 7.19 – 7.13 (m, 2H), 7.10 – 7.06 (m, 1H), 6.99 – 6.89 (m, 4H), 6.72 (s, 1H), 3.84 – 3.78 (m, 2H), 3.78 – 3.73 (m, 4H), 3.69 – 3.63 (m, 4H), 3.31 – 3.26 (m, 2H), 3.13 (s, 3H), 2.93 – 2.86 (m, 2H), 1.11 – 0.98 (m, 1H), 0.56 – 0.51 (m, 2H), 0.29 – 0.25 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 164.67, 164.00, 160.92, 157.63, 156.80, 155.60, 134.93, 130.09, 129.83, 123.17, 119.27, 118.63, 90.12, 66.75, 51.67, 44.54, 44.12, 35.73, 33.25, 10.90, 3.49. HRMS [C₉₂H₈₂F₃N₄O₃ + H]^+: 464.2268 calculated, 464.2267 found.

**N-(Cyclopropylmethyl)-2-(methyl(3-phenoxyphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (44).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (25 mg, 84 μmol, 1 eq), amine 121m (28 mg, 0.12 mmol, 1.5 eq) and DiPEA (60 μL, 0.34 mmol, 4 eq). Total heating time: 5 d at 120 °C. Purification by HPLC (C18 reverse phase, 40% → 50% CH₃CN/H₂O + 0.2% TFA, RT 11.2 min) afforded the product (14 mg, 29 μmol, 35%). TLC: Rf = 0.5 (30% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.00 (br s, 1H), 7.35 – 7.28 (m, 2H), 7.29 – 7.20 (m, 1H), 7.13 – 7.06 (m, 1H), 6.99 – 6.94 (m, 3H), 6.92 – 6.87 (m, 1H), 6.86 – 6.83 (m, 1H), 6.71 (s, 1H), 3.84 – 3.77 (m, 2H), 3.76 – 3.70 (m, 4H), 3.67 – 3.61 (m, 4H), 3.30 – 3.24 (m, 2H), 3.12 (s, 3H), 2.93 – 2.83 (m, 2H), 1.11 – 0.98 (m, 1H), 0.57 – 0.49 (m, 2H), 0.30 – 0.24 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.67, 163.98, 160.89, 157.41, 157.32, 156.81, 142.03, 129.86, 123.91, 123.26, 119.57, 118.70, 116.91, 90.19, 66.75, 51.48, 44.52, 44.14, 35.69, 33.87, 10.90, 3.51. HRMS [C₉₂H₈₂F₃N₄O₃ + H]^+: 488.2656 calculated, 488.2653 found.

**N-(Cyclopropylmethyl)-2-(methyl(2-phenoxyphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (45).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (34 mg, 0.10 mmol, 1 eq), amine 121n (37 mg, 0.16 mmol, 1.6 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 3 d at 120 °C. Column chromatography (30% → 50% EtOAc/pentane) afforded the product (45 mg, 90 μmol, 90%). TLC: Rf = 0.5 (40% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.06 (t, J = 5.4 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.26 (dd, J = 7.4, 1.5 Hz, 1H), 7.17 (td, J = 7.8, 1.7 Hz, 1H), 7.12 – 7.00 (m, 2H), 6.93 (dd, J = 8.6, 0.9 Hz, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 3.90 – 3.79 (m, 2H), 3.76 – 3.54 (m, 8H), 3.27 (t, J = 6.4 Hz, 2H), 3.07 (s, 3H), 2.99 – 2.88 (m, 2H), 1.11 – 0.98 (m, 1H), 0.60 – 0.44 (m, 2H), 0.27 (q, J = 4.7 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.74, 163.94, 160.90, 157.74, 156.72, 155.09, 131.31, 129.89, 127.84, 123.92, 122.99, 119.36, 118.07, 89.94, 66.70, 50.17, 44.44, 44.03, 35.57, 28.69, 10.92, 3.49. HRMS [C₉₂H₈₂F₃N₄O₃ + H]^+: 488.2656 calculated, 488.2653 found.
 Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401

2-[(2-[(1,1'- Biphenyl)-2-yl]ethyl](methyl)amino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (46). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (29 mg, 96 μmol, 1 eq), amine 1210 (31 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 24 h at 160 °C with μW irradiation. Column chromatography (30% – 60% EtOAc/pentane) afforded the product (43 mg, 91 μmol, 95%). TLC: Rf = 0.4 (30% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.97 (t, J = 5.9 Hz, 1H), 7.41 – 7.19 (m, 9H), 6.68 (s, 1H), 3.77 – 3.70 (m, 4H), 3.66 – 3.57 (m, 6H), 3.28 (dd, J = 7.0, 5.8 Hz, 2H), 2.94 – 2.89 (m, 2H), 2.77 (s, 3H), 1.10 – 1.00 (m, 1H), 0.59 – 0.49 (m, 2H), 0.31 – 0.25 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.69, 163.87, 160.70, 156.65, 142.44, 141.63, 137.33, 130.26, 129.83, 129.28, 128.15, 127.56, 126.94, 126.29, 89.99, 66.72, 51.00, 44.44, 44.04, 35.31, 30.93, 10.90, 3.47. HRMS [C28H34N2O + H]⁺: 472.2707 calculated, 472.2703 found.

N-(Cyclopropylmethyl)-2-(methyl[2-(pyridin-4-yl)ethyl]amino)-6-morpholinopyrimidine-4-carboxamide (47). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), N-methyl-2-(pyridin-4-yl)ethan-1-amine (21 μL, 0.15 mmol, 1.5 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 17 h at 120 °C. Column chromatography (2% – 6% MeOH/DCM) afforded the product (8 mg, 21 μmol, 21%). TLC: Rf = 0.2 (4% MeOH/DCM). 1H NMR (400 MHz, CDCl3) δ 8.51 (d, J = 5.7 Hz, 2H), 7.96 (br s, 1H), 7.15 (d, J = 5.7 Hz, 2H), 6.74 (s, 1H), 3.90 – 3.80 (m, 2H), 3.80 – 3.72 (m, 4H), 3.72 – 3.53 (m, 4H), 3.36 – 3.24 (m, 2H), 3.11 (s, 3H), 2.98 – 2.85 (m, 2H), 1.12 – 0.99 (m, 1H), 0.64 – 0.47 (m, 2H), 0.28 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.54, 163.96, 160.83, 156.80, 149.96, 148.99, 124.32, 90.46, 66.74, 50.59, 44.50, 44.13, 35.87, 33.44, 10.91, 3.51. HRMS [C21H28N2O + H]⁺: 397.2347 calculated, 397.2345 found.

N-(Cyclopropylmethyl)-2-(methyl[2-(pyridin-3-yl)ethyl]amino)-6-morpholinopyrimidine-4-carboxamide (48). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), N-methyl-2-(pyridin-3-yl)ethan-1-amine (21 μL, 0.15 mmol, 1.5 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 17 h at 120 °C. Column chromatography (2% – 6% MeOH/DCM) afforded the product (11 mg, 29 μmol, 29%). TLC: Rf = 0.15 (4% MeOH/DCM). 1H NMR (400 MHz, CDCl3) δ 8.65 – 8.28 (m, 2H), 7.95 (br s, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.21 (dd, J = 7.9, 4.8 Hz, 1H), 6.72 (s, 1H), 3.89 – 3.69 (m, 6H), 3.69 – 3.53 (m, 4H), 3.29 (t, J = 6.4 Hz, 2H), 3.11 (s, 3H), 2.92 (t, J = 7.4 Hz, 2H), 1.12 – 0.99 (m, 1H), 0.66 – 0.45 (m, 2H), 0.36 – 0.19 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.57, 163.95, 160.86, 156.77, 150.27, 147.86, 136.33, 135.30, 123.50, 90.36, 66.74, 51.19, 44.49, 44.15, 35.84, 31.23, 10.91, 3.51. HRMS [C21H28N2O + H]⁺: 397.2347 calculated, 397.2345 found.

N-(Cyclopropylmethyl)-2-(methyl[2-(pyridin-2-yl)ethyl]amino)-6-morpholinopyrimidine-4-carboxamide (49). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), N-methyl-2-(pyridin-2-yl)ethan-1-amine (21 μL, 0.15 mmol, 1.5 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 8 h at 160 °C with μW irradiation. Column chromatography (3% – 4% MeOH/DCM) afforded the product (26 mg, 66 μmol, 66%). TLC: Rf = 0.3 (3% MeOH/DCM). 1H NMR (400 MHz, CDCl3) δ 8.66 – 8.44 (m, 1H), 8.18 (br s, 1H), 7.58 (td, J = 7.6, 1.7 Hz, 1H), 7.21 – 7.03 (m, 2H), 6.72 (s, 1H), 3.99 (t, J = 7.2 Hz, 2H), 3.88 – 3.71 (m, 4H), 3.71 – 3.54 (m, 4H), 3.31 (t, J = 6.4 Hz, 2H), 3.21 – 3.03 (m, 5H), 1.16 – 1.00 (m, 1H), 0.62 – 0.43 (m, 2H), 0.29 (q, J = 4.8 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.62, 163.91, 160.79, 159.86, 156.60, 149.21,
Chapter 3

136.68, 123.60, 121.48, 90.12, 66.72, 49.98, 44.48, 44.01, 36.15, 35.62, 10.94, 3.45. HRMS \([C_{2}H_{2}N_{2}O_{2} + H]^{+}\): 397.2347 calculated, 397.2345 found.

**N-(Cyclopropylmethyl)-2-(methyl(2-thiophen-2-yl)ethyl)amino)-6-morpholinopyrimidine-4-carboxamide (50).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), DiPEA (52 μL, 0.30 mmol, 3 eq) and N-methyl-2-thiopheneethyamine (18 μL, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (16 mg, 40 μmol, 40%). TLC: Rf = 0.4 (50% EtOAc/pentane). \(\text{H} NMR (400 MHz, CDCl}_3 \delta 8.04 (t, J = 5.3 Hz, 1H), 7.15 (dd, J = 5.1, 1.1 Hz, 1H), 6.94 (dd, J = 5.1, 3.4 Hz, 1H), 6.83 (d, J = 2.9 Hz, 1H), 6.73 (s, 1H), 3.88 – 3.80 (m, 2H), 3.80 – 3.72 (m, 4H), 3.71 – 3.62 (m, 4H), 3.33 – 3.26 (m, 2H), 3.20 – 3.08 (m, 5H), 1.13 – 0.99 (m, 1H), 0.60 – 0.48 (m, 2H), 0.28 (q, J = 4.7 Hz, 2H). \(^{13}\text{C} NMR (101 MHz, CDCl}_3 \delta 164.62, 163.97, 160.84, 156.81, 142.18, 127.06, 125.03, 123.68, 90.26, 66.75, 51.90, 44.51, 44.13, 35.75, 27.94, 10.91, 3.55. HRMS \([C_{20}H_{27}N_{4}O_{2} + H]^{+}\): 402.1958 calculated, 402.1956 found.

**N-(Cyclopropylmethyl)-2-(ethyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (51).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (28 mg, 93 μmol, 1 eq), amine 123a (21 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 12 h at 160 °C with μW irradiation. Column chromatography (20% -> 50% EtOAc/pentane) afforded the product (15 mg, 40 μmol, 43%). TLC: Rf = 0.3 (30% EtOAc/pentane). \(\text{H} NMR (400 MHz, CDCl}_3 \delta 8.04 (t, J = 5.9 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.20 (m, 3H), 6.72 (s, 1H), 3.80 – 3.73 (m, 6H), 3.70 – 3.63 (m, 4H), 3.58 (q, J = 7.0 Hz, 2H), 3.30 (dd, J = 7.1, 5.8 Hz, 2H), 2.97 – 2.89 (m, 2H), 1.18 (t, J = 7.0 Hz, 3H), 1.11 – 1.01 (m, 1H), 0.59 – 0.51 (m, 2H), 0.31 – 0.25 (m, 2H). \(^{13}\text{C} NMR (101 MHz, CDCl}_3 \delta 164.74, 164.12, 160.29, 156.86, 140.06, 128.83, 128.62, 126.32, 90.06, 66.78, 49.83, 44.53, 44.09, 43.04, 34.76, 13.24, 10.90, 3.44. HRMS \([C_{29}H_{34}N_{4}O_{2} + H]^{+}\): 410.2551 calculated, 410.2549 found.

**N-(Cyclopropylmethyl)-2-(isopropyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (52).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (59 mg, 0.20 mmol, 1 eq), amine 123b (50 mg, 0.30 mmol, 1.5 eq) and DiPEA (140 μL, 0.80 mmol, 4 eq). Total heating time: 12 h at 160 °C with μW irradiation. Column chromatography (50% -> 60% EtOAc/pentane) afforded the product (19 mg, 40 μmol, 20%). TLC: Rf = 0.4 (50% EtOAc/pentane). \(\text{H} NMR (400 MHz, CDCl}_3 \delta 8.05 (br s, 1H), 7.37 – 7.29 (m, 2H), 7.29 – 7.20 (m, 3H), 6.75 (s, 1H), 4.96 (hept, J = 6.8 Hz, 1H), 3.82 – 3.74 (m, 4H), 3.72 – 3.64 (m, 4H), 3.64 – 3.55 (m, 2H), 3.35 – 3.26 (m, 2H), 3.01 – 2.88 (m, 2H), 1.24 (d, J = 6.8 Hz, 6H), 1.11 – 1.00 (m, 1H), 0.60 – 0.49 (m, 2H), 0.33 – 0.23 (m, 2H). \(^{13}\text{C} NMR (101 MHz, CDCl}_3 \delta 164.79, 164.06, 160.40, 156.81, 140.36, 128.68, 128.65, 126.35, 90.26, 66.77, 46.38, 44.57, 44.48, 44.17, 36.29, 20.65, 10.90, 3.51. HRMS \([C_{28}H_{33}N_{4}O_{2} + H]^{+}\): 424.2707 calculated, 424.2705 found.

**2-(Cyclopropyl(phenethyl)amino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (53).** The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine 123c (25 mg, 0.16 mmol, 1.6 eq) and DiPEA (115 μL, 0.60 mmol, 6 eq). Total heating time: 36 h at 160 °C with μW irradiation. Purification by HPLC (C18 reverse phase, 37% -> 47% CH3CN/H2O + 0.2% TFA) afforded the product (7 mg, 20 μmol, 20%). TLC: Rf = 0.4 (40% EtOAc/pentane). \(\text{H} NMR (400 MHz, CDCl}_3 \delta 8.17 (s, 1H), 7.34 – 7.24 (m, 3H),
Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401

7.25 – 7.16 (m, 3H), 6.79 (s, 1H), 3.87 – 3.73 (m, 6H), 3.69 (t, J = 4.7 Hz, 4H), 3.30 (dd, J = 7.1, 5.7 Hz, 2H), 2.98 – 2.85 (m, 2H), 2.73 – 2.64 (m, 1H), 1.14 – 0.98 (m, 1H), 0.90 – 0.77 (m, 2H), 0.68 – 0.59 (m, 2H), 0.59 – 0.49 (m, 2H), 0.35 – 0.22 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.62, 163.99, 162.12, 156.64, 140.18, 128.88, 128.59, 126.31, 91.08, 66.78, 50.52, 44.57, 44.11, 34.58, 30.41, 10.86, 8.67, 3.42. HRMS [C29H35N5O2 + H]+: 422.2551 calculated, 422.2549 found.

N-(Cyclopropylmethyl)-6-morpholino-2-(phenethyl(phenyl)amino)pyrimidine-4-carboxamide (54). A microwave vial with a magnetic stir bar under N2 was charged with 2-chloropyrimidine 28 (29 mg, 98 μmol, 1eq), amine 122 (24 mg, 0.12 mmol, 1.2 eq) and dry toluene (0.1 ml). The vial was capped and the solution purged with N2. This was followed by the addition of RuPhosPd G3 (0.01 M THF solution, 100 μL, 1 μmol, 0.01 eq) and NaOtBu (2 M THF solution, 60 μL, 0.12 mmol, 1.2 eq) and the mixture was purged again with N2, and stirred in a preheated oil bath at 110 °C. After 24 h the reaction was complete as judged by LC-MS. The mixture was filtered through a plug of Celite and the filtrate concentrated under reduced pressure to provide the crude material. Purification by HPLC (C18 reverse phase, 5% -> 50% CH3CN/H2O + 0.2% TFA, RT 12.0 min) afforded the product (12 mg, 26 μmol, 27%). TLC: Rf = 0.4 (40% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.79 (t, J = 4.9 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.32 – 7.17 (m, 8H), 6.79 (s, 1H), 4.28 – 4.11 (m, 2H), 3.79 – 3.67 (m, 4H), 3.60 (t, J = 4.8 Hz, 4H), 3.20 (dd, J = 7.1, 5.7 Hz, 2H), 3.09 – 2.96 (m, 2H), 1.02 – 0.89 (m, 1H), 0.55 – 0.41 (m, 2H), 0.27 – 0.12 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.24, 163.97, 160.50, 156.93, 144.67, 139.63, 128.84, 128.62, 127.72, 126.40, 125.73, 91.42, 66.71, 50.52, 44.51, 43.96, 34.64, 10.70, 3.34. HRMS [C27H23N5O2 + H]+: 458.2864 calculated, 458.2861 found.

2-(Benzyllphenylamino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (55). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (26 mg, 88 μmol, 1 eq), amine 122d (28 mg, 0.13 mmol, 1.5 eq) and DiPEA (44 μL, 0.25 mmol, 3 eq). Total heating time: 7 d at 120 °C. Column chromatography (30% -> 50% EtOAc/pentane) afforded the product (20 mg, 40 μmol, 45%). TLC: Rf = 0.6 (40% EtOAc/pentane). 1H NMR (400 MHz, MeOD + CDCl3) δ 7.36 – 7.04 (m, 10H), 6.67 (s, 1H), 4.74 (s, 2H), 3.91 – 3.50 (m, 10H), 3.19 (br s, 2H), 2.94 – 2.79 (m, 2H), 0.98 (br s, 1H), 0.50 (br s, 2H), 0.21 (br s, 2H). 13C NMR (101 MHz, CDCl3) δ 164.60, 164.09, 160.81, 156.93, 139.90, 139.50, 128.82, 128.62, 128.57, 127.31, 127.04, 126.34, 90.66, 66.72, 51.39, 49.88, 44.56, 44.13, 34.22, 10.84, 3.47. HRMS [C27H23N5O2 + H]+: 472.2707 calculated, 472.2704 found.

N-(Cyclopropylmethyl)-2-(diphenethylamino)-6-morpholinopyrimidine-4-carboxamide (56). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine 123e (37 mg, 0.16 mmol, 1.6 eq) and DiPEA (70 μL, 0.40 mmol, 4 eq). Total heating time: 12 h at 160 °C with μW irradiation. Column chromatography (20% -> 50% EtOAc/pentane) afforded the product (24 mg, 50 μmol, 50%). TLC: Rf = 0.5 (30% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.02 (t, J = 5.8 Hz, 1H), 7.34 – 7.26 (m, 4H), 7.24 – 7.15 (m, 6H), 6.75 (s, 1H), 3.83 – 3.60 (m, 12H), 3.30 (dd, J = 7.1, 5.8 Hz, 2H), 2.97 – 2.82 (m, 4H), 1.12 – 1.00 (m, 1H), 0.63 – 0.49 (m, 2H), 0.35 – 0.23 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.66, 164.08, 160.34, 156.84, 139.91, 128.82, 128.62, 126.35, 90.34, 66.75, 50.69, 44.57, 44.23, 34.58, 10.86, 3.52. HRMS [C29H35N5O2 + H]+: 486.2864 calculated, 486.2861 found.
**Chapter 3**

*-$N$-(Cyclopropylmethyl)-2-(3,4-dihydroisoquinolin-2(1H)-yl)-6-morpholinopyrimidine-4-carboxamide* (57). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (29 mg, 97 µmol, 1 eq), 1,2,3,4-tetrahydroisoquinoline (19 µL, 0.15 mmol, 1.5 eq) and DiPEA (70 µL, 0.40 mmol, 4 eq). Total heating time: 18 h at 120 °C. Column chromatography (20% -> 60% EtOAc/pentane) afforded the product (34 mg, 90 µmol, 93%). TLC: Rf = 0.5 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.04 (t, J = 6.0 Hz, 1H), 7.25 – 7.13 (m, 4H), 6.76 (s, 1H), 4.90 (s, 2H), 4.04 (t, J = 5.9 Hz, 2H), 3.81 – 3.62 (m, 8H), 3.36 – 3.28 (m, 2H), 2.93 (t, J = 5.8 Hz, 2H), 1.16 – 1.01 (m, 1H), 0.61 – 0.51 (m, 2H), 0.31 (dt, J = 6.1, 4.6 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.61, 163.99, 160.78, 156.88, 135.40, 134.49, 128.77, 127.56, 127.40, 126.23, 90.80, 66.76, 46.46, 44.54, 44.10, 41.63, 29.14, 10.99, 3.54. HRMS [C22H27N2O2 + H]+: 394.2238 calculated, 394.2231 found.

*(±)-N-(Cyclopropylmethyl)-6-morpholino-2-(3-phenylpyrrolidin-1-yl)pyrimidine-4-carboxamide* (58). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), (±)-3-phenylpyrrolidine (22 µL, 0.15 mmol, 1.5 eq) and DiPEA (70 µL, 0.40 mmol, 4 eq). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (30% -> 70% EtOAc/pentane) afforded the product (39 mg, 95 µmol, 95%). TLC: Rf = 0.4 (40% EtOAc/pentane). 1H NMR (500 MHz, CDCl3) δ 8.09 (br s, 1H), 7.40 – 7.29 (m, 4H), 7.29 – 7.24 (m, 1H), 6.75 (s, 1H), 4.18 – 4.03 (m, 1H), 3.88 (t, J = 9.5 Hz, 1H), 3.79 – 3.71 (m, 4H), 3.71 – 3.59 (m, 5H), 3.58 – 3.51 (m, 1H), 3.51 – 3.43 (m, 1H), 3.35 – 3.20 (m, 2H), 2.43 – 2.33 (m, 1H), 2.18 – 2.06 (m, 1H), 1.13 – 0.97 (m, 1H), 0.61 – 0.44 (m, 2H), 0.34 – 0.20 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.65, 163.89, 159.58, 156.77, 142.22, 128.70, 127.29, 126.84, 90.15, 66.73, 53.27, 46.49, 44.42, 44.19, 44.02, 33.28, 10.90, 3.49. HRMS [C22H27N2O2 + H]+: 408.2394 calculated, 408.2391 found.

*(±)-N-(Cyclopropylmethyl)-6-morpholino-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide* (59). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), (±)-3-phenylpiperidine (24 µL, 0.15 mmol, 1.5 eq) and DiPEA (70 µL, 0.40 mmol, 4 eq). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (40% -> 70% EtOAc/pentane) afforded the product (37 mg, 88 µmol, 88%). TLC: Rf = 0.3 (40% EtOAc/pentane). 1H NMR (500 MHz, CDCl3) δ 7.97 (t, J = 5.9 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.32 – 7.22 (m, 3H), 6.73 (s, 1H), 4.89 – 4.70 (m, 2H), 3.74 (t, J = 4.8 Hz, 4H), 3.69 – 3.56 (m, 4H), 3.37 – 3.16 (m, 2H), 2.97 – 2.83 (m, 2H), 2.76 (tt, J = 11.5, 3.7 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.91 – 1.83 (m, 1H), 1.82 – 1.72 (m, 1H), 1.72 – 1.57 (m, 1H), 1.11 – 0.99 (m, 1H), 0.61 – 0.43 (m, 2H), 0.27 (q, J = 5.1 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.60, 164.07, 160.94, 156.93, 144.28, 128.65, 127.30, 126.66, 90.57, 66.71, 51.24, 44.67, 44.48, 44.04, 42.63, 32.27, 25.56, 10.94, 3.50, 3.48. HRMS [C26H31N2O2 + H]+: 422.2551 calculated, 422.2548 found.

*(±)-2-(2-Benzylpyrrolidin-1-yl)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide* (60). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), (±)-2-benzylpyrrolidine (24 µL, 0.15 mmol, 1.5 eq) and DiPEA (70 µL, 0.40 mmol, 4 eq). Total heating time: 3 d at 120 °C. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (42 mg, 0.10 mmol, 99%). TLC: Rf = 0.5 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.11 (t, J = 5.8 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.26 – 7.18 (m, 3H), 6.76 (s, 1H), 4.48 – 4.34 (m, 1H), 3.80 – 3.73 (m, 4H), 3.73 – 3.65 (m, 4H), 3.65 – 3.59 (m, 1H), 3.59 – 3.50 (m, 1H), 3.37 – 3.24 (m, 3H), 2.59 (dd, J = 13.1, 9.7 Hz, 1H), 1.91 – 1.82 (m, 4H), 1.14 – 0.98 (m, 1H), 0.65 – 0.46
(±)-2-(2-Benzylpiperidin-1-yl)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (61). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), (±)-2-benzylpiperidine hydrochloride (52 mg, 0.24 mmol, 2.4 eq) and DiPEA (104 µL, 0.60 mmol, 6 eq). Total heating time: 6 d at 120 °C. Column chromatography (30% → 60% EtOAc/pentane) afforded the product (12 mg, 27 µmol, 27%). TLC: Rf = 0.4 (50% EtOAc/pentane).1H NMR (600 MHz, CDCl3) δ 7.98 (t, J = 5.2 Hz, 1H), 7.26 (t, J = 7.4 Hz, 2H), 7.24 – 7.16 (m, 3H), 6.70 (s, 1H), 5.13 – 4.97 (m, 1H), 4.77 – 4.60 (m, 1H), 3.82 – 3.73 (m, 4H), 3.66 (br s, 4H), 3.40 – 3.21 (m, 2H), 3.07 – 2.98 (m, 1H), 2.95 (dd, J = 13.1, 10.0 Hz, 1H), 2.81 (dd, J = 13.1, 5.1 Hz, 1H), 1.85 – 1.73 (m, 2H), 1.73 – 1.67 (m, 2H), 1.57 – 1.46 (m, 2H), 1.13 – 1.04 (m, 1H), 0.63 – 0.53 (m, 2H). 13C NMR (151 MHz, CDCl3) δ 164.75, 163.97, 156.81, 156.80, 140.16, 129.26, 128.47, 126.16, 90.34, 66.78, 52.27, 44.53, 44.24, 39.47, 35.32, 26.29, 25.82, 19.30, 10.95, 3.65, 3.61. HRMS [C29H33N6O2 + H]+: 436.2707 calculated, 436.2706 found.

(±)-N-(Cyclopropylmethyl)-2-(2-(cyclohexylmethyl)piperidin-1-yl)-6-morpholinopyrimidine-4-carboxamide. The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (24 mg, 80 µmol, 1 eq), DiPEA (70 µL, 0.4 mmol, 5 eq) and (±)-(cyclohexylmethyl)piperidin (22 mg, 0.12 mmol, 1.5 eq). Total heating time: 24 h at 160 °C with µW irradiation. Column chromatography (10% → 60% EtOAc/pentane) afforded the product (6 mg, 14 µmol, 18%). TLC: Rf = 0.6 (50% EtOAc/pentane).1H NMR (500 MHz, CDCl3) δ 7.98 (s, 1H), 6.67 (s, 1H), 5.07 – 4.94 (m, 1H), 4.61 (dd, J = 13.8, 4.4 Hz, 1H), 3.81 – 3.70 (m, 4H), 3.70 – 3.56 (m, 4H), 3.37 – 3.17 (m, 2H), 2.90 (td, J = 13.1, 2.5 Hz, 1H), 1.80 (dd, J = 25.9, 12.9 Hz, 2H), 1.73 – 1.59 (m, 8H), 1.56 – 1.38 (m, 3H), 1.24 – 1.10 (m, 4H), 1.10 – 1.00 (m, 1H), 0.99 – 0.86 (m, 2H), 0.62 – 0.47 (m, 2H), 0.27 (q, J = 4.8 Hz, 2H).13C NMR (126 MHz, CDCl3) δ 164.86, 164.07, 160.88, 156.90, 89.87, 66.82, 47.48, 44.55, 44.22, 38.83, 36.74, 34.55, 34.22, 33.47, 29.85, 28.23, 26.76, 26.48, 26.42, 25.94, 19.46, 10.90, 3.57, 3.54. HRMS [C31H34N6O2 + H]+: 442.3177 calculated, 442.3174 found.

(±)-N-(Cyclopropylmethyl)-2-(2-(4-methoxybenzyl)piperidin-1-yl)-6-morpholinopyrimidine-4-carboxamide (63). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), (±)-2-(4-methoxybenzyl)piperidine (46 mg, 0.22 mmol, 2.2 eq) and DiPEA (70 µL, 0.40 mmol, 4 eq). Total heating time: 28 h at 160 °C with µW irradiation. Purification by HPLC (C18 reverse phase, 5% → 90% CH3CN/H2O + 0.2% TFA, RT 9.3 min) afforded the product (13 mg, 29 µmol, 29%). TLC: Rf = 0.3 (40% EtOAc/pentane).1H NMR (400 MHz, CDCl3) δ 7.98 (t, J = 5.8 Hz, 1H), 7.16 – 7.10 (m, 2H), 6.85 – 6.75 (m, 2H), 6.69 (s, 1H), 5.00 (dt, J = 10.4, 4.9 Hz, 1H), 4.67 (dd, J = 13.5, 3.7 Hz, 1H), 3.84 – 3.72 (m, 7H), 3.65 (t, J = 4.8 Hz, 4H), 3.40 – 3.21 (m, 2H), 3.00 (td, J = 13.2, 2.8 Hz, 1H), 2.90 (dd, J = 13.2, 10.0 Hz, 1H), 2.74 (dd, J = 13.2, 5.1 Hz, 1H), 1.85 – 1.71 (m, 2H), 1.65 (s, 2H), 1.59 – 1.42 (m, 2H), 1.15 – 1.01 (m, 1H), 0.64 – 0.50 (m, 2H), 0.36 – 0.25 (m, 2H).13C NMR (101 MHz, CDCl3) δ 164.78, 164.00, 160.88, 158.03, 156.84, 132.18, 130.15, 113.89, 90.31, 66.79, 55.40, 52.38, 44.54, 44.23, 39.47, 34.37, 26.18, 25.83, 19.29, 10.97, 3.65, 3.61. HRMS [C26H35N6O2 + H]+: 466.2813 calculated, 466.2809 found.

Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401.
Chapter 3

(±)-N-(Cyclopropylmethyl)-6-morpholino-2-(2-phenylmorpholino)pyrimidine-4-carboxamide (64). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), DiPEA (52 µL, 0.30 mmol, 3 eq) and (±)-2-phenylmorpholine (21 µL, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (40% → 60% EtOAc/pentane) afforded the product (37 mg, 87%). TLC: Rf = 0.4 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.92 (br s, 1H), 7.50 – 7.31 (m, 5H), 6.80 (s, 1H), 4.66 (d, J = 13.3 Hz, 1H), 4.59 – 4.48 (m, 2H), 4.20 – 4.13 (m, 1H), 3.80 (td, J = 11.8, 2.8 Hz, 1H), 3.77 – 3.70 (m, 4H), 3.70 – 3.59 (m, 4H), 3.36 – 3.22 (m, 2H), 3.22 – 3.12 (m, 1H), 2.97 (dd, J = 13.3, 10.6 Hz, 1H), 1.12 – 0.99 (m, 1H), 0.60 – 0.46 (m, 2H), 0.28 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.34, 163.92, 160.97, 156.85, 139.91, 128.62, 128.23, 126.51, 91.50, 78.26, 67.02, 66.67, 50.63, 44.47, 44.11, 43.99, 10.94, 3.53. HRMS [C32H36N5O3 + H]+: 423.2434 calculated, 424.2430 found.

(±)-N-(Cyclopropylmethyl)-6-morpholino-2-[3-phenylpiperazino-1-yl]pyrimidine-4-carboxamide (65). A round-bottom flask was charged with Cbz-protected amine 67 (56 mg, 0.10 mmol, 1 eq) and MeOH (0.5 mL). The solution was purged with N2 and Pd/C (10% w/w, 50 mg, 50 µmol, 0.5 eq) was added. The mixture was purged with N2 and then with H2 and stirred for 2 h under an H2 atmosphere (balloon). The mixture was filtered through a plug of Celite, washed with MeOH and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1% → 4% MeOH/DCM) to afford the product (38 mg, 90 µmol, 90%). TLC: Rf = 0.3 (2% MeOH/DCM). 1H NMR (400 MHz, CDCl3) δ 7.94 (t, J = 5.9 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.43 – 7.30 (m, 3H), 6.76 (s, 1H), 4.69 (d, J = 12.5 Hz, 2H), 3.88 – 3.78 (m, 1H), 3.78 – 3.71 (m, 4H), 3.68 – 3.61 (m, 4H), 3.32 – 3.23 (m, 2H), 3.21 (d, J = 10.6 Hz, 1H), 3.13 – 2.94 (m, 2H), 2.90 (t, J = 11.7 Hz, 1H), 2.11 (br s, 1H), 1.09 – 1.00 (m, 1H), 0.57 – 0.47 (m, 2H), 0.30 – 0.24 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.51, 163.99, 161.01, 156.89, 142.01, 128.73, 127.97, 127.32, 91.05, 66.72, 60.57, 51.48, 46.27, 44.49, 44.26, 44.10, 10.97, 3.55. HRMS [C26H30N6O2 + H]+: 423.2503 calculated, 423.2501 found.

(±)-2-[4-Benzyl-3-phenylpiperazino-1-yl]-N-(cyclopropylmethyl)-6-morpholopyrimidine-4-carboxamide (66). A round-bottom flask was charged with amine 65 (19 mg, 45 µmol, 1 eq) in dry CH2CN (0.5 mL). This was followed by DiPEA (16 µL, 90 µmol, 2 eq) and benzyl bromide (6.4 µL, 54 µmol, 1.2 eq). The reaction was stirred for 4 h at rt after which the solvents were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1% → 5% MeOH/DCM) affording the product (17 mg, 33 µmol, 73%). TLC: Rf = 0.5 (2% MeOH/DCM). 1H NMR (400 MHz, CDCl3) δ 7.90 (t, J = 5.7 Hz, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.36 – 7.27 (m, 5H), 7.25 – 7.18 (m, 1H), 6.74 (s, 1H), 4.70 – 4.54 (m, 2H), 3.83 (d, J = 13.4 Hz, 1H), 3.77 – 3.67 (m, 4H), 3.66 – 3.54 (m, 4H), 3.35 (dd, J = 10.6, 3.1 Hz, 1H), 3.32 – 3.18 (m, 2H), 3.08 (td, J = 12.7, 2.7 Hz, 1H), 3.03 – 2.92 (m, 2H), 2.87 (d, J = 13.4 Hz, 1H), 2.17 (td, J = 11.8, 3.0 Hz, 1H), 1.09 – 0.95 (m, 1H), 0.57 – 0.44 (m, 2H), 0.25 (q, J = 4.6 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.48, 164.02, 160.74, 156.91, 141.70, 138.93, 128.92, 128.87, 128.29, 128.20, 127.87, 127.00, 90.97, 67.34, 66.71, 59.23, 51.90, 51.73, 44.47, 44.36, 44.08, 10.92, 3.53, 3.51. HRMS [C30H36N6O2 + H]+: 513.2973 calculated, 513.2973 found.
(±)-Benzyl 4-(4-((cyclopropylmethyl)carbamoyl)-6-morpholinopyrimidin-2-yl)-2-phenylpiperazine-1-carboxylate (67). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), amine 130 (45 mg, 0.12 mmol, 1.2 eq) and DIPEA (70 µL, 0.40 mmol, 4 eq). Total heating time: 41 h at 120 °C. Column chromatography (40% -> 70% EtOAc/pentane) afforded the product (56 mg, 0.10 mmol, 99%). TLC: Rf = 0.3 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.90 (t, J = 5.9 Hz, 1H), 7.45 – 7.19 (m, 10H), 6.77 (s, 1H), 5.47 (br s, 1H), 5.31 – 5.12 (m, 2H), 5.04 (d, J = 13.8 Hz, 1H), 4.52 – 4.31 (m, 1H), 4.17 (d, J = 9.4 Hz, 1H), 3.75 (t, J = 4.8 Hz, 4H), 3.71 – 3.60 (m, 4H), 3.53 (d, J = 13.4 Hz, 1H), 3.29 (t, J = 6.5 Hz, 2H), 3.17 (d, J = 9.2 Hz, 2H), 1.13 – 0.97 (m, 1H), 0.61 – 0.46 (m, 2H), 0.34 – 0.21 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.36, 163.88, 160.76, 156.82, 155.79, 139.31, 136.59, 128.68, 128.65, 128.23, 128.03, 127.44, 127.04, 91.44, 67.65, 66.70, 45.36, 44.54, 44.13, 43.82, 39.89, 10.93, 3.53. HRMS [C31H39N4O4 + H]+: 557.2871 calculated, 557.2869 found.

N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(piperidin-1-yl)pyrimidine-4-carboxamide (68). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117k (44 mg, 0.15 mmol, 1 eq), DIPEA (105 µL, 0.60 mmol, 4 eq) and N-methylphenethylamine HBr salt (49 mg, 0.23 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (20% -> 50% EtOAc/pentane) afforded the product (37 mg, 94 µmol, 63%). TLC: Rf = 0.4 (20% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.07 (t, J = 4.8 Hz, 1H), 7.35 – 7.16 (m, 5H), 6.76 (s, 1H), 3.84 – 3.75 (m, 2H), 3.67 (br s, 4H), 3.34 – 3.25 (m, 2H), 3.13 (s, 3H), 2.95 – 2.87 (m, 2H), 1.74 – 1.65 (m, 2H), 1.65 – 1.55 (m, 4H), 1.13 – 1.00 (m, 1H), 0.59 – 0.50 (m, 2H), 0.28 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 165.02, 163.41, 161.01, 156.35, 140.10, 128.88, 128.56, 126.22, 90.36, 51.80, 45.37, 44.07, 35.66, 33.94, 25.77, 24.95, 10.91, 3.48. HRMS [C24H22N4O2 + H]+: 394.2601 calculated, 394.2592 found.

N-(Cyclopropylmethyl)-6-(3,3-difluoropiperidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (69). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117l (50 mg, 0.15 mmol, 1 eq), DIPEA (78 µL, 0.45 mmol, 3 eq) and N-methylphenethylamine (33 µL, 0.27 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (10% -> 30% EtOAc/pentane) afforded the product (10 mg, 23 µmol, 15%). TLC: Rf = 0.5 (20% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.02 (br s, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.18 (m, 3H), 6.78 (s, 1H), 4.01 (t, J = 11.7 Hz, 2H), 3.86 – 3.73 (m, 2H), 3.71 – 3.58 (m, 2H), 3.35 – 3.25 (m, 2H), 3.13 (s, 3H), 2.95 – 2.86 (m, 2H), 2.17 – 2.03 (m, 2H), 1.88 – 1.78 (m, 2H), 1.12 – 1.01 (m, 1H), 0.61 – 0.50 (m, 2H), 0.29 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.61, 163.70, 160.80, 157.10, 139.92, 128.91, 128.63, 126.32, 119.79 (t, J = 244.2 Hz), 90.16, 51.89, 49.40 (t, J = 32.8 Hz), 44.14, 43.73, 35.80, 33.92, 33.03 (t, J = 23.5 Hz), 22.07 (t, J = 4.4 Hz), 10.91, 3.50. HRMS [C31H29F2N4O2 + H]+: 430.2413 calculated, 430.2419 found.

N-(Cyclopropylmethyl)-6-(4,4-difluoropiperidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (70). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117m (45 mg, 0.14 mmol, 1 eq), DIPEA (73 µL, 0.42 mmol, 3 eq) and N-methylphenethylamine (31 µL, 0.21 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (5% -> 30% EtOAc/pentane) afforded the product (27 mg, 63 µmol, 45%). TLC: Rf = 0.5 (15% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.03 (t, J = 5.2 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 6.79 (s, 1H), 3.88 – 3.74 (m, 6H), 3.36 – 3.25 (m, 2H), 3.13 (s, 3H), 2.95 – 2.85 (m, 2H), 2.06 – 1.92 (m, 4H), 1.13 – 0.99 (m, 1H), 0.63 – 0.50 (m, 2H), 0.29 (q, J = 4.7 Hz, 2H). 13C
The residue was purified.

\[ \text{N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-thiomorpholinopyrimidine-4-carboxamide (71).} \]

The title compound was prepared according to general procedure A using 2-chloropyrimidine 117n (41 mg, 0.13 mmol, 1 eq), DIPEA (91 \( \mu \)L, 0.52 mmol, 4 eq) and N-methylphenylethylamine HBr salt (43 mg, 0.20 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with \( \mu \)W irradiation. Column chromatography (10% -> 40% EtOAc/pentane) afforded the product (51 mg, 0.12 mmol, 92%). TLC: \( R_f = 0.4 \) (25% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.05 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 6.73 (s, 1H), 4.03 (br s, 4H), 3.84 – 3.74 (m, 2H), 3.35 – 3.26 (m, 2H), 3.13 (s, 3H), 2.96 – 2.85 (m, 2H), 2.70 – 2.58 (m, 4H), 1.13 – 0.99 (m, 1H), 0.55 (q, \( J = 5.7 \) Hz, 2H), 0.29 (q, \( J = 4.9 \) Hz, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 164.67, 163.05, 156.85, 139.87, 128.80, 128.58, 126.29, 90.34, 51.74, 47.24, 44.08, 35.71, 33.90, 26.68, 10.88, 3.47. HRMS [C\(_{22}\)H\(_{29}\)N\(_2\)OS + H]\(^+\): 412.2166 calculated, 412.2159 found.

\[ \text{N-(Cyclopropylmethyl)-6-(1,1-dioxidothiomorpholino)-2-(methyl (phenethyl)amino)pyrimidine-4-carboxamide (72).} \]

The title compound was prepared according to general procedure A using 2-chloropyrimidine 117o (4:1 mixture of regioisomers) (35 mg, 0.10 mmol, 1 eq), DIPEA (70 \( \mu \)L, 0.40 mmol, 4 eq) and N-phenylethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 2 d at 120 °C. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (35 mg, 79 \mu\text{mol}, 79%). TLC: \( R_f = 0.6 \) (25% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.99 (br s, 1H), 7.36 – 7.26 (m, 2H), 7.26 – 7.16 (m, 3H), 6.81 (s, 1H), 4.20 (br s, 4H), 3.83 (t, \( J = 7.5 \) Hz, 2H), 3.30 (t, \( J = 6.4 \) Hz, 2H), 3.13 (s, 3H), 3.04 (br s, 4H), 2.91 (t, \( J = 7.4 \) Hz, 2H), 1.14 – 1.00 (m, 1H), 0.66 – 0.49 (m, 2H), 0.37 – 0.24 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 164.04, 162.66, 160.94, 157.93, 139.56, 128.76, 128.68, 126.49, 89.88, 51.67, 51.54, 44.19, 43.04, 35.82, 33.95, 10.86, 3.50. HRMS [C\(_{22}\)H\(_{29}\)N\(_2\)O\(_5\)S + H]\(^+\): 444.2064 calculated, 444.2074 found.

\[ \text{N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(4-methylpiperazin-1-yl)pyrimidine-4-carboxamide (73).} \]

The title compound was prepared according to general procedure A using 2-chloropyrimidine 117p (42 mg, 0.14 mmol, 1 eq), DIPEA (98 \( \mu \)L, 0.56 mmol, 4 eq) and N-phenylethylamine HBr salt (44 mg, 0.20 mmol, 1.5 eq). Total heating time: 45 h at 120 °C. Purification by preparative HPLC (C18 reverse phase, 25% to 35% CH\(_3\)CN/H\(_2\)O + 0.2% TFA, RT 8.98 min) afforded the product (21 mg, 51 \mu\text{mol}, 36%). TLC: \( R_f = 0.3 \) (5% MeOH/DCM). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.03 (t, \( J = 5.4 \) Hz, 1H), 7.33 – 7.26 (m, 2H), 7.25 – 7.18 (m, 3H), 6.74 (s, 1H), 3.87 – 3.73 (m, 6H), 3.34 – 3.25 (m, 2H), 3.13 (s, 3H), 2.94 – 2.86 (m, 2H), 2.64 – 2.51 (m, 4H), 2.42 (s, 3H), 1.12 – 1.00 (m, 1H), 0.60 – 0.50 (m, 2H), 0.29 (q, \( J = 4.9 \) Hz, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 164.70, 163.60, 160.91, 156.82, 139.95, 128.85, 128.60, 126.30, 90.22, 54.58, 51.72, 45.88, 44.12, 43.58, 35.71, 33.94, 10.89, 3.49. HRMS [C\(_{23}\)H\(_{29}\)N\(_4\)O + H]\(^+\): 409.2710 calculated, 409.2708 found.

\[ \text{N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(piperazin-1-yl)pyrimidine-4-carboxamide (74).} \]

A round-bottom flask was charged with Cbz-protected amine 77 (175 mg, 0.33 mmol, 1 eq), dry MeOH (3 mL) and AcOH (0.3 mL). The flask was purged with N\(_2\), followed by addition of Pd/C (10% w/w, 18 mg, 0.02 mmol, 5 mol%) and then purging with H\(_2\) (balloon). The reaction was stirred for 2 days, then filtered over a cellulose filter (Whatman) which was washed with MeOH. The filtrate was concentrated under reduced pressure and the residue was purified.
using silica gel column chromatography (2.5% -> 5% MeOH/DCM with 5% Et₃N) affording the product (82 mg, 0.21 mmol, 64%). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (t, J = 5.5 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.26 – 7.17 (m, 3H), 6.74 (s, 1H), 3.84 – 3.76 (m, 2H), 3.75 – 3.58 (m, 4H), 3.30 (t, J = 6.5 Hz, 2H), 3.13 (s, 3H), 2.96 – 2.85 (m, 6H), 1.96 (s, 1H), 1.13 – 1.00 (m, 1H), 0.61 – 0.47 (m, 2H), 0.28 (q, J = 4.7 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.78, 163.74, 160.85, 156.51, 139.95, 128.80, 128.52, 126.20, 90.16, 51.66, 45.94, 45.26, 44.02, 35.62, 33.88, 10.84, 3.42. HRMS [C₂₂H₁₉₂O₃N₅O⁺ + H⁺]^+: 395.2554 calculated, 395.2558 found.

6-(4-Acetylpiperazin-1-yl)-N-(cyclopropylmethyl)-2-(methyl(phenethyl) amino)pyrimidine-4-carboxamide (75). A round-bottom flask was charged with amine 74 (22 mg, 56 μmol, 1 eq) in dry DCM (1.5 mL). This was followed by addition of DIPEA (49 μL, 0.28 mmol, 5 eq) and Ac₂O (10.5 μL, 0.11 mmol, 2 eq). The reaction was stirred for 3 h at rt after which it was diluted with EtOAc (25 mL). The organic layer was washed with sat. aq. NaHCO₃ (1 x 25 mL) and brine (1 x 25 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2.5% -> 10% MeOH/DCM) affording the product (19 mg, 44 μmol, 79%). TLC: Rₕ = 0.8 (10% MeOH/DCM). ¹H NMR (400 MHz, CDCl₃) δ 8.02 (t, J = 5.3 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.26 – 7.17 (m, 3H), 6.74 (s, 1H), 3.87 – 3.77 (m, 2H), 3.77 – 3.65 (m, 6H), 3.59 – 3.50 (m, 2H), 3.34 – 3.26 (m, 2H), 3.13 (s, 3H), 2.95 – 2.86 (m, 2H), 2.15 (s, 3H), 1.14 – 0.99 (m, 1H), 0.61 – 0.50 (m, 2H), 0.29 (q, J = 4.7 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 169.32, 164.57, 163.63, 160.85, 156.97, 139.84, 128.82, 128.61, 126.33, 90.13, 51.70, 45.94, 44.12, 43.82, 42.12, 35.73, 33.92, 21.57, 10.87, 3.48. HRMS [C₂₂H₂₂N₄O₂+ H⁺]^+: 437.2660 calculated, 437.2661 found.

6-(4-Benzoylpiperazin-1-yl)-N-(cyclopropylmethyl)-2-(methyl(phenethyl) amino)pyrimidine-4-carboxamide (76). A round-bottom flask was charged with amine 74 (22 mg, 56 μmol, 1 eq) in dry DCM (1.5 mL). This was followed by Et₃N (16 μL, 0.11 mmol, 2 eq) and benzoyl chloride (8 μL, 67 μmol, 1.2 eq). The reaction was stirred for 3 h at rt after which it was diluted with EtOAc (25 mL). The organic layer was washed with sat. aq. NaHCO₃ (1 x 25 mL) and brine (1 x 25 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60 -> 80% EtOAc/pentane) affording the product (20 mg, 40 μmol, 71%). TLC: Rₕ = 0.3 (60% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.03 (br s, 1H), 7.49 – 7.40 (m, 5H), 7.32 – 7.25 (m, 2H), 7.25 – 7.17 (m, 3H), 6.75 (s, 1H), 3.95 – 3.74 (m, 6H), 3.66 (br s, 2H), 3.52 (br s, 2H), 3.36 – 3.25 (m, 2H), 3.12 (s, 3H), 2.94 – 2.82 (m, 2H), 1.14 – 0.99 (m, 1H), 0.63 – 0.48 (m, 2H), 0.29 (q, J = 4.7 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 170.77, 164.61, 163.71, 160.87, 156.99, 139.85, 135.48, 130.14, 128.83, 128.76, 128.62, 128.49, 127.23, 126.34, 90.21, 51.70, 47.55, 44.16, 42.05, 35.75, 33.94, 10.88, 3.50. HRMS [C₂₂H₂₂N₄O₂+ H⁺]^+: 499.2816 calculated, 499.2825 found.

Benzyl 4-(6-((cyclopropylmethyl)carbamoyl)-2-(methyl(phenethyl)amino) pyrimidin-4-yl)piperazine-1-carboxylate (77). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117q (202 mg, 0.47 mmol, 1 eq). DIPEA (0.40 mL, 2.28 mmol, 5 eq) and N-methylphenethylamine HBr salt (161 mg, 0.74 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (30% -> 60% EtOAc/pentane) afforded the product (199 mg, 0.38 mmol, 81%). TLC: Rₕ = 0.6 (50% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.02 (t, J = 5.4 Hz, 1H), 7.42 – 7.25 (m, 7H), 7.24 – 7.17 (m, 3H), 6.73 (s, 1H), 5.17 (s, 2H), 3.86 – 3.77 (m, 2H), 3.69 (br s, 4H), 3.62 – 3.53 (m, 4H), 3.34 – 3.26 (m, 2H), 3.12 (s, 3H), 2.94 – 2.85 (m, 2H), 1.12 – 1.00 (m, 1H), 0.61 – 0.50 (m, 2H), 0.28 (q, J = 4.7 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.58, 163.64, 160.85, 156.90, 155.32, 139.84, 136.56, 128.79, 128.62, 128.56, 128.23, 128.08, 126.27, 90.16, 51.66, 45.94, 45.26, 44.02, 35.62, 33.88, 10.84, 3.42. HRMS [C₁₅H₁₄N₄O₃NCl+ H⁺]^+: 395.2554 calculated, 395.2558 found.
N-(Cyclopropylmethyl)-6-(dimethylamino)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (78). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117r (27 mg, 0.11 mmol, 1 eq), N-methylphenethylamine HBr salt (35 mg, 0.16 mmol, 1.6 eq) and DiPEA (92 μL, 0.53 mmol, 5 eq). Total heating time: 8 h at 160 °C with μW irradiation. Column chromatography (20% → 50% EtOAc/pentane) afforded the product (32 mg, 90 μmol, 82%). TLC: Rf = 0.6 (40% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.08 (t, J = 5.8 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 6.69 (s, 1H), 3.92 – 3.70 (m, 2H), 3.30 (dd, J = 7.1, 5.8 Hz, 2H), 3.23 – 3.01 (m, 9H), 3.00 – 2.80 (m, 2H), 1.17 – 0.98 (m, 1H), 0.64 – 0.46 (m, 2H), 0.36 – 0.22 (m, 2H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) δ 164.89, 164.01, 160.68, 155.88, 140.01, 128.79, 128.47, 126.12, 90.10, 51.66, 43.98, 37.16, 35.52, 33.84, 10.82, 3.39. HRMS [C\(_{30}\)H\(_{36}\)N\(_6\)O\(_3\) + H\(^+\)]\(^+\): 529.2922 calculated, 529.2933 found.

N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(methylamino)pyrimidine-4-carboxamide (79). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117s (25 mg, 0.10 mmol, 1 eq), DiPEA (52 μL, 0.30 mmol, 3 eq) and N-methylphenethylamine (22 μL, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (50% → 70% EtOAc/pentane) afforded the product (26 mg, 77 μmol, 77%). TLC: Rf = 0.5 (50% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.03 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.26 – 7.18 (m, 3H), 6.54 (s, 1H), 5.13 – 4.72 (m, 1H), 3.93 – 3.66 (m, 2H), 3.34 – 3.24 (m, 2H), 3.13 (s, 3H), 2.98 (d, J = 4.9 Hz, 3H), 2.94 – 2.87 (m, 2H), 1.12 – 1.00 (m, 1H), 0.61 – 0.50 (m, 2H), 0.28 (q, J = 4.7 Hz, 2H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) δ 164.71, 161.06, 156.00, 140.05, 128.89, 128.55, 126.24, 92.54, 51.66, 44.06, 35.62, 33.93, 28.23, 10.89, 3.48. HRMS [C\(_{18}\)H\(_{27}\)N\(_2\)O + H\(^+\)]\(^+\): 340.2132 calculated, 340.2138 found.

N-(Cyclopropylmethyl)-6-((2-hydroxyethyl)(methyl)amino)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (80). The title compound was prepared according to general procedure C using dichloropyrimidine 116a (39 mg, 0.16 mmol, 1 eq), DiPEA (43 μL, 0.24 mmol, 1.5 eq) and N-methylethanolamine (13 μL, 0.16 mmol, 1.0 eq) in MeOH (1.6 mL), followed by concentration and addition of DiPEA (84 μL, 0.48 mmol, 3 eq), N-methylphenethylamine (35 μL, 0.24 mmol, 1.5 eq) and n-BuOH (0.75 mL). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (20% → 40% EtOAc/pentane) afforded the product (15 mg, 33 μmol, 21%). TLC: Rf = 0.4 (80% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.02 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.26 – 7.18 (m, 3H), 6.68 (s, 1H), 4.12 – 3.52 (m, 7H), 3.33 – 3.26 (m, 2H), 3.14 (s, 3H), 3.11 (s, 3H), 2.93 – 2.86 (m, 2H), 1.12 – 1.00 (m, 1H), 0.60 – 0.51 (m, 2H), 0.29 (q, J = 4.7 Hz, 2H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) δ 164.63, 160.52, 156.34, 139.80, 128.86, 128.60, 126.32, 90.28, 62.14, 52.62, 51.83, 44.12, 37.11, 35.91, 33.97, 10.86, 3.48. HRMS [C\(_{21}\)H\(_{29}\)N\(_2\)O + H\(^+\)]\(^+\): 384.2394 calculated, 384.2399 found.

N-(Cyclopropylmethyl)-6-(diethylamino)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (81). The title compound was prepared according to general procedure A using 2-chloropyrimidine 177t (37 mg, 0.13 mmol, 1 eq), DiPEA (68 μL, 0.39 mmol, 3 eq) and N-methylphenethylamine (28 μL, 0.20 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (20% → 40% EtOAc/pentane) afforded the product (30 mg, 79 μmol, 61%). TLC: Rf = 0.8 (50% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.10 (br s, 1H), 7.40 – 7.14 (m, 5H), 6.65 (s, 1H), 3.92 – 3.71 (m, 2H), 3.54 (br s, 4H), 3.30 (t, J = 6.3 Hz, 2H), 3.14 (s, 3H), 3.02 – 2.85 (m, 2H), 1.20 (t, J = 6.9 Hz, 6H), 0.48 (m, 9H).
1.13 – 0.99 (m, 1H), 0.64 – 0.46 (m, 2H), 0.37 – 0.21 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 165.05, 162.59, 160.96, 155.94, 140.12, 128.87, 128.55, 126.21, 90.19, 51.79, 44.03, 42.44, 35.60, 34.04, 13.26, 10.92, 3.46. HRMS [C\(_{22}H_{31}N_4O + H\)^+] : 382.2601 calculated, 382.2599 found.

\(N\)-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(azetidin-1-yl)pyrimidine-4-carboxamide (82). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117u (27 mg, 0.10 mmol, 1 eq), DiPEA (52 \(\mu\)L, 0.30 mmol, 3 eq) and \(N\)-methylphenethylamine (22 \(\mu\)L, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with \(\mu\)W irradiation. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (25 mg, 68 \mu\)mol, 68%). TLC: \(R_f\) = 0.6 (50% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.04 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.26 – 7.16 (m, 3H), 6.38 (s, 1H), 4.11 (t, \(J = 7.5\) Hz, 4H), 3.85 – 3.71 (m, 2H), 3.35 – 3.26 (m, 2H), 3.13 (s, 3H), 2.94 – 2.84 (m, 2H), 2.40 (p, \(J = 7.5\) Hz, 2H), 1.14 – 1.00 (m, 1H), 0.60 – 0.48 (m, 2H), 0.28 (q, \(J = 4.7\) Hz, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.78, 164.75, 160.96, 155.60, 140.10, 128.90, 128.55, 126.22, 89.42, 51.73, 49.83, 44.07, 35.54, 33.88, 16.75, 10.90, 3.49. HRMS [C\(_{21}H_{27}N_4O + H\)^+] : 366.2288 calculated, 366.2296 found.

\(N\)-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-([(3,3)heptan-6-yl)pyrimidine-4-carboxamide (83). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117u (31 mg, 0.10 mmol, 1 eq), DiPEA (52 \(\mu\)L, 0.30 mmol, 3 eq) and \(N\)-methylphenethylamine (22 \(\mu\)L, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with \(\mu\)W irradiation. Column chromatography (70% -> 90% EtOAc/pentane) afforded the product (7 mg, 17 \mu\)mol, 17%). TLC: \(R_f\) = 0.4 (80% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.00 (br s, 1H), 7.35 – 7.27 (m, 2H), 7.26 – 7.19 (m, 3H), 6.39 (s, 1H), 4.85 (s, 4H), 4.24 (s, 4H), 3.84 – 3.71 (m, 2H), 3.36 – 3.22 (m, 2H), 3.12 (s, 3H), 2.94 – 2.82 (m, 2H), 1.13 – 0.98 (m, 1H), 0.60 – 0.48 (m, 2H), 0.28 (q, \(J = 4.7\) Hz, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.68, 164.52, 160.91, 156.07, 139.97, 128.89, 128.62, 126.32, 89.61, 81.23, 59.40, 51.71, 44.12, 39.24, 35.61, 33.89, 10.90, 3.51. HRMS [C\(_{21}H_{29}N_4O_2 + H\)^+] : 408.2394 calculated, 408.2396 found.

\(N\)-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(pyrrolidin-1-yl)pyrimidine-4-carboxamide (84). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117w (28 mg, 0.10 mmol, 1 eq), DiPEA (52 \(\mu\)L, 0.30 mmol, 3 eq) and \(N\)-methylphenethylamine (22 \(\mu\)L, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with \(\mu\)W irradiation. Column chromatography (30% -> 50% EtOAc/pentane) afforded the product (26 mg, 69 \mu\)mol, 69%). TLC: \(R_f\) = 0.7 (40% EtOAc/pentane). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.09 (t, \(J = 5.3\) Hz, 1H), 7.33 – 7.27 (m, 2H), 7.27 – 7.18 (m, 3H), 6.54 (s, 1H), 3.89 – 3.71 (m, 2H), 3.62 (br s, 2H), 3.53 – 3.34 (m, 2H), 3.30 (dd, \(J = 6.9, 5.9\) Hz, 2H), 3.14 (s, 3H), 2.97 – 2.85 (m, 2H), 2.15 – 1.85 (m, 4H), 1.12 – 1.01 (m, 1H), 0.63 – 0.47 (m, 2H), 0.35 – 0.22 (m, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.03, 161.92, 160.90, 155.49, 140.19, 128.89, 128.54, 126.18, 91.37, 51.73, 46.43, 44.05, 35.55, 33.95, 25.78, 25.01, 10.91, 3.47. HRMS [C\(_{22}H_{26}N_4O + H\)^+] : 380.2445 calculated, 380.2452 found.

\(N\)-(Cyclopropylmethyl)-6-(3,3-difluoropyrrolidin-1-yl)-2-(methyl(phenethyl) amino)pyrimidine-4-carboxamide (85). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117x (32 mg, 0.10 mmol, 1 eq), DiPEA (52 \(\mu\)L, 0.30 mmol, 3 eq) and \(N\)-methylphenethylamine (22 \(\mu\)L, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with \(\mu\)W irradiation. Column chromatography (20% -> 40% EtOAc/pentane) afforded the product (34 mg, 82 \mu\)mol, 82%). TLC: \(R_f\) = 0.8 (40% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.03 (br s, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m,
The title compound was prepared according to general procedure A using 2-chloropyrimidine 177 (65 mg, 0.22 mmol, 1 eq), DiPEA (115 µL, 0.66 mmol, 3 eq) and N-methylphenethylamine (48 µL, 0.33 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (70% EtOAc/pentane) afforded the product (60 mg, 0.15 mmol, 68%). TLC: Rf = 0.4 (80% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.10 (t, J = 5.2 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.25 – 7.17 (m, 3H), 6.50 (s, 1H), 4.58 (br s, 1H), 3.98 – 3.33 (m, 6H), 3.31 – 3.23 (m, 2H), 3.11 (s, 3H), 3.02 – 2.62 (m, 3H), 2.08 (br s, 2H), 1.10 – 0.98 (m, 1H), 0.63 – 0.45 (m, 2H), 0.27 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 165.08, 162.07, 160.78, 155.35, 140.10, 128.87, 128.54, 126, 19.91, 54.89, 51.73, 44.36, 44.10, 35.57, 33.91, 10.83, 3.48. HRMS [C22H22N2O + H]+: 396.2394 calculated, 396.2403 found.

(R)-N-(Cyclopropylmethyl)-6-(3-hydroxypyrrolidin-1-yl)-2-(methyl (phenethyl)amino)pyrimidine-4-carboxamide (87). The title compound was prepared according to general procedure A using 2-chloropyrimidine 177z (38 mg, 0.13 mmol, 1 eq), DiPEA (67 µL, 0.38 mmol, 3 eq) and N-methylphenethylamine (28 µL, 0.19 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (80% EtOAc/pentane) afforded the product (37 mg, 94 µmol, 72%). ee: >99% (as determined by chiral HPLC using 75:25 hexane/ethanol, Chiralcel OD). TLC: Rf = 0.3 (80% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.09 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 6.52 (s, 1H), 4.59 (br s, 1H), 3.79 (dd, J = 8.7, 5.8 Hz, 2H), 3.74 – 3.37 (m, 4H), 3.33 – 3.22 (m, 2H), 3.12 (s, 3H), 2.96 – 2.82 (m, 2H), 2.70 – 2.21 (m, 1H), 2.09 (br s, 2H), 1.12 – 0.99 (m, 1H), 0.61 – 0.49 (m, 2H), 0.28 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 165.04, 162.12, 160.82, 155.49, 140.13, 128.90, 128.58, 126.22, 91.28, 70.52, 54.92, 51.75, 44.34, 44.12, 35.60, 33.93, 10.87, 3.50. HRMS [C23H24N2O + H]+: 396.2394 calculated, 396.2394 found.

(S)-N-(Cyclopropylmethyl)-6-(3-hydroxypyrrolidin-1-yl)-2-(methyl (phenethyl)amino)pyrimidine-4-carboxamide (88). The title compound was prepared according to general procedure A using 2-chloropyrimidine 177aa (36 mg, 0.12 mmol, 1 eq), DiPEA (63 µL, 0.36 mmol, 3 eq) and N-methylphenethylamine (27 µL, 0.18 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (80% EtOAc/pentane) afforded the product (36 mg, 91 µmol, 76%). ee: 97% (as determined by chiral HPLC using 75:25 hexane/ethanol, Chiralcel OD). TLC: Rf = 0.3 (80% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.10 (t, J = 5.1 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.15 (m, 3H), 6.51 (s, 1H), 4.58 (br s, 1H), 3.82 – 3.74 (m, 2H), 3.74 – 3.35 (m, 4H), 3.32 – 3.22 (m, 2H), 3.12 (s, 3H), 2.94 – 2.84 (m, 2H), 2.80 – 2.48 (m, 1H), 2.08 (br s, 2H), 1.12 – 0.98 (m, 1H), 0.60 – 0.48 (m, 2H), 0.27 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 165.07, 162.07, 160.77, 155.36, 140.10, 128.88, 128.55, 126.20, 91.26, 70.88, 70.32, 54.89, 51.74, 44.35, 44.11, 35.58, 33.91, 10.83, 3.48. HRMS [C22H22N2O + H]+: 396.2394 calculated, 396.2394 found.
(±)-N-(Cyclopropylmethyl)-6-(3-methoxypyrrolidin-1-yl)-2-(methylphenethyl)amino)pyrimidine-4-carboxamide (89). A round-bottom flask was charged with alcohol 86 (35 mg, 88 µmol, 1 eq) in dry DCM (0.5 mL) and cooled to 0 °C. NaH (60% in mineral oil, 4 mg, 106 µmol, 1.2 eq) was added and the mixture was stirred for 15 min followed by addition of methyl iodide (6.0 µL, 97 µmol, 1.1 eq). The reaction was allowed to warm to rt while stirring overnight. The reaction was quenched with H₂O (20 mL) followed by extraction with DCM (3 × 20 mL), drying (Na₂SO₄), filtering and concentration under reduced pressure. The residue was purified by silica gel column chromatography (60 -> 70% EtOAc/pentane) affording the product (16 mg, 39 µmol, 44%). TLC: Rᵣ = 0.4 (60% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.07 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 6.54 (s, 1H), 4.07 (br s, 1H), 3.88 – 3.72 (m, 3H), 3.72 – 3.45 (m, 3H), 3.37 (s, 3H), 3.33 – 3.23 (m, 2H), 3.13 (s, 3H), 2.98 – 2.84 (m, 2H), 2.29 – 1.96 (m, 2H), 1.14 – 0.99 (m, 1H), 0.62 – 0.48 (m, 2H), 0.29 (q, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 207.96, 164.96, 162.10, 160.86, 155.62, 140.16, 128.91, 128.57, 126.22, 91.25, 79.95, 79.15, 56.76, 51.75, 51.42, 44.42, 44.09, 35.62, 33.94, 30.45, 10.91, 3.50. HRMS [C₂₂H₂₃N₃O₂ + H⁺]: 410.2551 calculated, 410.2549 found.

(±)-N-(Cyclopropylmethyl)-6-(3-dimethylaminopropyl)pyrrolidin-1-yl)-2-(methylphenethyl)amino)pyrimidine-4-carboxamide (90). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117ab (50 mg, 0.15 mmol, 1 eq), DiPEA (78 µL, 0.60 mmol, 4 eq) and N-methylphenethylamine (33 µL, 0.23 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (2.5% -> 10% MeOH/DCM) afforded the product (3 mg, 7 µmol, 5%). TLC: Ri = 0.5 (5% MeOH/DCM). ¹H NMR (600 MHz, CDCl₃) δ 8.10 (br s, 1H), 7.31 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 6.69 (s, 1H), 3.98 (dd, J = 10.6, 7.2 Hz, 1H), 3.92 – 3.64 (m, 3H), 3.58 – 3.50 (m, 1H), 3.42 (br s, 1H), 3.35 – 3.25 (m, 2H), 2.99 (br s, 3H), 2.89 (t, J = 7.7 Hz, 2H), 2.41 (br s, 6H), 2.24 (br s, 1H), 2.06 – 1.89 (m, 1H), 1.80 – 1.51 (m, 1H), 1.12 – 1.02 (m, 1H), 0.59 – 0.49 (m, 2H), 0.34 – 0.24 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 164.89, 163.37, 159.54, 156.17, 128.99, 128.68, 126.44, 90.62, 65.56, 51.98, 45.61, 44.02, 33.80, 28.71, 11.00, 3.52. HRMS [C₂₄H₂₈N₆O₂ + H⁺]: 423.2867 calculated, 423.2868 found.

(±)-N-(Cyclopropylmethyl)-2-(methylphenethyl)amino)-6-(3-phenylpyrrolidin-1-yl)pyrimidine-4-carboxamide (91). The title compound was prepared according to general procedure C using dichloropyrimidine 116a (40 mg, 0.16 mmol, 1 eq), DiPEA (43 µL, 0.24 mmol, 1.5 eq) and (±)-3-phenylpyrrolidin-2 (24 µL, 0.16 mmol, 1.0 eq) in MeOH (1.6 mL), followed by concentration and addition of DiPEA (84 µL, 0.48 mmol, 3 eq), N-methylphenethylamine (35 µL, 0.24 mmol, 1.5 eq) and n-BuOH (0.75 mL). Total heating time: 4 h at 160 °C with µW irradiation. Column chromatography (70% -> 90% EtOAc/pentane) afforded the product (35 mg, 91 µmol, 57%). TLC: Ri = 0.4 (30% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.08 (br s, 1H), 7.39 – 7.32 (m, 2H), 7.32 – 7.17 (m, 8H), 6.57 (s, 1H), 4.19 (br s, 1H), 3.94 (br s, 1H), 3.81 (br s, 2H), 3.74 – 3.38 (m, 3H), 3.30 (t, J = 6.4 Hz, 2H), 3.14 (s, 3H), 2.92 (br s, 2H), 2.42 (br s, 1H), 2.16 (br s, 1H), 1.14 – 1.00 (m, 1H), 0.62 – 0.46 (m, 2H), 0.29 (q, J = 4.9 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.96, 161.90, 160.92, 155.72, 141.79, 140.15, 128.92, 128.80, 128.57, 127.19, 126.97, 126.23, 91.13, 52.89, 51.76, 46.36, 44.10, 43.39, 35.62, 33.98, 33.31, 10.93, 3.51. HRMS [C₂₈H₃₃N₃O + H⁺]: 456.2758 calculated, 456.2757 found.
The title compound was prepared according to general procedure A using dichloropyrimidine 116a (37 mg, 0.15 mmol, 1 eq), DiPEA (39 µL, 0.23 mmol, 1.5 eq) and N-methylbenzylamine (19 µL, 0.15 mmol, 1.0 eq) in MeOH (1.5 mL), followed by concentration and addition of DiPEA (78 µL, 0.45 mmol, 3 eq), N-methylphenethylamine (33 µL, 0.23 mmol, 1.5 eq) and n-BuOH (0.75 mL). Total heating time: 4 h at 160 °C with μW irradiation. Purification by HPLC (C18 reverse phase, 43% to 49% CH₂CN/H₂O + 0.2% TFA) afforded the product (47 mg, 0.11 mmol, 73%). TLC: Rᵥ = 0.6 (40% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.08 (br s, 1H), 7.36 – 7.28 (m, 2H), 7.28 – 7.03 (m, 6H), 6.75 (br s, 1H), 4.86 (br s, 2H), 3.77 (br s, 2H), 3.39 – 3.22 (m, 2H), 3.13 (s, 3H), 3.08 (br s, 2H), 2.86 (br s, 2H), 1.14 – 0.98 (m, 1H), 0.62 – 0.48 (m, 2H), 0.29 (q, J = 4.8 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.88, 164.13, 160.83, 156.51, 139.96, 128.89, 128.74, 128.57, 127.24, 126.24, 90.07, 51.85, 44.14, 35.75, 33.95, 10.94, 3.52. HRMS [C₂₀H₁₃N₂O + H]⁺: 430.2601 calculated, 430.2604 found.

N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (93). The title compound was prepared according to general procedure A using dichloropyrimidine 116a (28 mg, 0.11 mmol, 1 eq), DiPEA (79 µL, 0.46 mmol, 4 eq) and N-methylphenethylamine (41 µL, 0.28 mmol, 2.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (20% → 40% EtOAc/pentane) afforded the product (30 mg, 68 µmol, 62%). TLC: Rᵥ = 0.6 (30% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.09 (t, J = 5.2 Hz, 1H), 7.32 – 7.24 (m, 4H), 7.24 – 7.12 (m, 6H), 6.68 (br s, 1H), 4.02 – 3.56 (m, 4H), 3.34 – 3.26 (m, 2H), 3.15 (s, 3H), 2.99 (br s, 3H), 2.96 – 2.87 (m, 4H), 1.15 – 1.01 (m, 1H), 0.60 – 0.48 (m, 2H), 0.29 (q, J = 4.8 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.96, 163.42, 160.86, 156.14, 140.03, 128.97, 128.90, 128.68, 128.60, 126.43, 126.25, 90.24, 51.72, 44.09, 35.71, 34.01, 33.85, 10.93, 3.50. HRMS [C₂₁H₁₄N₂O + H]⁺: 444.2758 calculated, 444.2765 found.

N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(1H-pyrazol-1-yl)pyrimidine-4-carboxamide (94). The title compound was prepared according to general procedure A using 2-chloropyrimidine 116ac (28 mg, 0.10 mmol, 1 eq), DiPEA (52 µL, 0.30 mmol, 3 eq) and N-methylphenethylamine (22 µL, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (20% → 40% EtOAc/pentane) afforded the product (30 mg, 80 µmol, 80%). TLC: Rᵥ = 0.5 (30% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.51 (s, 1H), 7.98 – 7.81 (m, 2H), 7.81 – 7.73 (m, 1H), 7.33 – 7.27 (m, 2H), 7.26 – 7.18 (m, 3H), 6.56 – 6.39 (m, 1H), 3.97 – 3.83 (m, 2H), 3.33 (dd, J = 6.9, 6.0 Hz, 2H), 3.21 (s, 3H), 3.01 – 2.91 (m, 2H), 1.18 – 1.00 (m, 1H), 0.57 (q, J = 5.4 Hz, 2H), 0.30 (q, J = 4.8 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 163.17, 160.57, 159.73, 159.48, 143.40, 139.40, 128.84, 128.69, 127.30, 126.52, 108.54, 94.69, 51.83, 44.24, 36.01, 33.79, 10.87, 3.52. HRMS [C₂₁H₁₄N₆O + H]⁺: 377.2084 calculated, 377.2088 found.

N-(Cyclopropylmethyl)-6-(1H-imidazol-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (95). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117ad (42 mg, 0.15 mmol, 1 eq), DiPEA (78 µL, 0.45 mmol, 3 eq) and N-methylphenethylamine (33 µL, 0.23 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Purification by preparative HPLC (C18 reverse phase, 35% to 45% CH₂CN/H₂O + 0.2% TFA, RT 8.87 min) afforded the product (27 mg, 72 µmol, 48%). TLC: Rᵥ = 0.5 (5% MeOH/DCM). ¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 7.99 – 7.72 (m, 1H), 7.68 (s, 1H), 7.33 – 7.27 (m, 3H), 7.25 – 7.17 (m, 4H), 4.00 – 3.81 (m, 2H), 3.38 – 3.29 (m, 2H), 3.22 (s, 3H), 3.02 – 2.90 (m, 2H), 1.16 – 1.03 (m,
Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-01

1H), 0.69 – 0.51 (m, 2H), 0.32 (q, J = 4.9 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 162.88, 160.89, 160.19, 157.03, 139.14, 135.37, 131.10, 128.82, 128.73, 126.61, 116.00, 93.80, 51.89, 44.36, 36.06, 33.78, 10.84, 3.56. HRMS [C21H23N6O + H]+: 377.2084 calculated, 377.2087 found.

\( \text{N-(Cyclopropylmethyl)-2-(methylphenethyl)amino)-6-phenoxypyrimidine-4-carboxamide (96).} \)

The title compound was prepared according to general procedure A using 2-chloropyrimidine 117ae (49 mg, 0.16 mmol, 1 eq), DiPEA (84 μL, 0.48 mmol, 3 eq) and N-methylphenethylamine (35 μL, 0.24 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (5% -> 25% EtOAc/pentane) afforded the product (40 mg, 99 μmol, 62%). TLC: \( R_f = 0.5 \) (20% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.91 (br s, 1H), 7.46 – 7.36 (m, 2H), 7.35 – 7.05 (m, 7H), 7.04 – 6.68 (m, 2H), 4.00 – 3.39 (m, 2H), 3.30 (t, J = 6.4 Hz, 2H), 3.10 (br s, 3H), 2.97 – 2.53 (m, 2H), 1.13 – 1.01 (m, 1H), 0.56 (q, J = 5.6 Hz, 2H), 0.35 – 0.23 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 171.62, 163.46, 160.96, 159.59, 152.85, 139.32, 129.64, 128.89, 128.50, 126.33, 125.47, 122.04, 51.85, 44.18, 35.78, 33.63, 10.88, 3.51. HRMS [C22H25N7O2 + H]+: 403.2129 calculated, 403.2137 found.

\( \text{N-(Cyclopropylmethyl)-2-(methylphenethyl)amino)-6-(pyridin-3-oxide) pyrimidine-4-carboxamide (97).} \)

The title compound was prepared according to general procedure A using 2-chloropyrimidine 117af (38 mg, 0.12 mmol, 1 eq), DiPEA (62 μL, 0.36 mmol, 3 eq) and N-methylphenethylamine (26 μL, 0.18 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (60% -> 100% EtOAc/pentane) afforded the product (26 mg, 64 μmol, 53%). TLC: \( R_f = 0.5 \) (80% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.86 – 8.42 (m, 2H), 7.90 (br s, 1H), 7.65 – 7.44 (m, 1H), 7.41 – 7.32 (m, 1H), 7.31 – 7.12 (m, 4H), 7.07 – 6.71 (m, 2H), 3.82 (br s, 1H), 3.51 (br s, 1H), 3.38 – 3.26 (m, 2H), 3.13 (br s, 2H), 2.93 (br s, 2H), 2.65 (br s, 1H), 1.15 – 1.02 (m, 1H), 0.57 (q, J = 5.1 Hz, 2H), 0.30 (q, J = 4.8 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 170.88, 163.22, 160.69, 160.01, 149.45, 146.41, 144.26, 129.68, 128.80, 128.56, 126.44, 123.96, 51.74, 44.23, 35.78, 33.59, 10.88, 3.53. HRMS [C22H25N7O2 + H]+: 404.2081 calculated, 404.2084 found.

\( \text{(S)-N-(Cyclopropylmethyl)-6-(dimethylamino)-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (98).} \)

The title compound was prepared according to general procedure A using 2-chloropyrimidine 117r (25 mg, 0.10 mmol, 1 eq), DiPEA (52 μL, 0.30 mmol, 3 eq) and (S)-3-phenylpiperidine (21 mg, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (30% -> 50% EtOAc/pentane) afforded the product (28 mg, 74 μmol, 74%). ee: >99% (as determined by chiral HPLC using 70:30 hexane/isopropanol, Chiralcell OD). TLC: \( R_f = 0.7 \) (50% EtOAc/pentane), \( \delta = 8.02 \) (br s, 1H), 7.43 – 7.16 (m, 5H), 6.70 (s, 1H), 4.84 (t, J = 14.1 Hz, 2H), 3.39 – 3.19 (m, 2H), 3.10 (s, 6H), 2.89 (t, J = 12.1 Hz, 2H), 2.77 (t, J = 10.2 Hz, 1H), 2.07 (d, J = 13.1 Hz, 1H), 1.88 – 1.60 (m, 3H), 1.14 – 0.98 (m, 1H), 0.65 – 0.44 (m, 2H), 0.36 – 0.20 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 164.91, 164.18, 160.89, 156.13, 144.43, 128.61, 127.31, 126.58, 90.71, 51.38, 44.70, 44.02, 42.56, 37.30, 32.21, 25.58, 10.96, 3.51, 3.49. HRMS [C23H27N6O + H]+: 380.2445 calculated, 380.2452 found.

\( \text{(R)-N-(Cyclopropylmethyl)-6-(dimethylamino)-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (99).} \)

The title compound was prepared according to general procedure A using 2-chloropyrimidine 117r (25 mg, 0.10 mmol, 1 eq), DiPEA (52 μL, 0.30 mmol, 3 eq) and (R)-3-phenylpiperidine (21 mg, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (30% -> 50% EtOAc/pentane) afforded the product (32 mg, 84 μmol, 84%). ee: >97% (as determined by chiral HPLC using 70:30 hexane/isopropanol, Chiralcell OD). TLC: \( R_f = 0.7 \) (50%}
Chapter 3

EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (t, $J = 5.4$ Hz, 1H), 7.39 – 7.28 (m, 4H), 7.28 – 7.21 (m, 1H), 6.70 (s, 1H), 4.95 – 4.74 (m, 2H), 3.40 – 3.18 (m, 2H), 3.10 (s, 6H), 2.96 – 2.83 (m, 2H), 2.83 – 2.70 (m, 1H), 2.07 (dd, $J = 13.9$ Hz, 1H), 1.90 – 1.81 (m, 1H), 1.81 – 1.62 (m, 2H), 1.11 – 0.99 (m, 1H), 0.59 – 0.46 (m, 2H), 0.27 (q, $J = 4.7$ Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.91, 164.18, 160.90, 156.12, 144.43, 128.61, 127.31, 126.58, 90.71, 51.38, 44.70, 44.02, 42.56, 37.30, 32.21, 25.58, 10.96, 3.51, 3.49. HRMS [C$_{24}$H$_{23}$N$_{3}$O$_2$ + H]$^+$: 380.2445 calculated, 380.2452 found.

(S)-N-(Cyclopropylmethyl)-6-morpholino-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (100). The title compound was prepared according to general procedure A using 2-chloropyrimidine 28 (30 mg, 0.10 mmol, 1 eq), DiPEA (52 µL, 0.30 mmol, 3 eq) and (S)-3-phenylpiperidine (21 mg, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (41 mg, 97 µmol, 97%). TLC: $R_f$ = 0.6 (50% EtOAc/pentane). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.97 (br s, 1H), 7.40 – 7.32 (m, 2H), 7.32 – 7.21 (m, 3H), 6.73 (s, 1H), 4.90 – 4.70 (m, 2H), 3.83 – 3.70 (m, 4H), 3.69 – 3.56 (m, 4H), 3.36 – 3.19 (m, 2H), 2.97 – 2.83 (m, 2H), 2.76 (tt, $J = 11.5$, 3.6 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.90 – 1.72 (m, 2H), 1.72 – 1.59 (m, 1H), 1.12 – 0.98 (m, 1H), 0.59 – 0.45 (m, 2H), 0.27 (q, $J = 4.7$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 164.63, 164.11, 160.97, 156.96, 144.30, 128.66, 127.30, 126.30, 90.60, 66.73, 51.27, 44.71, 44.52, 44.06, 42.64, 32.28, 25.57, 10.94, 3.50, 3.48. HRMS [C$_{24}$H$_{23}$N$_{3}$O$_2$ + H]$^+$: 422.2551 calculated, 422.2549 found.

(S)-N-(Cyclopropylmethyl)-6-(1,1-dioxidothiomorpholino)-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (101). The title compound was prepared according to general procedure A using 2-chloropyrimidine 117o (4:1 mixture of regioisomers) (35 mg, 0.10 mmol, 1 eq), DiPEA (53 µL, 0.30 mmol, 3 eq) and (S)-3-phenylpiperidine (21 mg, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with μW irradiation. Purification by preparative HPLC (C18 reverse phase, 45% to 55% CH$_3$CN/H$_2$O + 0.2% TFA, RT 12.52 min) afforded the product (27 mg, 57 µmol, 57%). TLC: $R_f$ = 0.5 (60% EtOAc/pentane). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.94 (br s, 1H), 7.43 – 7.32 (m, 2H), 7.32 – 7.27 (m, 3H), 6.83 (s, 1H), 4.78 (t, $J = 11.0$ Hz, 2H), 4.19 (br s, 4H), 3.38 – 3.19 (m, 2H), 3.12 – 2.99 (m, 4H), 2.94 (t, $J = 12.2$ Hz, 2H), 2.82 – 2.68 (m, 1H), 2.10 (dd, $J = 17.2$, 4.5 Hz, 1H), 1.88 (d, $J = 13.1$ Hz, 1H), 1.85 – 1.72 (m, 1H), 1.72 – 1.57 (m, 1H), 1.11 – 0.96 (m, 1H), 0.54 (q, $J = 5.3$ Hz, 2H), 0.28 (q, $J = 4.9$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 164.07, 162.85, 160.95, 158.16, 143.95, 128.77, 127.24, 126.85, 90.31, 51.54, 51.28, 44.77, 44.14, 43.08, 42.71, 32.18, 25.50, 10.92, 3.52, 3.50. HRMS [C$_{24}$H$_{23}$N$_{3}$O$_2$S + H]$^+$: 470.2220 calculated, 470.2223 found.

N-(Cyclopropylmethyl)-6-[[R]-3-hydroxypropylidin-1-yl]-2-[[S]-3-phenylpiperidin-1-yl]pyrimidine-4-carboxamide (102, LEI-401) The title compound was prepared according to general procedure A using 2-chloropyrimidine 117z (24 mg, 81 µmol, 1 eq), DiPEA (42 µL, 0.24 mmol, 3 eq) and (S)-3-phenylpiperidine (17 mg, 0.11 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with μW irradiation. Column chromatography (70% -> 90% EtOAc/pentane) afforded the product (23 mg, 55 µmol, 68%). TLC: $R_f$ = 0.4 (80% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (br s, 1H), 7.39 – 7.22 (m, 5H), 6.54 (s, 1H), 4.84 (t, $J = 14.0$ Hz, 2H), 4.57 (s, 1H), 3.86 – 3.37 (m, 4H), 3.37 – 3.17 (m, 2H), 2.87 (t, $J = 12.0$ Hz, 2H), 2.81 – 2.70 (m, 1H), 2.16 – 1.93 (m, 3H), 1.90 – 1.54 (m, 4H), 1.11 – 0.97 (m, 1H), 0.59 – 0.45 (m, 2H), 0.27 (q, $J = 4.7$ Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.93, 162.20, 160.91, 155.71, 144.42, 128.64, 127.33, 126.60, 91.76, 54.96, 51.30, 44.67, 44.38, 44.07, 42.59, 32.24, 25.59, 10.93, 3.52. HRMS [C$_{24}$H$_{31}$N$_{3}$O$_2$ + H]$^+$: 422.2551 calculated, 422.2551 found.
Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401

\[
\begin{align*}
N\text{-}(\text{Cyclopropylmethyl})-6\text{-}(\text{(R)}-3\text{-hydroxy} & \text{pyrrolidin-1-yl})\text{-}2\text{-}(\text{(R)}-3\text{-phenylpiperidin-1-yl})\text{pyrimidine-4-carboxamide (103). The title compound was} \\
& \text{prepared according to general procedure A using 2-chloropyrimidine 117z (22 mg, 74 \mu mol, 1 eq), DIPEA (39 \mu L, 0.22 mmol, 3 eq) and (R)-3-phenylpiperidine (16 mg, 96 \mu mol, 1.3 eq). Total heating time: 4 h at 160 °C with \mu W irradiation. Column chromatography (70% -> 90% EtOAc/pentane) afforded the product (23 mg, 55 \mu mol, 74%). TLC: Rf = 0.4 (80% EtOAc/pentane).} \text{H NMR (400 MHz, CDCl}_3 \delta 8.03 (t, J = 5.7 Hz, 1H), 7.40 – 7.19 (m, 5H), 6.53 (s, 1H), 4.84 (t, J = 14.3 Hz, 2H), 4.57 (s, 1H), 3.90 – 3.37 (m, 4H), 3.37 – 3.17 (m, 2H), 2.94 – 2.81 (m, 2H), 2.81 – 2.69 (m, 1H), 2.07 (d, J = 12.7 Hz, 3H), 1.89 – 1.57 (m, 4H), 1.10 – 0.98 (m, 1H), 0.60 – 0.42 (m, 2H), 0.26 (q, J = 4.7 Hz, 2H).} \underline{13}^C NMR (101 MHz, CDCl}_3 \delta 164.96, 162.19, 160.91, 155.67, 144.43, 128.62, 127.32, 125.9, 91.75, 70.36, 54.95, 51.36, 44.68, 44.38, 44.06, 42.54, 32.20, 25.60, 10.92, 3.51. HRMS [C_{24}H_{31}N_2O_2 + H]^+: 422.2551 calculated, 422.2552 found. \\
\end{align*}
\]

\[
\begin{align*}
N\text{-}(\text{Cyclopropylmethyl})-6\text{-}(\text{(S)}-3\text{-hydroxy} & \text{pyrrolidin-1-yl})\text{-}2\text{-}(\text{(S)}-3\text{-phenylpiperidin-1-yl})\text{pyrimidine-4-carboxamide (104). The title compound was} \\
& \text{prepared according to general procedure A using 2-chloropyrimidine 117aa (37 mg, 0.12 mmol, 1 eq), DIPEA (65 \mu L, 0.37 mmol, 3 eq) and (S)-3-phenylpiperidine (26 mg, 0.16 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with \mu W irradiation. Column chromatography (70% -> 100% EtOAc/pentane) afforded the product (26 mg, 62 \mu mol, 52%). TLC: Rf = 0.4 (80% EtOAc/pentane).} \text{H NMR (400 MHz, CDCl}_3 \delta 8.03 (br s, 1H), 7.40 – 7.20 (m, 5H), 6.53 (s, 1H), 4.84 (t, J = 14.3 Hz, 2H), 4.57 (s, 1H), 3.91 – 3.37 (m, 4H), 3.36 – 3.18 (m, 2H), 2.96 – 2.81 (m, 2H), 2.81 – 2.70 (m, 1H), 2.17 – 1.94 (m, 3H), 1.93 – 1.50 (m, 4H), 1.11 – 0.97 (m, 1H), 0.59 – 0.43 (m, 2H), 0.26 (q, J = 4.7 Hz, 2H).} \underline{13}^C NMR (101 MHz, CDCl}_3 \delta 164.97, 162.17, 160.90, 155.63, 144.41, 128.62, 127.31, 126.58, 91.75, 71.02, 70.38, 54.95, 51.36, 44.68, 44.39, 44.05, 42.53, 32.19, 25.59, 10.91, 3.50. HRMS [C_{24}H_{31}N_2O_2 + H]^+: 422.2551 calculated, 422.2555 found. \\
\end{align*}
\]

\[
\begin{align*}
N\text{-}(\text{Cyclopropylmethyl})-6\text{-}(\text{(S)}-3\text{-hydroxy} & \text{pyrrolidin-1-yl})\text{-}2\text{-}(\text{(R)}-3\text{-phenylpiperidin-1-yl})\text{pyrimidine-4-carboxamide (105). The title compound was} \\
& \text{prepared according to general procedure A using 2-chloropyrimidine 117aa (32 mg, 0.11 mmol, 1 eq), DIPEA (56 \mu L, 0.32 mmol, 3 eq) and (R)-3-phenylpiperidine (23 mg, 0.14 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with \mu W irradiation. Column chromatography (70% -> 100% EtOAc/pentane) afforded the product (26 mg, 56 \mu mol, 51%). TLC: Rf = 0.4 (80% EtOAc/pentane).} \text{H NMR (400 MHz, CDCl}_3 \delta 8.03 (t, J = 5.7 Hz, 1H), 7.40 – 7.19 (m, 5H), 6.53 (s, 1H), 4.84 (t, J = 14.3 Hz, 2H), 4.57 (s, 1H), 3.90 – 3.37 (m, 4H), 3.37 – 3.17 (m, 2H), 2.94 – 2.81 (m, 2H), 2.81 – 2.69 (m, 1H), 2.16 – 1.96 (m, 3H), 1.89 – 1.57 (m, 4H), 1.10 – 0.98 (m, 1H), 0.60 – 0.42 (m, 2H), 0.26 (q, J = 4.7 Hz, 2H).} \underline{13}^C NMR (101 MHz, CDCl}_3 \delta 164.84, 162.10, 160.81, 155.58, 144.32, 128.52, 127.22, 126.48, 91.64, 70.84, 70.16, 54.84, 51.19, 44.55, 44.27, 43.95, 42.47, 32.13, 25.48, 10.82, 3.40. HRMS [C_{24}H_{31}N_2O_2 + H]^+: 422.2551 calculated, 422.2552 found. \\
\end{align*}
\]

Methyl 4-chloro-6-(methyl(phenethyl)amino)picolinate (107). A round-bottom flask was charged with methyl 4,6-dichloropicolinate (106) (206 mg, 0.99 mmol, 1 eq), N-methylphenethylamine HBr salt (218 mg, 1.01 mmol, 1.02 eq), DIPEA (436 \mu L, 2.5 mmol, 2.5 eq) and dry MeOH (2 mL). The solution was stirred at rt for 3 d and then refluxed for 24 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (5% -> 35% EtOAc/pentane) affording the product (122 mg, 0.40 mmol, 40%). TLC: Rf = 0.2 (5% EtOAc/pentane). \text{H NMR}
(400 MHz, CDCl₃) δ 7.35 – 7.26 (m, 3H), 7.23 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 7.0 Hz, 2H), 6.56 (d, J = 2.3 Hz, 1H), 3.96 (s, 3H), 3.63 (t, J = 7.3 Hz, 2H), 2.93 – 2.81 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 165.68, 155.45, 152.41, 147.85, 138.19, 128.84, 128.80, 126.84, 107.83, 107.79, 53.84, 53.05, 38.50, 33.14. Regioselectivity was confirmed by ¹H,¹³C-HMBC and ¹H-NOESY 2D NMR. HRMS [C₁₈H₁₇ClN₂O₂ + H]⁺: 305.1051 calculated, 305.1054 found.

4-Chloro-6-(methyl(phenethyl)amino)picolinic acid (108). A round-bottom flask was charged with methyl ester 107 (122 mg, 0.4 mmol, 1 eq) and THF (2 mL). An aqueous 1.5 M NaOH solution (0.53 mL, 0.8 mmol, 2 eq) was added dropwise and the reaction was stirred for 1.5 h at rt. The mixture was cooled to 0 °C and acidified to pH 1 by dropwise addition of 37% w/w aq. HCl. The mixture was then extracted with DCM (3 x 5 mL), the combined organic layers were washed with brine (1 x 15 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to afford the product (104 mg, 0.36 mmol, 99%). TLC Rₗ = 0.1 (5% MeOH/DCM with 3 drops of AcOH).

¹H NMR (400 MHz, CDCl₃) δ 8.92 (br s, 1H), 7.37 – 7.20 (m, 4H), 7.20 – 7.12 (m, 2H), 6.57 (d, J = 2.4 Hz, 1H), 3.66 (t, J = 7.2 Hz, 2H), 2.96 – 2.81 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 164.25, 156.33, 150.90, 146.25, 138.01, 128.96, 128.86, 127.01, 105.87, 54.04, 38.78, 33.21.

4-Chloro-N-(cyclopropylmethyl)-6-(methyl(phenethyl)amino)picolinamide (109). A round-bottom flask was charged with carboxylic acid 108 (104 mg, 0.36 mmol, 1 eq), HOBT (73 mg, 0.47 mmol, 1.3 eq), EDC hydrochloride (102 mg, 0.53 mmol, 1.5 eq) and dry DCM (1.8 mL). The suspension was stirred for 1 h at rt followed by the addition of cyclopropylmethanamine (37 μL, 0.43 mmol, 1.2 eq). After stirring for 20 h the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (10 mL) and washed with 1 M aq. HCl (1 x 10 mL), sat. aq. NaHCO₃ (1 x 10 mL) and brine (1 x 10 mL). The organic layer was dried (MgSO₄), filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (isocratic, 30% EtOAc/pentane) affording the product (30 mg, 87 μmol, 24%). Rₗ = 0.35 (30% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 7.99 (t, J = 5.9 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.28 – 7.18 (m, 1H), 7.20 – 7.15 (m, 2H), 6.50 (d, J = 2.4 Hz, 1H), 3.64 (t, J = 7.3 Hz, 2H), 3.30 (dd, J = 7.1, 5.9 Hz, 2H), 2.91 – 2.84 (m, 5H), 1.13 – 1.01 (m, 1H), 0.58 – 0.52 (m, 2H), 0.31 – 0.26 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 163.90, 155.94, 151.08, 150.38, 138.41, 128.93, 128.90, 126.86, 106.84, 104.87, 54.02, 44.51, 38.71, 33.25, 10.92, 3.76.

Methyl 2-chloro-6-morpholinoisonicotinate (111). A round-bottom flask was charged with methyl-2,6-dichloroisonicotinate (110) (0.41 g, 2.0 mmol, 1 eq), K₂CO₃ (0.55 g, 4.0 mmol, 2 eq) morpholine (0.26 mL, 3.0 mmol, 1.5 eq) and dry CH₃CN (10 mL). The mixture was heated to reflux. After 45 h the reaction was complete as judged by TLC and cooled to room temperature. The mixture was filtered and the filtrate concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (10% → 30% EtOAc/pentane) affording the product (0.32 g, 1.3 mmol, 65%). TLC: Rₗ = 0.6 (30% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, J = 0.9 Hz, 1H), 7.07 (d, J = 1.0 Hz, 1H), 3.92 (s, 3H), 3.86 – 3.76 (m, 4H), 3.64 – 3.52 (m, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 165.16, 159.40, 150.36, 141.33, 111.77, 104.69, 66.55, 52.83, 45.26. HRMS [C₁₁H₁₃ClN₂O₂ + H]⁺: 257.0688 calculated, 257.0690 found.

2-Chloro-6-morpholinoisonicotinic acid (112). A round-bottom flask was charged with methyl ester 111 (0.32 g, 1.3 mmol, 1 eq) and THF (5 mL). A 1 M aqueous solution of NaOH (2.5 mL, 2.5 mmol, 2 eq) was added dropwise. After stirring 20 minutes at room temperature the reaction mixture was acidified carefully with 37% w/w HCl to pH 1 and THF was removed under reduced pressure. The mixture was extracted with DCM (3 x 10 mL), the combined organic layers were washed with brine (1 x 15 mL), dried (MgSO₄), filtered and concentrated under reduced pressure affording the product (0.33 g, 1.3 mmol, 99%). TLC: Rₗ = 0.2
(30% EtOAc/pentane with 3 drops of AcOH). \(^1\)H NMR (400 MHz, MeOD + CDCl\(_3\)) \(\delta\) 7.12 (s, 1H), 7.09 (s, 1H), 3.78 (t, \(J = 4.9\) Hz, 4H), 3.54 (t, \(J = 4.9\) Hz, 4H). \(^13\)C NMR (101 MHz, MeOD + CDCl\(_3\)) \(\delta\) 167.10, 160.29, 150.79, 143.21, 112.56, 105.74, 67.18, 45.94. HRMS \([\text{C}_{12}\text{H}_{13}\text{ClN}_2\text{O}_2 + H]^+\): 243.0531 calculated, 243.0533 found.

**2-Chloro-\(N\)-(cyclopropylmethyl)-6-morpholinoisonicotinamide (113).** A round-bottom flask was charged with carboxylic acid 112 (0.33 g, 1.3 mmol, 1 eq), EDC hydrochloride (0.30 g, 2.0 mmol, 1.5 eq) and HOBT (0.30 g, 2.0 mmol, 1.5 eq) and dry DCM (7 mL). The suspension was stirred for 1 h at room temperature followed by addition of cyclopropylmethanamine (0.14 mL, 1.6 mmol, 1.2 eq). After 20 h DCM was removed under reduced pressure and the residue was dissolved in EtOAc (15 mL) and sequentially washed with 1M HCl (aq) (2 x 15 mL), sat. aq. NaHCO\(_3\) (2 x 15 mL) and brine (1 x 20 mL). The organic layer was washed with \(\text{MgSO}_4\), filtered and concentrated under reduced pressure. The resulting crude material was purified by silica gel column chromatography (30% - 60% EtOAc/pentane) affording the product (0.88 g, 4.0 mmol, 80%). TLC: \(R_f\) 0.30 (40% EtOAc/pentane).

**2,6-Dichloropyrimidine-4-carboxyl chloride (115).** In a 500 mL round-bottom flask orotic acid (114) (15.6 g, 100 mmol, 1 equiv.) was dissolved in phosphorous oxychloride (46 mL, 500 mmol, 5 equiv.) and 10 drops of DMF were added. The mixture was heated to reflux and stirred for 19 h. n-Hexane (250 mL) was added and the mixture was stirred vigorously for 10 min and then transferred to a separatory funnel containing 100 mL H\(_2\)O. The flask was washed with 50 mL hexane. After shaking, the aqueous layer was removed and the organic layer was washed with brine (1 x 100 mL), dried (\(\text{MgSO}_4\)) and concentrated under reduced pressure to yield the product (12.8 g, 60.4 mmol, 60%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.00 (s, 1H). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 167.17, 165.27, 161.56, 158.19, 119.70.

**2,6-Dichloro-\(N\)-(cyclopropylmethyl)pyrimidine-4-carboxamide (116a).** The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carboxyl chloride 115 (0.63 mL, 5.0 mmol, 1 eq), Et\(_3\)N (0.91 mL, 6.5 mmol, 1.3 eq) and cyclopropylmethanamine (444 \(\mu\)L, 5.13 mmol, 1.025 eq). Column chromatography (5% - 20% EtOAc/pentane) afforded the product (0.99 g, 4.0 mmol, 80%). TLC: \(R_f\) = 0.8 (20% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.11 (s, 1H), 7.96 (bs s, 1H), 7.34 – 3.27 (m, 2H), 1.20 – 1.03 (m, 1H), 0.68 – 0.52 (m, 2H), 0.32 (q, \(J = 4.8\) Hz, 2H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.74, 160.44, 160.04, 159.77, 118.22, 44.72, 10.57, 3.67. HRMS \([\text{C}_{8}\text{H}_{11}\text{Cl}_2\text{N}_2\text{O} + H]^+\): 246.0195 calculated, 246.0196 found.

**2,6-Dichloro-\(N\)-methylpyrimidine-4-carboxamide (116b).** The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carboxyl chloride 115 (0.63 mL, 5.0 mmol, 1 eq), Et\(_3\)N (1.6 mL, 11.5 mmol, 2.3 eq) and methylamine HCl salt (0.35 g, 5.13 mmol, 1.025 eq). Column chromatography (10% - 30% EtOAc/pentane) afforded the product (0.97 g, 4.7 mmol, 94%). TLC: \(R_f\) = 0.3 (20% EtOAc/pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.10 (s, 1H), 7.90 (bs s, 1H), 3.08 (d, \(J = 5.1\) Hz, 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.84, 160.85, 160.25, 159.82, 118.11, 26.51. HRMS \([\text{C}_{8}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O} + H]^+\): 205.9882 calculated, 205.9884 found.

**2,6-Dichloro-\(N\)-ethylpyrimidine-4-carboxamide (116c).** The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carboxyl chloride 115 (0.63 mL, 5.0 mmol, 1 eq), Et\(_3\)N (1.6 mL, 11.5 mmol, 2.3 eq) and ethylamine HCl salt (0.42 g, 5.13 mmol, 1.025 eq). Column chromatography (5% - 20% EtOAc/pentane) afforded the product (0.88 g, 4.0 mmol, 80%). TLC: \(R_f\) = 0.6 (20% EtOAc/pentane). \(^1\)H NMR
(400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.83 (br s, 1H), 3.65 – 3.38 (m, 2H), 1.30 (t, J = 7.3 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.84, 160.47, 160.06, 159.83, 118.18, 34.86, 14.63. HRMS [C₁₂H₁₃Cl₂N₂O + H⁺]: 220.0039 calculated, 220.0040 found.

2,6-Dichloro-N-butyl-pyrimidine-4-carboxamide (116d). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride 115 (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.60 mmol, 1.3 eq) and n-butylamine (0.20 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% -> 20% EtOAc/pentane) afforded the product (0.50 g, 2.0 mmol, 99%). TLC: Rₜ = 0.7 (20% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.83 (br s, 1H), 3.49 (q, J = 7.0 Hz, 2H), 1.74 – 1.56 (m, 2H), 1.53 – 1.35 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.78, 160.46, 160.13, 159.78, 118.18, 39.64, 31.40, 20.09, 13.72. HRMS [C₁₂H₁₃Cl₂N₂O + H⁺]: 248.0352 calculated, 248.0354 found.

2,6-Dichloro-N-hexyl-pyrimidine-4-carboxamide (116e). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride 115 (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.60 mmol, 1.3 eq) and n-hexylamine (0.27 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% -> 20% EtOAc/pentane) afforded the product (0.50 g, 2.0 mmol, 99%). TLC: Rₜ = 0.6 (10% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.79 (br s, 1H), 3.65 (d, J = 6.6 Hz, 2H), 1.46 – 1.23 (m, 6H), 0.98 – 0.83 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.71, 160.46, 160.06, 159.73, 118.14, 39.91, 31.38, 29.30, 26.55, 22.48, 13.96. HRMS [C₁₂H₁₃Cl₂N₂O + H⁺]: 276.0665 calculated, 276.0668 found.

2,6-Dichloro-N-isobutylpyrimidine-4-carboxamide (116f). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride 115 (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.60 mmol, 1.3 eq) and isobutylamine (0.20 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% -> 20% EtOAc/pentane) afforded the product (0.50 g, 2.0 mmol, 99%). TLC: Rₜ = 0.8 (20% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (s, 1H), 7.94 (br s, 1H), 3.33 (t, J = 6.6 Hz, 2H), 2.07 – 1.87 (m, 1H), 1.00 (d, J = 6.8 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 164.68, 160.41, 160.15, 159.70, 118.17, 47.10, 28.52, 20.07. HRMS [C₁₂H₁₃Cl₂N₂O + H⁺]: 248.0352 calculated, 248.0354 found.

2,6-Dichloro-N-neopentylpyrimidine-4-carboxamide (116g). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride 115 (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.60 mmol, 1.3 eq) and neopentylamine (0.24 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% -> 20% EtOAc/pentane) afforded the product (0.50 g, 2.0 mmol, 99%). TLC: Rₜ = 0.9 (20% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (s, 1H), 7.91 (br s, 1H), 3.30 (d, J = 6.7 Hz, 2H), 1.01 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 164.69, 160.38, 160.22, 159.71, 118.24, 50.89, 32.35, 27.20. HRMS [C₁₂H₁₃Cl₂N₂O + H⁺]: 262.0508 calculated, 262.0510 found.

2,6-Dichloro-N-(prop-2-yn-1-yl)pyrimidine-4-carboxamide (116h). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride 115 (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.60 mmol, 1.3 eq) and propargylamine (0.13 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% -> 20% EtOAc/pentane) afforded the product (0.44 g, 1.9 mmol, 95%). TLC: Rₜ = 0.6 (20% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.24 – 8.00 (m, 2H), 4.30 (dd, J = 5.7, 2.6 Hz, 2H), 2.36 (t, J = 2.6 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 164.92, 160.08, 159.94, 159.63, 118.35, 78.30, 72.42, 29.52. HRMS [C₁₂H₁₃Cl₂N₂O + H⁺]: 229.9882 calculated, 229.9884 found.
Methyl (2,6-dichloropyrimidine-4-carbonyl)glycinate (116i). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride 115 (0.32 mL, 2.5 mmol, 1 eq) and glycine methyl ester hydrochloride (0.32 g, 2.56 mmol, 1.025 eq). Column chromatography (5% -> 20% EtOAc/pentane) afforded the product (0.51 g, 1.95 mmol, 78%). TLC: Rf = 0.5 (30% EtOAc/pentane). 1H NMR (500 MHz, CDCl3) δ 8.31 (br s, 1H), 8.08 (s, 1H), 7.39 – 7.23 (m, 5H), 4.63 (d, J = 6.2 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.81, 160.20, 160.17, 159.81, 137.00, 128.81, 127.90, 127.86, 118.35, 43.82. HRMS [C9H5Cl2N3O+H]+: 263.9937 calculated, 263.9939 found.

2,6-Dichloropyrimidine-N-benzyl-4-carboxamide (116j). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride 115 (0.63 mL, 5.0 mmol, 1 eq) and benzylamine (0.56 mL, 5.13 mmol, 1.05 eq). Column chromatography (10% -> 30% EtOAc/pentane) afforded the product (1.38 g, 4.9 mmol, 98%). TLC: Rf = 0.7 (20% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.18 (br s, 1H), 8.08 (s, 1H), 7.39 – 7.23 (m, 5H), 4.63 (d, J = 6.2 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.81, 160.20, 160.17, 159.81, 137.00, 128.81, 127.90, 127.86, 118.35, 43.82. HRMS [C18H13Cl2N3O+H]+: 282.0195 calculated, 282.0197 found.

2,6-Dichloropyrimidine-N-[[1,1'-biphenyl]-4-ylmethyl]-4-carboxamide (116k). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride 115 (0.63 mL, 5.0 mmol, 1 eq), Et3N (0.91 mL, 6.5 mmol, 1.3 eq) and 4-phenylbenzylamine (0.94 g, 5.13 mmol, 1.025 eq). Column chromatography (10% -> 30% EtOAc/pentane) afforded the product (1.46 g, 4.1 mmol, 82%). TLC: Rf = 0.8 (20% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.16 (t, J = 5.7 Hz, 1H), 8.07 (s, 1H), 7.54 (d, J = 7.9 Hz, 4H), 7.46 – 7.29 (m, 5H), 4.65 (d, J = 6.2 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 164.86, 160.26, 160.14, 159.86, 140.82, 140.40, 136.01, 128.84, 128.43, 127.52, 127.49, 127.03, 118.37, 43.57. HRMS [C18H13Cl2N3O+H]+: 358.0508 calculated, 358.0508 found.

2-Chloro-N-methyl-6-morpholinopyrimidine-4-carboxamide (117a). The title compound was prepared according to general procedure E using dichloropyrimidine 116b (0.31 g, 1.5 mmol, 1 eq), DiPEA (0.39 mL, 2.3 mmol, 1.5 eq) and morpholine (0.14 mL, 1.6 mmol, 1.05 eq). Column chromatography (40% -> 80% EtOAc/pentane) afforded the product as an 8.5:1 mixture of regioisomers (0.39 g, 1.5 mmol, 99%). TLC: Rf = 0.4 (100% EtOAc/pentane). Major regioisomer: 1H NMR (400 MHz, CDCl3) δ 7.93 – 7.77 (m, 1H), 7.26 (s, 1H), 3.83 – 3.61 (m, 8H), 3.00 (d, J = 5.2 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 163.82, 162.92, 159.79, 157.70, 99.16, 66.34, 44.60, 44.38, 26.19. HRMS [C10H13ClN2O2+H]+: 257.0800 calculated, 257.0800 found.

2-Chloro-N-ethyl-6-morpholinopyrimidine-4-carboxamide (117b). The title compound was prepared according to general procedure E using dichloropyrimidine 116c (0.42 g, 1.9 mmol, 1 eq), DiPEA (0.49 mL, 2.8 mmol, 1.5 eq) and morpholine (0.17 mL, 2.0 mmol, 1.05 eq). Column chromatography (50% -> 70% EtOAc/pentane) afforded the product (0.48 g, 1.8 mmol, 95%). TLC: Rf = 0.2 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.82 (br s, 1H), 7.27 (s, 1H), 3.99 – 3.55 (m, 8H), 3.54 – 3.37 (m, 2H), 1.25 (t, J = 7.3 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 163.86, 162.17, 159.85, 157.93, 99.27, 66.39, 44.63, 34.53, 14.71. HRMS [C12H15ClN2O2+H]+: 271.0956 calculated, 271.0957 found.
2-Chloro-N-butyl-6-morpholinopyrimidine-4-carboxamide (117c). The title compound was prepared according to general procedure E using dichloropyrimidine 116d (193 mg, 0.78 mmol, 1 eq), DiPEA (203 µL, 1.17 mmol, 1.5 eq) and morpholine (71 µL, 0.82 mmol, 1.05 eq). Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (212 mg, 0.71 mmol, 91%). TLC: Rf = 0.4 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.84 (br s, 1H), 7.27 (s, 1H), 3.91 – 3.61 (m, 8H), 3.43 (q, J = 7.1 Hz, 2H), 1.70 – 1.51 (m, 2H), 1.48 – 1.34 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 163.79, 162.19, 159.75, 157.88, 99.21, 66.31, 44.57, 39.29, 31.48, 20.07, 13.72. HRMS [C13H12CIN2O2 + H]+: 299.1269 calculated, 299.1269 found.

2-Chloro-N-hexyl-6-morpholinopyrimidine-4-carboxamide (117d). The title compound was prepared according to general procedure E using dichloropyrimidine 116e (0.28 g, 1.02 mmol, 1 eq), DiPEA (0.27 mL, 1.54 mmol, 1.5 eq) and morpholine (94 µL, 1.08 mmol, 1.05 eq). Column chromatography (40% -> 70% EtOAc/pentane) afforded the product (0.31 g, 0.95 mmol, 93%). TLC: Rf = 0.5 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.87 (t, J = 5.8 Hz, 1H), 7.28 (s, 1H), 4.01 – 3.53 (m, 8H), 3.42 (q, J = 6.9 Hz, 2H), 1.61 (p, J = 7.7, 7.3 Hz, 2H), 1.46 – 1.22 (m, 6H), 0.99 – 0.80 (m, 3H). 13C NMR (101 MHz, CDCl3) δ 163.71, 162.11, 159.68, 157.81, 99.17, 66.25, 44.55, 39.56, 31.37, 29.34, 26.53, 22.45, 13.97. HRMS [C13H13CIN2O2 + H]+: 327.1582 calculated, 327.1582 found.

2-Chloro-N-isobutyl-6-morpholinopyrimidine-4-carboxamide (117e). The title compound was prepared according to general procedure E using dichloropyrimidine 116f (0.28 g, 1.11 mmol, 1 eq), DiPEA (0.29 mL, 1.66 mmol, 1.5 eq) and morpholine (101 µL, 1.16 mmol, 1.05 eq). Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (0.33 g, 1.11 mmol, 99%). TLC: Rf = 0.5 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.91 (t, J = 5.8 Hz, 1H), 7.28 (s, 1H), 4.01 – 3.52 (m, 8H), 3.36 (l, J = 6.7 Hz, 2H), 2.00 – 1.81 (m, 1H), 0.97 (d, J = 6.7 Hz, 6H). 13C NMR (101 MHz, CDCl3) δ 163.75, 162.25, 159.71, 157.83, 99.23, 66.26, 46.82, 44.56, 28.58, 20.11. HRMS [C13H13CIN2O2 + H]+: 299.1269 calculated, 299.1270 found.

2-Chloro-6-morpholino-N-neopentylpyrimidine-4-carboxamide (117f). The title compound was prepared according to general procedure E using dichloropyrimidine 116g (0.25 g, 0.96 mmol, 1 eq), DiPEA (0.25 mL, 1.44 mmol, 1.5 eq) and morpholine (88 µL, 1.01 mmol, 1.05 eq). Column chromatography (30% -> 60% EtOAc/pentane) afforded the product (0.30 g, 0.96 mmol, 99%). TLC: Rf = 0.5 (40% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.92 (br s, 1H), 7.28 (s, 1H), 3.96 – 3.50 (m, 8H), 3.24 (d, J = 6.7 Hz, 2H), 0.98 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 163.77, 162.36, 159.74, 157.82, 99.30, 66.27, 50.64, 44.60, 32.34, 27.23. HRMS [C14H14CIN2O2 + H]+: 313.1424 calculated, 313.1424 found.

2-Chloro-6-morpholino-N-(prop-2-yn-1-yl)pyrimidine-4-carboxamide (117g). The title compound was prepared according to general procedure E using dichloropyrimidine 116h (221 mg, 0.96 mmol, 1 eq), DiPEA (251 µL, 1.44 mmol, 1.5 eq) and morpholine (88 µL, 1.01 mmol, 1.05 eq). Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (249 mg, 0.89 mmol, 93%). TLC: Rf = 0.5 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.00 (br s, 1H), 7.26 (s, 1H), 4.22 (dd, J = 5.7, 2.6 Hz, 2H), 3.88 – 3.59 (m, 8H), 2.29 (t, J = 2.6 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 163.84, 162.23, 160.04, 157.20, 99.53, 78.84, 72.05, 66.41, 29.32. HRMS [C15H15CIN2O2 + H]+: 281.0800 calculated, 281.0800 found.
Methyl (2-chloro-6-morpholinopyrimidine-4-carbonyl)glycinate (117h). The title compound was prepared according to general procedure E using dichloropyrimidine 116i (0.40 g, 1.50 mmol, 1 eq), DIPEA (0.39 mL, 2.25 mmol, 1.5 eq) and morpholine (137 µL, 1.58 mmol, 1.05 eq). Column chromatography (60% -> 80% EtOAc/pentane) afforded the product (0.30 g, 0.95 mmol, 63%). TLC: Rf = 0.5 (70% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.25 (t, J = 5.4 Hz, 1H), 7.25 (s, 1H), 4.22 (d, J = 5.9 Hz, 2H), 3.90 – 3.61 (m, 11H). 13C NMR (101 MHz, CDCl3) δ 169.59, 163.83, 162.85, 160.06, 157.09, 99.50, 66.39, 52.51, 41.29. HRMS [C12H13ClN2O4 + H]+: 315.0855 calculated, 315.0851 found.

2-Chloro-N-benzyl-6-morpholinopyrimidine-4-carboxamide (117l). The title compound was prepared according to general procedure E using dichloropyrimidine 116j (0.71 g, 2.50 mmol, 1 eq), DIPEA (0.65 mL, 3.75 mmol, 1.5 eq) and morpholine (0.23 mL, 2.63 mmol, 1.05 eq). Column chromatography (30% -> 60% EtOAc/pentane) afforded the product (0.68 g, 2.03 mmol, 81%). TLC: Rf = 0.6 (60% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.18 (br s, 1H), 7.39 – 7.24 (m, 6H), 4.61 (d, J = 6.2 Hz, 2H), 3.90 – 3.54 (m, 8H). 13C NMR (101 MHz, CDCl3) δ 163.79, 162.37, 159.88, 157.63, 137.59, 128.77, 127.92, 127.67, 99.52, 66.37, 44.47, 43.60. HRMS [C13H12ClN4O2 + H]+: 333.1113 calculated, 333.1112 found.

2-Chloro-N-[(1,1′-biphenyl)-4-ylmethyl]-6-morpholinopyrimidine-4-carboxamide (117j). The title compound was prepared according to general procedure E using dichloropyrimidine 116k (0.31 g, 1.0 mmol, 1 eq), DIPEA (0.26 mL, 1.5 mmol, 1.5 eq) and morpholine (91 µL, 1.05 mmol, 1.05 eq). Column chromatography (20% -> 50% EtOAc/pentane) afforded the product (0.38 g, 0.94 mmol, 94%). TLC: Rf = 0.4 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 8.24 (t, J = 6.0 Hz, 1H), 7.61 – 7.52 (m, 4H), 7.47 – 7.31 (m, 5H), 7.28 (s, 1H), 4.64 (d, J = 6.2 Hz, 2H), 3.91 – 3.45 (m, 8H). 13C NMR (101 MHz, CDCl3) δ 163.79, 162.44, 159.91, 159.17, 162.42, 159.31, 140.62, 136.62, 128.86, 128.43, 127.48, 127.11, 99.53, 66.37, 44.65, 43.36. HRMS [C17H12ClN4O2 + H]+: 409.1426 calculated, 409.1421 found.

2-Chloro-N-(cyclopropylmethyl)-6-(piperidin-1-yl)pyrimidine-4-carboxamide (117k). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (0.26 g, 1.05 mmol, 1 eq), DIPEA (0.27 mL, 1.58 mmol, 1.5 eq) and piperidine (109 µL, 1.10 mmol, 1.05 eq). Column chromatography (10% -> 40% EtOAc/pentane) afforded the product (0.29 g, 0.99 mmol, 94%). TLC: Rf = 0.2 (20% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.95 (br s, 1H), 7.27 (s, 1H), 3.71 (br s, 4H), 3.29 (t, J = 6.5 Hz, 2H), 1.85 – 1.52 (m, 6H), 1.15 – 0.98 (m, 1H), 0.55 (q, J = 5.4 Hz, 2H), 0.28 (q, J = 4.8 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 163.12, 162.45, 159.77, 157.35, 99.29, 44.31, 25.55, 24.31, 10.61, 3.58. HRMS [C14H13ClN2O2 + H]+: 295.1320 calculated, 295.1321 found.

2-Chloro-N-(cyclopropylmethyl)-6-(3,3-difluoropiperidin-1-yl)pyrimidine-4-carboxamide (117l). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (0.10 g, 0.41 mmol, 1 eq), DIPEA (0.10 g, 0.57 mmol, 2.4 eq) and 3,3-difluoropiperidine HCl salt (68 mg, 0.43 mmol, 1.05 eq). Column chromatography (10% -> 40% EtOAc/pentane) afforded the product (88 mg, 0.26 mmol, 63%). TLC: Rf = 0.4 (20% EtOAc/pentane). 1H NMR (300 MHz, CDCl3) δ 7.91 (br s, 1H), 7.35 (s, 1H), 3.99 (br s, 2H), 3.74 (br s, 2H), 3.29 (t, J = 6.5 Hz, 2H), 2.13 (tt, J = 13.3, 6.3 Hz, 2H), 2.02 – 1.74 (m, 2H), 1.17 – 0.95 (m, 1H), 0.67 – 0.44 (m, 2H), 0.28 (q, J = 5.1 Hz, 2H). 13C NMR (75 MHz, CDCl3) δ 164.08, 162.15, 159.87, 158.33, 119.17 (t, J = 244.8 Hz), 99.62, 44.54, 44.05, 32.63 (t, J = 23.5 Hz), 29.76, 21.70 (t, J = 4.5 Hz). 10.72, 3.71. HRMS [C14H12ClF2N2O2 + H]+: 331.1132 calculated, 331.1127 found.
2-Chloro-N-(cyclopropylmethyl)-6-(4,4-difluoropiperidin-1-yl)pyrimidine-4-carboxamide (117m). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (0.12 g, 0.49 mmol, 1 eq), DiPEA (0.21 mL, 1.23 mmol, 2.5 eq) and 4,4-difluoropiperidine HCl salt (86 mg, 0.52 mmol, 1.05 eq). Column chromatography (5% -> 25% EtOAc/pentane) afforded the product (90 mg, 0.27 mmol, 55%). TLC: Rf = 0.4 (15% EtOAc/pentane). 1H NMR (300 MHz, CDCl3) δ 7.91 (br s, 1H), 7.35 (s, 1H), 3.89 (br s, 4H), 3.38 – 3.20 (m, 2H), 2.06 (tt, J = 13.2, 5.9 Hz, 4H), 1.13 – 0.98 (m, 1H), 0.64 – 0.48 (m, 2H), 0.29 (q, J = 4.8 Hz, 2H). 13C NMR (75 MHz, CDCl3) δ 163.47, 162.18, 160.08, 158.40, 121.29 (t, J = 242.4 Hz), 99.44, 44.55, 41.49, 33.82 (t, J = 23.7 Hz), 10.72, 3.72. HRMS [C17H17ClF2N2O + H]+: 331.1132 calculated, 331.1127 found.

2-Chloro-N-(cyclopropylmethyl)-6-thiomorpholinopyrimidine-4-carboxamide (117n). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (0.12 g, 0.48 mmol, 1 eq), DiPEA (0.12 mL, 0.71 mmol, 1.5 eq) and thiomorpholine (51 μL, 0.50 mmol, 1.05 eq). Column chromatography (20% -> 50% EtOAc/pentane) afforded the product (48 mg, 0.15 mmol, 31%). TLC: Rf = 0.2 (20% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.41 (s, 1H), 4.26 (br s, 4H), 3.24 (d, J = 7.1 Hz, 2H), 3.18 – 3.12 (m, 4H), 1.10 – 0.98 (m, 1H), 1.15 – 0.99 (m, 1H), 0.65 – 0.48 (m, 2H), 0.29 (q, J = 4.8 Hz, 2H). 13C NMR (126 MHz, CDCl3) δ 163.33, 162.30, 160.04, 158.07, 99.66, 44.55, 27.05, 10.73, 3.74. HRMS [C13H17ClIN2O2S + H]+: 345.0783 calculated, 345.0782 found.

2-Chloro-N-(cyclopropylmethyl)-6-(1,1-dioxidothiomorpholinopyrimidine-4-carboxamide (117o). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (92 mg, 0.37 mmol, 1 eq), DiPEA (98 μL, 0.56 mmol, 1.5 eq) and thiomorpholine-1,1-dioxide (53 mg, 0.39 mmol, 1.05 eq). Column chromatography (60% -> 70% EtOAc/pentane) afforded the product as a 4:1 mixture of regioisomers (69 mg, 0.20 mmol, 54%). TLC: Rf = 0.5 (60% EtOAc/pentane). Major regioisomer: 1H NMR (500 MHz, CDCl3 + MeOD) δ 7.41 (s, 1H), 4.26 (br s, 4H), 3.24 (d, J = 7.1 Hz, 2H), 3.18 – 3.12 (m, 4H), 1.10 – 0.98 (m, 1H), 0.59 – 0.49 (m, 2H), 0.32 – 0.21 (m, 2H). 13C NMR (126 MHz, CDCl3 + MeOD) δ 163.16, 162.11, 159.92, 158.47, 99.62, 51.14, 44.23, 42.86, 42.43, 10.18, 3.19. HRMS [C13H17ClIN2O2S + H]+: 345.0783 calculated, 345.0782 found.

2-Chloro-N-(cyclopropylmethyl)-6-(4-methylpiperazin-1-yl)pyrimidine-4-carboxamide (117p). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (96 mg, 0.39 mmol, 1 eq), DiPEA (102 μL, 0.59 mmol, 1.5 eq) and 4-methylpiperazine (45 μL, 0.41 mmol, 1.05 eq). Column chromatography (5% -> 10% MeOH/DCM) afforded the product (77 mg, 0.25 mmol, 64%). TLC: Rf = 0.4 (5% MeOH/DCM). 1H NMR (500 MHz, CDCl3) δ 7.99 – 7.84 (m, 1H), 7.28 (s, 1H), 3.96 – 3.58 (m, 4H), 3.35 – 3.24 (m, 2H), 2.54 – 2.44 (m, 4H), 2.34 (s, 3H), 1.12 – 0.99 (m, 1H), 0.64 – 0.50 (m, 2H), 0.28 (q, J = 4.8 Hz, 2H). 13C NMR (126 MHz, CDCl3) δ 163.61, 162.39, 159.88, 157.74, 99.52, 54.50, 46.06, 44.49, 43.44, 10.70, 3.71. HRMS [C14H19ClIN2O + H]+: 310.1429 calculated, 310.1429 found.

Benzyl-4-(2-chloro-6-(cyclopropylmethyl)carbamoyl)pyrimidin-4-ylpiperazine-1-carboxylate (117q). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (181 mg, 0.74 mmol, 1 eq), DiPEA (193 μL, 1.11 mmol, 1.5 eq) and 1-Cbz-piperazine (149 μL, 0.77 mmol, 1.05 eq). Column chromatography (30% -> 60% EtOAc/pentane) afforded the product (290 mg, 0.67 mmol, 91%). TLC: Rf = 0.5 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.92 (t, J = 5.7 Hz, 1H), 7.40 – 7.30 (m, 5H), 7.28 (s, 1H), 5.17 (s, 2H), 3.74 (br s, 4H), 3.65 – 3.55 (m, 4H), 3.34 – 3.22 (m, 2H), 1.12 – 0.98 (m, 1H), 0.63 – 0.46 (m, 2H), 0.36 – 0.19 (m, 2H). 13C NMR (101 MHz, CDCl3) δ...
Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401

163.64, 162.10, 159.81, 158.01, 155.01, 136.26, 128.54, 128.20, 128.00, 99.44, 67.50, 44.40, 43.17, 10.63, 3.61.

2-Chloro-N-(cyclopropylmethyl)-6-(dimethylamino)pyrimidine-4-carboxamide (117t). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (0.25 g, 1.0 mmol, 1 eq), DIPEA (0.26 mL, 1.5 mmol, 1.5 eq) and dimethylamine (2 M in THF, 0.53 mL, 1.05 mmol, 1.05 eq). Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (225 mg, 0.88 mmol, 88%). TLC: Rf = 0.2 (80% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.92 (br s, 1H), 7.40 – 7.04 (m, 1H), 6.62 – 6.20 (m, 1H), 3.29 (br s, 2H), 3.17 (br s, 4H), 2.87 (m, 4H), 2.12 (t, J = 7.2 Hz, 2H), 1.51 (m, 2H), 0.89 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 163.91, 162.30, 159.95, 156.54, 98.54, 50.20, 44.44, 16.51, 10.69, 3.69. HRMS [C13H15ClN2O + H]+: 267.1007 calculated, 267.1005 found.

2-Chloro-N-(cyclopropylmethyl)-6-(methylamino)pyrimidine-4-carboxamide (117s). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (123 mg, 0.50 mmol, 1 eq), DIPEA (218 µL, 1.25 mmol, 2.5 eq) and methylamine HCl salt (35 mg, 0.53 mmol, 1.05 eq). Column chromatography (50% -> 70% EtOAc/pentane) afforded the product (77 mg, 0.32 mmol, 64%). TLC: Rf = 0.2 (50% EtOAc/pentane). 1H NMR (500 MHz, CDCl3) δ 7.93 (br s, 1H), 7.40 – 7.04 (m, 1H), 6.62 – 6.20 (m, 1H), 3.29 (br s, 2H), 3.17 (br s, 4H), 2.87 (m, 4H), 2.12 (t, J = 7.2 Hz, 2H), 1.51 (m, 2H), 0.89 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 167.64, 162.57, 159.79, 157.11, 99.29, 44.41, 42.96, 42.73, 12.64, 10.69, 3.67. HRMS [C13H13ClN2O + H]+: 241.0851 calculated, 241.0849 found.

2-Chloro-N-(cyclopropylmethyl)-6-(diethylamino)pyrimidine-4-carboxamide (117t). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (123 mg, 0.50 mmol, 1 eq), DIPEA (131 µL, 0.75 mmol, 1.5 eq) and diethylamine (55 µL, 0.53 mmol, 1.05 eq). Column chromatography (20% -> 50% EtOAc/pentane) afforded the product (94 mg, 0.33 mmol, 66%). TLC: Rf = 0.5 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.93 (br s, 1H), 7.40 – 7.04 (m, 1H), 6.62 – 6.20 (m, 1H), 3.29 (br s, 2H), 3.17 (br s, 4H), 2.87 (m, 4H), 2.12 (t, J = 7.2 Hz, 2H), 1.51 (m, 2H), 0.89 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 167.64, 162.57, 159.79, 157.11, 99.29, 44.41, 42.96, 42.73, 12.64, 10.69, 3.67. HRMS [C13H13ClN2O + H]+: 267.1007 calculated, 267.1005 found.
2-Chloro-N-(cyclopropylmethyl)-6-(pyrrolidin-1-yl)pyrimidine-4-carboxamide (117w). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (123 mg, 0.50 mmol, 1 eq), DiPEA (131 μL, 0.75 mmol, 1.5 eq) and pyrrolidine (43 μL, 0.53 mmol, 1.05 eq). Column chromatography (30% -> 60% EtOAc/pentane) afforded the product (150 mg, 0.40 mmol, 80%). TLC: Rf = 0.5 (40% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.93 (br s, 1H), 7.05 (s, 1H), 3.65 (t, J = 6.6 Hz, 2H), 3.46 (t, J = 6.7 Hz, 2H), 3.29 (t, J = 6.5 Hz, 2H), 2.09 (p, J = 6.3 Hz, 2H), 2.00 (p, J = 6.3 Hz, 2H), 1.13 – 0.99 (m, 1H), 0.56 (q, J = 5.2 Hz, 2H), 0.29 (q, J = 4.9 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 162.11, 160.06, 157.10, 98.96, 80.71, 59.73, 44.56, 39.16, 10.72, 3.76. HRMS [C13H12ClN3O2 + H]+: 309.1113 calculated, 309.1110 found.

2-Chloro-N-(cyclopropylmethyl)-6-(3,3-difluoropyrrolidin-1-yl)pyrimidine-4-carboxamide (117x). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (98 mg, 0.40 mmol, 1 eq), DiPEA (174 μL, 1.0 mmol, 2.5 eq) and 3,3-difluoropyrrolidine HCl salt (60 mg, 0.42 mmol, 1.05 eq). Column chromatography (20% -> 40% EtOAc/pentane) afforded the product (108 mg, 0.34 mmol, 85%). TLC: Rf = 0.6 (40% EtOAc/pentane). 1H NMR (500 MHz, CDCl3) δ 7.90 (br s, 1H), 7.22 – 6.87 (m, 1H), 4.19 – 3.59 (m, 4H), 3.36 – 3.22 (m, 2H), 2.55 (br s, 2H), 1.14 – 0.97 (m, 1H), 0.63 – 0.50 (m, 2H), 0.37 – 0.18 (m, 2H). 13C NMR (126 MHz, CDCl3) δ 162.52, 162.11, 159.61, 156.52, 100.53, 47.23, 46.98, 44.43, 25.52, 24.82, 10.69, 3.69. HRMS [C13H12ClF2N4 + H]+: 281.1164 calculated, 281.1160 found.

(t)-2-Chloro-N-(cyclopropylmethyl)-6-(3-hydroxyxopyrrolidin-1-yl)pyrimidine-4-carboxamide (117y). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (98 mg, 0.40 mmol, 1 eq), DiPEA (174 μL, 1.0 mmol, 2.5 eq) and (t)-3-hydroxyxopyrrolidine HCl salt (52 mg, 0.42 mmol, 1.05 eq). Column chromatography (70% -> 100% EtOAc/pentane) afforded the product (89 mg, 0.30 mmol, 75%). TLC: Rf = 0.2 (80% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.98 (t, J = 5.3 Hz, 1H), 7.08 – 6.89 (m, 1H), 4.73 – 4.55 (m, 1H), 3.87 – 3.45 (m, 4H), 3.33 – 3.20 (m, 2H), 2.25 – 2.07 (m, 2H), 1.12 – 0.98 (m, 1H), 0.63 – 0.50 (m, 2H), 0.29 (q, J = 4.9 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 162.63, 162.32, 162.16, 159.59, 156.38, 100.55, 100.49, 70.46, 69.78, 55.58, 55.35, 45.26, 45.02, 44.58, 33.87, 33.29, 10.62, 3.75. HRMS [C13H12ClF2N4 + H]+: 297.1113 calculated, 297.1110 found.

(R)-2-Chloro-N-(cyclopropylmethyl)-6-(3-hydroxyxopyrrolidin-1-yl)pyrimidine-4-carboxamide (117z). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (98 mg, 0.40 mmol, 1 eq), DiPEA (174 μL, 1.0 mmol, 2.5 eq) and (R)-3-hydroxyxopyrrolidine HCl salt (52 mg, 0.42 mmol, 1.05 eq). Column chromatography (70% -> 100% EtOAc/pentane) afforded the product (105 mg, 0.35 mmol, 88%). TLC: Rf = 0.2 (80% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.98 (t, J = 5.4 Hz, 1H), 7.08 – 6.91 (m, 1H), 4.74 – 4.54 (m, 1H), 3.90 – 3.39 (m, 5H), 3.34 – 3.20 (m, 2H), 2.24 – 2.07 (m, 2H), 1.13 – 0.98 (m, 1H), 0.63 – 0.48 (m, 2H), 0.36 – 0.17 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 162.64, 162.34, 162.18, 159.73, 159.60, 156.40, 100.57, 100.52, 70.50, 69.81, 55.59, 55.36, 45.27, 45.03, 44.59, 33.87, 33.32, 10.63, 3.76. HRMS [C13H17ClN3O2 + H]+: 297.1113 calculated, 297.1110 found.

(S)-2-Chloro-N-(cyclopropylmethyl)-6-(3-hydroxyxopyrrolidin-1-yl)pyrimidine-4-carboxamide (117aa). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (98 mg, 0.40 mmol, 1 eq), DiPEA (174 μL, 1.0 mmol, 2.5 eq) and (S)-3-hydroxyxopyrrolidine HCl salt (52 mg, 0.42

Chapter 3
mmol, 1.05 eq). Column chromatography (70% -> 100% EtOAc/pentane) afforded the product (97 mg, 0.33 mmol, 83%). TLC: Rf = 0.2 (80% EtOAc/pentane). 1H NMR (300 MHz, CDCl$_3$) δ 7.98 (t, J = 5.2 Hz, 1H), 7.11 – 6.86 (m, 1H), 4.81 – 4.47 (m, 1H), 3.93 – 3.35 (m, 5H), 3.33 – 3.21 (m, 2H), 2.25 – 2.06 (m, 2H), 1.16 – 0.96 (m, 1H), 0.57 (q, J = 5.5 Hz, 2H), 0.29 (q, J = 4.7 Hz, 2H). 13C NMR (75 MHz, CDCl$_3$) δ 162.65, 162.34, 162.19, 159.73, 159.61, 156.41, 100.55, 100.51, 70.48, 69.79, 55.58, 55.35, 45.27, 45.03, 44.58, 33.87, 33.31, 10.62, 3.74. HRMS [C$_{13}$H$_{17}$ClN$_2$O$_2$ + H$^+$]: 297.1113 calculated, 297.1110 found.

(2)-2-Chloro-N-(cyclopropylmethyl)-6-(3-dimethylamino)pyrrolidin-1-ylpyrimidine-4-carboxamide (117ab). The title compound was prepared according to general procedure E using dichloropyrimidine 116a (98 mg, 0.40 mmol, 1 eq), DiPEA (244 μL, 1.4 mmol, 3.5 eq) and (t)-3-(dimethylamino)pyrrolidine double HCl salt (79 mg, 0.42 mmol, 1.05 eq). Column chromatography (2.5% -> 10% MeOH/DCM) afforded the product (50 mg, 0.15 mmol, 38%). TLC: Rf = 0.4 (5% MeOH/DCM). 1H NMR (400 MHz, CDCl$_3$) δ 8.10 – 7.77 (m, 1H), 7.06 (s, 1H), 4.06 – 3.91 (m, 2H), 3.90 – 3.60 (m, 1H), 3.59 – 3.32 (m, 2H), 3.32 – 2.35 (m, 2H), 2.95 – 2.70 (m, 1H), 2.40 – 2.30 (m, 6H), 2.30 – 2.17 (m, 1H), 2.08 – 1.78 (m, 1H), 1.13 – 0.99 (m, 1H), 0.66 – 0.45 (m, 2H), 0.35 – 0.21 (m, 2H). 13C NMR (101 MHz, CDCl$_3$) δ 171.69, 163.73, 162.56, 162.47, 162.15, 161.99, 159.76, 159.69, 159.50, 158.70, 158.27, 157.69, 106.57, 100.46, 100.22, 93.93, 65.41, 64.76, 53.71, 51.47, 51.33, 50.76, 46.42, 46.22, 45.79, 44.54, 44.51, 44.42, 44.28, 44.02, 30.41, 29.81, 10.90, 10.85, 10.74, 3.76, 3.51, 3.47. HRMS [C$_{15}$H$_{17}$ClN$_2$O + H$^+$]: 324.1586 calculated, 324.1583 found.

2-Chloro-N-(cyclopropylmethyl)-6-(1H-pyrazol-1-yl)pyrimidine-4-carboxamide (117ac). The title compound was prepared according to general procedure F using dichloropyrimidine 116a (123 mg, 0.50 mmol, 1 eq), K$_2$CO$_3$ (104 mg, 0.75 mmol, 1.5 eq) and pyrazole (36 mg, 0.53 mmol, 1.05 eq). Column chromatography (10% -> 30% EtOAc/pentane) afforded the product (76 mg, 0.27 mmol, 54%). TLC: Rf = 0.8 (30% EtOAc/pentane). 1H NMR (400 MHz, CDCl$_3$) δ 8.61 (s, 1H), 8.56 (d, J = 2.7 Hz, 1H), 7.92 (br s, 1H), 7.85 (d, J = 1.3 Hz, 1H), 6.55 (dd, J = 2.8, 1.6 Hz, 1H), 3.36 (dd, J = 7.1, 5.9 Hz, 2H), 1.19 – 1.00 (m, 1H), 0.71 – 0.49 (m, 2H), 0.32 (q, J = 4.7 Hz, 2H). 13C NMR (101 MHz, CDCl$_3$) δ 161.28, 160.88, 160.48, 159.64, 145.18, 128.34, 110.22, 105.51, 44.73, 3.76. HRMS [C$_{15}$H$_{17}$ClN$_2$O + H$^+$]: 278.0803 calculated, 278.0802 found.

2-Chloro-N-(cyclopropylmethyl)-6-(1H-imidazol-1-yl)pyrimidine-4-carboxamide (117ad). The title compound was prepared according to general procedure F using dichloropyrimidine 116a (123 mg, 0.50 mmol, 1 eq), K$_2$CO$_3$ (104 mg, 0.75 mmol, 1.5 eq) and imidazole (36 mg, 0.53 mmol, 1.05 eq). Column chromatography (60% -> 80% EtOAc/pentane) afforded the product as an inseparable mixture of regioisomers (2:5:1, 6-imidazolyl : 2-imidazolyl), that was used for the following step without further purification (100 mg, 0.36 mmol, 72%). TLC: Rf = 0.4 (5% MeOH/DCM). 1H NMR (400 MHz, CDCl$_3$) δ 8.56 (s, 1H), 8.10 (s, 1H), 7.98 (br s, 1H), 7.77 (t, J = 1.4 Hz, 1H), 7.26 (s, 1H), 3.47 – 3.26 (m, 2H), 1.18 – 1.03 (m, 1H), 0.68 – 0.53 (m, 2H), 0.41 – 0.27 (m, 2H). 13C NMR (101 MHz, CDCl$_3$) δ 161.93, 160.55, 159.94, 158.14, 135.73, 132.38, 116.02, 104.68, 44.84, 10.66, 3.76. HRMS [C$_{15}$H$_{17}$ClN$_2$O + H$^+$]: 278.0803 calculated, 278.0800 found.

2-Chloro-N-(cyclopropylmethyl)-6-phenoxypryimidin-4-carboxamide (117ae). The title compound was prepared according to general procedure F using dichloropyrimidine 116a (100 mg, 0.41 mmol, 1 eq), K$_2$CO$_3$ (86 mg, 0.62 mmol, 1.5 eq) and phenol (44 mg, 0.43 mmol, 1.05 eq). Column chromatography (5% -> 30% EtOAc/pentane) afforded the product (100 mg, 0.33 mmol, 80%). TLC: Rf = 0.4 (20% EtOAc/pentane). 1H NMR (300 MHz, CDCl$_3$) δ 7.90 (br s, 1H), 7.54 (s, 1H), 7.50 – 7.39 (m, 2H), 7.36 – 7.28 (m, 1H), 7.20 – 7.08 (m, 2H), 3.41 – 3.17 (m, 2H), 1.15 – 0.96 (m, 1H), 0.66 – 0.47 (m, 2H), 0.29 (q, J = 4.7 Hz, 2H). 13C NMR (75 MHz,
Chapter 3

\[ \text{CDCl}_3 \delta 172.25, 161.17, 161.02, 159.73, 151.84, 130.19, 126.62, 121.27, 104.58, 44.68, 10.70, 3.75. \] HRMS \([\text{C}_3\text{H}_3\text{ClN}_2\text{O}_2 + \text{H}]^+\): 304.0847 calculated, 304.0845 found.

2-Chloro-N-(cyclopropylmethyl)-6-(pyridin-3-yl)pyrimidine-4-carboxamide (117af). The title compound was prepared according to general procedure F using dichloropyrimidine 116a (0.11 g, 0.45 mmol, 1 eq), \( \text{K}_2\text{CO}_3 \) (93 mg, 0.68 mmol, 1.5 eq) and pyridine-3-ol (45 mg, 0.47 mmol, 1.05 eq). Column chromatography (60% -> 100% EtOAc/pentane) afforded the product (70 mg, 0.23 mmol, 51%). TLC: \( R_f = 0.4 \) (80% EtOAc/pentane). \( ^1\text{H} \) NMR (300 MHz, CDCl\(_3\)) \( \delta 8.56 \) (dd, \( J = 9.3, 3.2 \text{ Hz}, 2\text{H} \)), 7.94 (br s, 1H), 7.69 (s, 1H), 7.63 – 7.50 (m, 1H), 7.43 (dd, \( J = 8.3, 4.7 \text{ Hz}, 1\text{H} \)), 3.46 – 3.39 (m, 2H), 1.17 – 0.99 (m, 1H), 0.66 – 0.51 (m, 2H), 0.31 (q, \( J = 4.8 \text{ Hz}, 2\text{H} \)). \( ^{13}\text{C} \) NMR (75 MHz, CDCl\(_3\)) \( \delta 171.32, 161.44, 160.74, 159.43, 148.48, 147.52, 143.41, 129.09, 124.31, 105.26, 44.66, 10.66, 3.71. \ HRMS [\text{C}_3\text{H}_3\text{ClN}_2\text{O}_2 + \text{H}]^+ \): 305.0800 calculated, 305.0796 found.

2-(3-Phenoxyphenyl)acetonitrile (119a). A round-bottom flask was charged with 1-(chloromethyl)-3-phenoxybenzene (118a) (0.37 mL, 2.0 mmol, 1 eq) in dioxane/EtOH/H\(_2\)O (2:2:1, 6 mL) and KCN (0.26 g, 4.0 mmol, 2 eq). The reaction mixture was stirred overnight at reflux. The mixture was diluted with water and extracted with EtOAc (3x). The organic layer was washed with brine, dried (Na\(_2\)SO\(_4\)), and filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (5% -> 7% EtOAc/pentane) to provide the product (0.35 g, 1.7 mmol, 85%). TLC: \( R_f = 0.6 \) (10% EtOAc/pentane). \( ^1\text{H} \) NMR (500 MHz, CDCl\(_3\)) \( \delta 7.37 – 7.19 \) (m, 3H), 7.15 – 7.03 (m, 1H), 7.04 – 6.94 (m, 3H), 6.95 – 6.84 (m, 2H), 3.56 (s, 2H). \( ^{13}\text{C} \) NMR (126 MHz, CDCl\(_3\)) \( \delta 157.73, 156.32, 131.81, 130.23, 129.71, 123.58, 122.34, 118.97, 117.96, 117.78, 117.51, 23.00.

2-[(1,1'-Biphenyl)-2-yl]acetonitrile (119b). A round-bottom flask was charged with 2-(bromomethyl)-1,1'-biphenyl (118b) (0.37 mL, 2.0 mmol, 1 eq), solvent mixture dioxane/EtOH/H\(_2\)O (2:2:1, 6 mL) and KCN (0.26 g, 4.0 mmol, 2 eq). The reaction mixture was stirred overnight at reflux. The mixture was diluted with water and extracted with EtOAc (3x). The organic layer was washed with brine, dried (Na\(_2\)SO\(_4\)), and filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0.5% -> 5% EtOAc/pentane) to provide the product (0.40 g, 2.0 mmol, 99%). TLC: \( R_f = 0.6 \) (3% EtOAc/pentane). \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta 7.59 – 7.12 \) (m, 9H), 3.57 (s, 2H). \( ^{13}\text{C} \) NMR (101 MHz, CDCl\(_3\)) \( \delta 141.72, 139.78, 130.35, 128.86, 128.84, 128.59, 128.12, 127.68, 118.23, 21.92.

\( \text{N-Methylphenethylamine HBr salt} \) (121a). A round-bottom flask was charged with methylamine (33 wt% in ethanol, 8.83 mL, 73.0 mmol, 10 eq) and cooled to 0 °C. (2-bromoethyl)benzene (1.0 mL, 7.3 mmol, 1 eq) was added and the reaction was stirred and allowed to warm up to room temperature. After 40 h the reaction showed complete conversion on TLC and the solvents were concentrated under reduced pressure. The product was obtained as a mixture with the disubstituted by product, \( \text{N-methyl-N-phenethyl-2-phenylethylamine} \) (9:1) and used without further purification (1.4 g, 6.6 mmol, 90%). TLC: \( R_f = 0.35 \) (6% MeOH/DCM). \( ^1\text{H} \) NMR (400 MHz, MeOD) \( \delta 7.52 – 6.99 \) (m, 5H), 3.42 – 3.10 (m, 2H), 3.10 – 2.85 (m, 2H), 2.67 (s, 3H). \( ^{13}\text{C} \) NMR (101 MHz, MeOD) \( \delta 137.75, 129.86, 129.78, 128.10, 51.50, 33.92, 33.31.

\( \text{N-Methyl-3-phenylpropan-1-amine} \) (121b). \( \text{Carbamoylation} \): The methyl carbamate was prepared according to general procedure G using 3-phenylpropan-1-amine (71 \( \mu \)L, 0.50 mmol, 1 eq), methylchloroformate (58 \( \mu \)L, 0.75 mmol, 1.5 eq) and DiPEA (174 \( \mu \)L, 1.0 mmol, 2 eq). Column chromatography (20% -> 50% EtOAc/pentane) afforded the product (91 mg, 0.47 mmol, 94%). TLC: \( R_f = 0.7 \) (50% EtOAc/pentane). \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta 7.33 – 7.22 \) (m, 2H), 7.22 – 7.13
(m, 3H), 4.82 (br s, 1H), 3.65 (s, 3H), 3.26 – 3.07 (m, 2H), 2.69 – 2.57 (m, 2H), 1.82 (p, J = 7.3 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 157.18, 141.47, 128.49, 128.40, 126.02, 52.08, 40.68, 33.06, 31.68. HRMS [C14H12N2O + H]+: 214.1176 calculated, 194.1175 found. 

Carbamate reduction: the title compound was prepared according to general procedure G using the methyl carbamate (91 mg, 0.47 mmol, 1 eq), LiAlH4 (2 M THF solution, 0.75 mL, 1.54 mmol, 3.3 eq) and was used without further purification (39 mg, 0.13 mmol, 28%). TLC: Rf = 0.1 (5% MeOH/DCM). 1H NMR (500 MHz, CDCl3) δ 7.31 – 7.13 (m, 5H), 2.68 – 2.63 (m, 2H), 2.63 – 2.58 (m, 2H), 2.42 (s, 3H), 1.90 – 1.76 (m, 2H), 1.71 – 1.58 (m, 1H). HRMS [C10H13N + H]+: 150.1277 calculated, 150.1278 found.

N-Methyl-4-phenylbutan-1-amine (121c). Carbamoylation: the methyl carbamate was prepared according to general procedure G using 4-phenylbutan-1-amine (79 µL, 0.50 mmol, 1 eq), methylchloroformate (58 µL, 0.75 mmol, 1.5 eq) and DiPEA (174 µL, 1.0 mmol, 2 eq). Column chromatography (10% -> 40% EtOAc/pentane) afforded the product (97 mg, 0.47 mmol, 94%). TLC: Rf = 0.6 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.26 (t, J = 7.5 Hz, 2H), 7.17 (t, J = 7.9 Hz, 3H), 4.80 (br s, 1H), 3.64 (s, 3H), 3.29 – 3.00 (m, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.51 (p, J = 6.9 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 157.15, 142.15, 128.42, 128.37, 125.84, 52.01, 40.93, 35.54, 29.65, 28.55. HRMS [C15H15NO2 + H]+: 208.1332 calculated, 208.1333 found. Carbamate reduction: the title compound was prepared according to general procedure G using the methyl carbamate (97 mg, 0.47 mmol, 1 eq), LiAlH4 (2 M THF solution, 0.38 mL, 0.75 mmol, 1.6 eq) and was used without further purification (64 mg, 0.39 mmol, 83%). TLC: Rf = 0.1 (5% MeOH/DCM). 1H NMR (400 MHz, CDCl3) δ 7.31 – 7.21 (m, 2H), 7.20 – 7.11 (m, 3H), 2.62 (t, J = 7.6 Hz, 2H), 2.59 – 2.54 (m, 2H), 2.40 (s, 3H), 1.77 – 1.57 (m, 3H), 1.57 – 1.46 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 142.51, 128.45, 128.31, 125.73, 52.05, 36.57, 35.90, 29.61, 29.24. HRMS [C10H13N + H]+: 164.1434 calculated, 164.1433 found.

2-(4-Chlorophenyl)-N-methylethan-1-amine (121d). Carbamoylation: the methyl carbamate was prepared according to general procedure G using 2-(4-chlorophenyl)ethan-1-amine (70 µL, 0.50 mmol, 1 eq), methylchloroformate (58 µL, 0.75 mmol, 1.5 eq) and DiPEA (174 µL, 1.0 mmol, 2 eq). Column chromatography (10% -> 50% EtOAc/pentane) afforded the product (104 mg, 0.50 mmol, 99%). TLC: Rf = 0.7 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.35 – 7.21 (m, 2H), 7.16 – 7.05 (m, 2H), 5.01 – 4.39 (m, 1H), 3.65 (s, 3H), 3.41 (q, J = 6.7 Hz, 2H), 2.78 (t, J = 7.0 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 157.04, 137.32, 132.39, 130.22, 128.80, 52.20, 42.17, 35.62. HRMS [C15H13ClNO + H]+: 214.0629 calculated, 214.0631 found. Carbamate reduction: the title compound was prepared according to general procedure G using the methyl carbamate (104 mg, 0.48 mmol, 1 eq), LiAlH4 (2 M THF solution, 0.39 mL, 0.77 mmol, 1.6 eq). Column chromatography (isocratic, 5% MeOH/DCM + 0.5% Et3N) afforded the product (36 mg, 0.21 mmol, 44%). TLC: Rf = 0.1 (2% MeOH/DCM with 3 drops of Et3N). 1H NMR (500 MHz, CDCl3) δ 7.28 – 7.20 (m, 2H), 7.19 – 7.10 (m, 2H), 2.92 – 2.74 (m, 4H), 2.66 – 2.52 (m, 1H), 2.45 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 138.30, 132.03, 130.14, 128.66, 52.87, 36.12, 35.26. HRMS [C9H12ClIN + H]+: 170.0731 calculated, 170.0732 found.

2-(3-Chlorophenyl)-N-methylethan-1-amine (121e). Carbamoylation: the methyl carbamate was prepared according to general procedure G using 2-(3-chlorophenyl)ethan-1-amine (70 µL, 0.40 mmol, 1 eq), methylchloroformate (58 µL, 0.75 mmol, 1.5 eq) and DiPEA (174 µL, 2.0 mmol, 2 eq). Column chromatography (20% -> 40% EtOAc/pentane) afforded the product (67 mg, 0.31 mmol, 78%). TLC: Rf = 0.7 (30% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.25 – 7.15 (m, 3H), 7.11 – 7.03 (m, 1H), 4.89 (br s, 1H), 3.65 (s, 3H), 3.41 (q, J = 6.8 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 157.05, 140.94, 134.37, 129.90, 128.93, 127.04, 126.75, 52.15, 42.04, 35.90. HRMS [C10H12ClNO + H]+: 214.0629 calculated, 214.0630 found. Carbamate reduction: the title compound was prepared according to general procedure G using the methyl carbamate (67 mg, 0.31 mmol, 1 eq), LiAlH4 (2 M THF solution, 0.250 mL, 0.50 mmol, 1.6 eq) and was used without further purification (33 mg,
0.14 mmol, 45%). $R_t = 0.15$ (6% MeOH/DCM).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.26 – 7.16 (m, 3H), 7.13 – 7.04 (m, 1H), 2.92 – 2.76 (m, 4H), 2.47 (s, 3H), 2.45 (br s, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.75, 134.40, 129.90, 128.92, 127.06, 126.63, 52.69, 36.06, 35.51. HRMS [C$_{10}$H$_{13}$ClNO + H]$^+$: 170.0731 calculated, 170.0730 found.

2-(2-Chlorophenyl)-N-methylethan-1-amine (121f). Carboxamoylation: the methyl carbamate was prepared according to general procedure G using 2-(2-chlorophenyl)ethan-1-amine (141 μL, 1.0 mmol, 1 eq), methylvchloroforme (116 μL, 1.5 mmol, 1.5 eq) and DiPEA (0.35 mL, 2.0 mmol, 2 eq). Column chromatography (30% -> 50% EtOAc/pentane) afforded the product (183 mg, 0.85 mmol, 87%). TLC: $R_t = 0.7$ (50% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.30 (m, 1H), 7.25 – 7.12 (m, 3H), 4.94 (br s, 1H), 3.65 (s, 3H), 3.44 (q, J = 6.7 Hz, 2H), 2.95 (t, J = 7.1 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.10, 136.50, 134.17, 131.06, 129.65, 128.06, 126.97, 52.10, 40.67, 33.93. HRMS [C$_{15}$H$_{13}$ClNO$_2$ + H]$^+$: 214.0629 calculated, 214.0630 found (m, 1H), 2.92 (t, J = 7.4 Hz, 2H), 2.32 (s, 3H). HRMS [C$_{15}$H$_{13}$N + H]$^+$: 150.1277 calculated, 150.1277 found.

N-Methyl-2-(p-tolyl)ethan-1-amine (121g). Carboxamoylation: the methyl carbamate was prepared according to general procedure G using 2-(p-tolyl)ethan-1-amine (145 μL, 1.0 mmol, 1 eq), methylvchloroforme (116 μL, 1.5 mmol, 1.5 eq) and DiPEA (0.35 mL, 2.0 mmol, 2 eq). Column chromatography (30% -> 50% EtOAc/pentane) afforded the product (198 mg, 1.0 mmol, 99%). TLC: $R_t = 0.7$ (50% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.18 – 6.91 (m, 4H), 5.02 (br s, 1H), 3.61 (s, 3H), 3.38 (q, J = 6.8 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H), 2.30 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.00, 135.82, 135.66, 129.18, 128.55, 51.85, 42.26, 35.60, 20.91. HRMS [C$_{15}$H$_{13}$NO$_2$ + H]$^+$: 194.1176 calculated, 194.1176 found. Carboxamoylation: the title compound was prepared according to general procedure G using the methyl carbamate (183 mg, 0.85 mmol, 1 eq), LiAlH$_4$ (2 M THF solution, 0.68 mL, 1.36 mmol, 1.6 eq) and was used without further purification (130 mg, 0.77 mmol, 91%). TLC: $R_t = 0.1$ (6% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.26 (m, 1H), 7.26 – 7.08 (m, 3H), 3.02 – 2.73 (m, 4H), 2.50 – 2.26 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 137.55, 134.08, 130.82, 129.58, 127.67, 126.81, 51.32, 36.18, 33.82. HRMS [C$_{10}$H$_{13}$ClN + H]$^+$: 170.0731 calculated, 170.0732 found.

N-Methyl-2-(o-tolyl)ethan-1-amine (121h). Carboxamoylation: the methyl carbamate was prepared according to general procedure G using 2-(o-tolyl)ethan-1-amine (70 μL, 0.50 mmol, 1 eq), methylvchloroforme (58 μL, 0.75 mmol, 1.5 eq) and DiPEA (174 μL, 1.0 mmol, 2 eq). Column chromatography (30% -> 50% EtOAc/pentane) afforded the product (102 mg, 0.50 mmol, 99%). TLC: $R_t = 0.7$ (50% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.19 – 7.07 (m, 4H), 2.83 – 2.72 (m, 4H), 2.41 (s, 3H), 2.33 – 2.28 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 136.87, 135.59, 129.17, 128.60, 80.66, 53.26, 36.28, 35.65, 21.02. HRMS [C$_{10}$H$_{13}$N + H]$^+$: 150.1277 calculated, 150.1277 found.
Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401

0.75 mmol, 1.5 eq) and DIPEA (174 µL, 1.0 mmol, 2 eq). Column chromatography (10% -> 40% EtOAc/pentane) afforded the product (108 mg, 0.50 mmol, 99%). TLC: Rf = 0.6 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.09 (d, J = 8.5 Hz, 2H), 6.83 (d, 2H), 4.93 (br s, 1H), 3.77 (s, 3H), 3.63 (s, 3H), 3.38 (q, J = 6.8 Hz, 2H), 2.73 (t, J = 7.1 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 158.21, 157.06, 154.06, 153.80, 130.80, 129.69, 113.99, 55.21, 51.96, 42.42, 35.21. HRMS [C21H23NO3 + H]+: 310.1215 calculated, 310.1215 found.

Carbamate reduction: the title compound was prepared according to general procedure G using the methyl carbamate (105 mg, 0.50 mmol, 1 eq), LiAlH4 (2 M THF solution, 0.40 mL, 0.80 mmol, 1.6 eq) and was used without further purification (176 mg, 0.97 mmol, 44%). TLC: Rf = 0.1 (5% MeOH/DCM with 3 drops of Et3N). 1H NMR (400 MHz, CDCl3) δ 7.17 – 7.05 (m, 2H), 6.87 – 6.77 (m, 2H), 3.77 (s, 3H), 2.87 – 2.65 (m, 4H), 2.49 – 2.19 (m, 4H). 13C NMR (101 MHz, CDCl3) δ 158.08, 132.00, 129.68, 55.30, 53.37, 36.29, 35.18. HRMS [C26H25NO + H]+: 366.1226 calculated, 366.1226 found.

2-(2-Methoxyphenyl)-N-methylethan-1-amine (112j). Carbamoylation: the methyl carbamate was prepared according to general procedure G using 2-(2-methoxyphenyl)ethan-1-amine (145 µL, 1.0 mmol, 1 eq), methylchloroformate (116 µL, 1.5 mmol, 1.5 eq) and DIPEA (348 µL, 2.0 mmol, 2 eq). Column chromatography (20% -> 40% EtOAc/pentane) afforded the product (230 mg, 1.0 mmol, 99%). TLC: Rf = 0.5 (30% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.19 (td, J = 8.0, 1.7 Hz, 1H), 7.11 (d, J = 6.9 Hz, 1H), 6.94 – 6.78 (m, 2H), 5.19 – 4.71 (m, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.39 (q, J = 6.6 Hz, 2H), 2.81 (t, J = 6.9 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 157.48, 157.04, 130.51, 127.75, 127.20, 120.51, 110.27, 55.14, 51.81, 41.08, 30.65. HRMS [C15H15NO2 + H]+: 210.1125 calculated, 210.1125 found.

Carbamate reduction: the title compound was prepared according to general procedure G using the methyl carbamate (230 mg, 1.0 mmol, 1 eq), LiAlH4 (1 M THF solution, 1.6 mL, 1.6 mmol, 1.6 eq) and was used without further purification (160 mg, 0.97 mmol, 97%). TLC: Rf = 0.3 (2% MeOH/DCM with 3 drops of Et3N). 1H NMR (400 MHz, CDCl3) δ 7.24 – 7.07 (m, 2H), 6.95 – 6.74 (m, 2H), 3.80 (s, 3H), 2.90 – 2.70 (m, 4H), 2.43 (s, 3H), 1.26 (br s, 1H). 13C NMR (101 MHz, CDCl3) δ 157.59, 130.33, 128.44, 127.36, 120.39, 110.30, 55.20, 51.85, 36.37, 30.70. HRMS [C10H13NO + H]+: 166.1226 calculated, 166.1225 found.

N-Methyl-2-(4-(trifluoromethyl)phenyl)ethan-1-amine (112k). Carbamoylation: the methyl carbamate was prepared according to general procedure G using 2-(4-(trifluoromethyl)phenyl)ethan-1-amine (80 µL, 0.50 mmol, 1 eq), methylchloroformate (58 µL, 0.75 mmol, 1.5 eq) and DIPEA (174 µL, 1.0 mmol, 2 eq). Column chromatography (5% -> 40% EtOAc/pentane) afforded the product (113 mg, 0.45 mmol, 90%). TLC: Rf = 0.7 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.56 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.89 – 4.64 (m, 1H), 3.66 (s, 3H), 3.45 (q, J = 6.7 Hz, 2H), 2.88 (t, J = 7.0 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 157.06, 143.06, 129.25, 128.82, 127.37, 125.62 (q, J = 3.8 Hz), 122.97, 52.25, 42.03, 36.14. HRMS [C15H13F3NO2 + H]+: 248.0893 calculated, 248.0896 found. Carbamate reduction: the title compound was prepared according to general procedure G using the methyl carbamate (113 mg, 0.45 mmol, 1 eq), LiAlH4 (2 M THF solution, 0.36 mL, 0.72 mmol, 1.6 eq). Column chromatography (isocratic, 5% MeOH/DCM + 0.5% Et3N) afforded the product (40 mg, 0.20 mmol, 44%). TLC: Rf = 0.3 (2% MeOH/DCM with 3 drops of Et3N). 1H NMR (500 MHz, CDCl3) δ 7.55 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 3.80 (br s, 1H), 2.99 – 2.91 (m, 4H), 2.51 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 143.51, 129.13, 125.57 (q, J = 3.7 Hz), 125.41, 123.25, 52.36, 35.73, 35.29. HRMS [C10H13F3N + H]+: 204.0995 calculated, 204.0996 found.

N-Methyl-2-(4-phenoxypyphenyl)ethan-1-amine (121l). Carbamoylation: the methyl carbamate was prepared according to general procedure G using 2-(4-phenoxypyphenyl)ethan-1-amine TFA salt (211 mg, 0.64 mmol, 1 eq), methylchloroformate (74 µL, 0.96 mmol, 1.5 eq) and DIPEA (245 µL, 1.41 mmol, 2.2 eq). Column chromatography (10% -> 40% EtOAc/pentane) afforded the product (145 mg, 0.53 mmol, 83%). TLC: Rf = 0.8
(100% EtOAc). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.27 (m, 2H), 7.22 – 7.04 (m, 3H), 7.03 – 6.89 (m, 4H), 4.96 – 4.65 (m, 1H), 3.65 (s, 3H), 3.51 – 3.29 (m, 2H), 2.77 (t, $J = 7.1$ Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.36, 157.05, 155.85, 133.69, 130.06, 129.77, 123.20, 119.12, 118.76, 52.08, 42.36, 35.48. HRMS [C$_{18}$H$_{22}$NO$_2$ + H$^+$]: 272.1281 calculated, 272.1281 found. **Carbamate reduction:** The title compound was prepared according to general procedure G using the methyl carbamate (144 mg, 0.53 mmol, 1 eq.), LiAlH$_4$ (2 M THF solution, 0.42 mL, 0.85 mmol, 1.6 eq.). Column chromatography (isocratic, 5% MeOH/DCM + 0.5% Et$_3$N) afforded the product (65 mg, 0.29 mmol, 55%). TLC: $R_f$ = 0.3 (5% MeOH/DCM with 3 drops of Et$_3$N). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.35 – 7.27 (m, 2H), 7.20 – 7.14 (m, 2H), 7.12 – 7.03 (m, 1H), 7.02 – 6.96 (m, 2H), 6.96 – 6.91 (m, 2H), 3.08 (br s, 1H), 2.92 – 2.80 (m, 4H), 2.48 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 157.46, 155.65, 134.48, 130.01, 129.77, 123.15, 119.13, 118.73, 53.02, 36.00, 35.00. HRMS [C$_{15}$H$_{17}$NO + H$^+$]: 228.1383 calculated, 228.1385 found.

**N-Methyl-2-(3-phenoxypyphenyl)ethan-1-amine (121m).** **Nitrile reduction:** A round-bottom flask was charged with nitrile 119a (211 mg, 1.0 mmol, 1 eq.), EtOH (5 mL) and 37% w/w aqueous HCl (0.16 mL, 2.0 mmol, 2 eq.). N$_2$ was bubbled through the solution for 5 min and Pd/C (10% w/w, 52 mg, 50 μmol, 5 mol%) was added. The mixture was purged with N$_2$ and then with H$_2$ and was kept under H$_2$ atmosphere (balloon). After 50 h the reaction was complete as judged by TLC. The mixture was filtered over a Whatman filter, which was washed with EtOH and the filtrate was concentrated under reduced pressure. This afforded the primary amine (120a) as the HCl salt, which was used without further purification (246 mg, 0.98 mmol, 98%). TLC: $R_f$ = 0.05 (6% MeOH/DCM). **Carbamoylation:** The methyl carbamate was prepared according to general procedure G using the primary amine 120a (246 mg, 0.98 mmol, 1 eq.), methylchloroformate (115 μL, 1.48 mmol, 1.5 eq) and DiPEA (517 μL, 3.0 mmol, 3 eq). Column chromatography (5% → 40% EtOAc/pentane) afforded the product (176 mg, 0.65 mmol, 66%). TLC: $R_f$ = 0.3 (10% EtOAc/pentane). **Carbamate reduction:** The title compound was prepared according to general procedure G using the methyl carbamate (170 mg, 0.62 mmol, 1 eq), LiAlH$_4$ (2 M THF solution, 0.52 mL, 1.04 mmol, 1.6 eq) and was used without further purification (125 mg, 0.55 mmol, 89%). TLC: $R_f$ = 0.1 (6% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.35 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.12 – 7.05 (m, 1H), 7.03 – 6.97 (m, 2H), 6.95 – 6.91 (m, 1H), 6.89 – 6.81 (m, 2H), 2.91 – 2.67 (m, 5H), 2.41 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.49, 157.19, 142.10, 129.77, 129.74, 123.65, 123.26, 119.12, 118.94, 116.55, 52.94, 36.27, 35.99. HRMS [C$_{15}$H$_{17}$NO + H$^+$]: 228.1383 calculated, 228.1384 found.

**N-Methyl-2-(2-phenoxypyphenyl)ethan-1-amine (121n).** **Carbamoylation:** The methyl carbamate was prepared according to general procedure G using 2-(2-phenoxypyphenyl)ethan-1-amine (99 μL, 0.50 mmol, 1 eq), methylchloroformate (58 μL, 0.75 mmol, 1.5 eq) and DiPEA (174 μL, 1.0 mmol, 2 eq). Column chromatography (20% → 40% EtOAc/pentane) afforded the product (115 mg, 0.42 mmol, 84%). TLC: $R_f$ = 0.7 (30% EtOAc/pentane). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.22 (m, 3H), 7.21 – 7.15 (m, 1H), 7.10 – 7.04 (m, 2H), 6.96 – 6.91 (m, 2H), 6.89 – 6.83 (m, 1H), 4.89 (br s, 1H), 3.62 (s, 3H), 3.44 (q, $J = 6.6$ Hz, 2H), 2.85 (t, $J = 6.9$ Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.49, 157.08, 154.97, 131.27, 130.31, 129.85, 128.11, 123.97, 123.02, 119.26, 118.07, 52.05, 41.35, 30.73. HRMS [C$_{15}$H$_{17}$NO + H$^+$]: 272.1281 calculated, 272.1281 found. **Carbamate reduction:** The title compound was prepared according to general procedure G using the methyl carbamate (115 mg, 0.42 mmol, 1 eq), LiAlH$_4$ (2 M THF solution, 0.34 mL, 0.67 mmol, 1.6 eq). Column chromatography (4% → 7% MeOH/DCM + 0.5% Et$_3$N) afforded the product (72 mg, 0.32 mmol, 76%). TLC: $R_f$ = 0.3 (4% MeOH/DCM with 3 drops of Et$_3$N). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.34 – 7.23 (m, 3H), 7.18 (t, $J = 7.8$, 1.7 Hz, 1H), 7.11 – 7.01 (m, 2H), 6.97 – 6.83 (m, 3H), 3.04 (br s, 1H), 2.87 (s, 4H), 2.42 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.79, 154.81, 131.17, 131.12, 129.80, 127.88, 123.99, 122.82, 119.58, 117.88, 51.55, 35.80, 30.23. HRMS [C$_{15}$H$_{17}$NO + H$^+$]: 228.1383 calculated, 228.1383 found.
**Optimization of pyrimidine-4-carboxamide NAPE-PLD inhibitors affords LEI-401**

2-[(1,1′-Biphenyl)-2-yl]-N-methylethen-1-amine (1210). Nitrile reduction: a round-bottom flask was charged with nitrile 119b (195 mg, 1.0 mmol, 1 eq), EtOH (5 mL) and 37% w/w aqueous HCl (0.16 mL, 2.0 mmol, 2 eq). N\textsubscript{2} was bubbled through the solution for 5 min and Pd/C (10% w/w, 52 mg, 50 μmol, 5 mol%) was added. The mixture was purged with N\textsubscript{2} and then with H\textsubscript{2} and was kept under an H\textsubscript{2} atmosphere (balloon). After 3.5 days the reaction was complete as judged by TLC. The mixture was filtered over a Whatman filter and the filtrate was concentrated under reduced pressure to afford the primary amine (120b) as the HCl salt, which was used without further purification (235 mg, 1.0 mmol, 99%). TLC: R\textsubscript{f} = 0.15 (6% MeOH/DCM). Carbamoylation: the methyl carbamate was prepared according to general procedure G using the amine HCl salt 120b (235 mg, 1.0 mmol, 1 eq), methylchloroformate (116 μL, 1.5 mmol, 1.5 eq) and DiPEA (522 μL, 3.0 mmol, 3 eq). Column chromatography (10% -> 40% EtOAc/pentane) afforded the product (210 mg, 0.82 mmol, 82%). TLC: R\textsubscript{f} = 0.5 (20% EtOAc/pentane). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.48 – 7.16 (m, 9H), 4.86 – 4.47 (m, 1H), 3.56 (s, 3H), 3.28 – 3.08 (m, 2H), 2.79 (t, J = 7.2 Hz, 2H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 156.89, 142.40, 141.50, 136.16, 130.32, 129.68, 129.19, 128.26, 127.64, 127.05, 126.46, 51.98, 41.83, 33.26. HRMS [C\textsubscript{29}H\textsubscript{32}N\textsubscript{2}O\textsubscript{2}]\textsuperscript{+}: 256.1332 calculated, 256.1333 found. Carbamate reduction: the title compound was prepared according to general procedure G using the methyl carbamate (210 mg, 0.82 mmol, 1 eq), LiAlH\textsubscript{4} (2 M THF solution, 0.66 mL, 1.32 mmol, 1.6 eq) and was used without further purification (157 mg, 0.74 mmol, 90%). TLC: R\textsubscript{f} = 0.3 (6% MeOH/DCM). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.42 – 7.36 (m, 2H), 7.35 – 7.19 (m, 7H), 2.83 – 2.73 (m, 2H), 2.70 – 2.58 (m, 2H), 2.26 (s, 3H), 2.11 (br s, 1H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 142.24, 141.70, 137.29, 130.25, 129.56, 129.22, 128.16, 127.50, 126.93, 126.13, 52.77, 36.06, 33.16. HRMS [C\textsubscript{16}H\textsubscript{19}N\textsubscript{2} + H\textsuperscript{+}]: 212.1434 calculated, 212.1434 found.

**N-Phenethylaniline (122).** A round-bottom flask under N\textsubscript{2} atmosphere was charged with phenylboronic acid (0.49 g, 4.0 mmol, 2 eq), Cu(OAc)\textsubscript{2}-H\textsubscript{2}O (40 mg, 0.2 mmol, 0.1 eq), powdered 4 Å molecular sieves (1.5 g) and dry DCE (16 mL). The suspension was stirred for 5 minutes at room temperature followed by addition of 2-phenethylamine (0.25 mL, 2.0 mmol, 1 eq). The blue mixture was purged using a balloon of O\textsubscript{2} causing a color shift to purple and stirred under an O\textsubscript{2} atmosphere for 26 h. The mixture was then filtered through a plug of Celite and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% -> 8% EtOAc/pentane) affording the product (127 mg, 0.64 mmol, 32%). TLC: R\textsubscript{f} = 0.6 (5% EtOAc/pentane). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.34 – 7.25 (m, 2H), 7.24 – 7.12 (m, 5H), 6.74 – 6.66 (m, 1H), 6.61 – 6.54 (m, 2H), 3.63 (br s, 1H), 3.36 (t, J = 7.1 Hz, 2H), 2.87 (t, J = 7.0 Hz, 2H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 148.06, 139.38, 129.35, 128.86, 128.67, 126.48, 117.50, 113.04, 45.08, 35.55. HRMS [C\textsubscript{14}H\textsubscript{15}N + H\textsuperscript{+}]: 198.1277 calculated, 198.1275 found.

**N-Ethyl-2-phenylethen-1-amine (123a).** A round-bottom flask was charged with acetaldehyde (56 μL, 1.0 mmol, 1 eq), 2-phenethylamine (189 μL, 1.5 mmol, 1.5 eq) and dry DCM (10 mL). The solution was stirred at room temperature for 10 minutes and then NaHB(OAc)\textsubscript{3} (424 mg, 2 mmol, 2 eq) was added. After 16 h the reaction was complete as judged by TLC. The mixture was diluted with DCM (20 mL), washed with sat. aq. NaHCO\textsubscript{3} (1 x 30 mL), brine (1 x 30 mL), dried (MgSO\textsubscript{4}), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% -> 7% MeOH/DCM with 0.5% Et\textsubscript{3}N) affording the product (27 mg, 0.18 mmol, 18%). TLC: R\textsubscript{f} = 0.3 (6% MeOH/DCM). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.34 – 7.24 (m, 2H), 7.24 – 7.16 (m, 3H), 2.96 – 2.77 (m, 4H), 2.68 (q, J = 7.1 Hz, 2H), 1.10 (t, J = 7.2 Hz, 3H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 140.14, 128.83, 128.59, 126.27, 51.11, 46.98, 44.09, 15.24. HRMS [C\textsubscript{13}H\textsubscript{15}N + H\textsuperscript{+}]: 150.1277 calculated, 150.1277 found.

**N-phenethylpropan-2-amine (123b).** A round-bottom flask was charged with NaBH\textsubscript{4} (218 mg, 5.8 mmol, 1.9 eq) and dry DCM (5 mL). The solution was stirred in an ice bath for 3 minutes and glacial acetic acid (1 mL, 14.4 mmol, 5.8 eq) was added. The mixture was stirred for 1 h at 0 °C and 30 minutes at room temperature. Separately, a solution of 2-phenethylamine...
(0.38 mL, 3.0 mmol, 1 eq) was prepared in dry DCM (2.5 mL) and acetone (198 μL, 2.7 mmol, 0.9 eq). This solution was added dropwise to the NaBH(OAc)₃ mixture and was stirred at rt overnight. After 20 hours the reaction mixture was acidified to pH 2 with 0.1 M HCl (aq.) and washed with DCM (2 x 30 mL) to remove by-products. Then, the solution was basified with 1 M NaOH (aq.) until pH 10 and extracted with DCM (3 x 50 mL). The combined organic layers were dried (Na₂SO₄), filtered, concentrated under reduced pressure and the residue was purified by silica gel column chromatography (isocratic, 0.5% Et₂O/DCM) to provide the product (277 mg, 1.7 mmol, 57%). TLC: Rᵋ = 0.3 (100% EtOAc with 3 drops of Et₂N). ¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 2.88 – 2.82 (m, 2H), 2.81 – 2.74 (m, 3H), 1.08 (br s, 1H), 1.03 (d, J = 6.4 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 139.98, 128.52, 128.28, 125.95, 48.70, 48.38, 36.48, 22.80. HRMS [C₁₃H₁₂N + H]⁺: 164.1434 calculated, 164.1434 found.

-N-Phenethylcyclopropanamine (123c). A round-bottom flask was charged with phenylacetaldehyde (125 μL, 1.0 mmol, 1 eq), cyclopropanamine (139 μL, 2.0 mmol, 2 eq) and dry DCM (5 mL). The solution was stirred at room temperature for 10 minutes and then NaBH(OAc)₃ (0.43 g, 2.0 mmol, 2 eq) and glacial AcOH (114 μL, 2.0 mmol, 2 eq) were added. After 21 h the reaction mixture was diluted with DCM (10 mL), washed with sat. aq. NaHCO₃ (1 x 15 mL), brine (1 x 15 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% -> 50% EtOAc/pentane with 0.5% Et₂N) affording the product (85 mg, 0.53 mmol, 53%), Rᵋ = 0.1 (6% MeOH/DCM). ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.07 (m, 5H), 3.01 – 2.93 (m, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.26 – 2.02 (m, 2H), 0.47 – 0.40 (m, 2H), 0.37 – 0.31 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 140.23, 128.78, 128.54, 126.19, 50.84, 36.37, 30.24, 6.33. HRMS [C₁₃H₁₂N + H]⁺: 162.1277 calculated, 162.1277 found.

-N-Benzyl-2-phenylethan-1-amine (123d). A round-bottom flask was charged with phenylacetaldehyde (125 μL, 1.0 mmol, 1 eq), benzylamine (218 μL, 2.0 mmol, 2 eq) and DCM (10 mL). The solution was stirred at room temperature for 3 minutes and then NaBH(OAc)₃ (0.42 g, 2.0 mmol, 2 eq) and glacial AcOH (114 μL, 2.0 mmol, 2 eq) were added. After 18 h the reaction mixture was diluted with DCM (20 mL), washed with sat. aq. NaHCO₃ (1 x 30 mL), brine (1 x 30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography with (4% -> 5% MeOH/DCM with 0.5% Et₂N) affording the product (125 mg, 0.57 mmol, 57%). TLC: Rᵋ = 0.4 (5% MeOH/DCM with 3 drops of Et₂N). ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.21 (m, 7H), 7.21 – 7.17 (m, 3H), 3.77 (s, 2H), 2.91 – 2.85 (m, 2H), 2.84 – 2.78 (m, 2H), 1.97 (br s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 140.21, 140.04, 128.77, 128.51, 128.44, 126.15, 126.98, 126.20, 53.88, 50.57, 36.36.

Diphenethylamine (123e). A round-bottom flask was charged with phenylacetaldehyde (125 μL, 1.0 mmol, 1 eq), 2-phenylethylamine (251 μL, 2.0 mmol, 2 eq) and dry DCM (5 mL). The solution was stirred for 10 minutes and then NaBH(OAc)₃ (0.43 g, 2.0 mmol, 2 eq) and glacial AcOH (114 μL, 2.0 mmol, 2 eq) were added. After 19 h the reaction mixture was diluted with DCM (5 mL), washed with sat. aq. NaHCO₃ (1 x 10 mL), brine (1 x 10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (isocratic, 5% MeOH/DCM with 0.5% Et₂N) affording the product (128 mg, 0.57 mmol, 57%). TLC: Rᵋ = 0.3 (6% MeOH/DCM with 3 drops of Et₂N). ¹H NMR (400 MHz, CDCl₃) δ 7.73 – 6.67 (m, 10H), 3.05 – 2.61 (m, 8H), 1.96 (br s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 139.91, 128.67, 128.45, 126.12, 51.00, 36.25. HRMS [C₁₉H₁₄N + H]⁺: 226.1590 calculated, 226.1591 found.
Methyl 2-chloro-6-morpholinopyrimidine-4-carboxylate (125). The title compound was prepared according to general procedure E using methyl 2,6-dichloropyrimidine-4-carboxylate (124) (0.62 g, 3.0 mmol, 1 eq), DiPEA (0.78 mL, 4.5 mmol, 1.5 eq) and morpholine (0.27 mL, 3.15 mmol, 1.05 eq). Column chromatography (40% → 60% EtOAc/pentane) afforded the product (0.69 g, 2.7 mmol, 90%). TLC: Rf = 0.3 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.19 (s, 1H), 3.96 (s, 3H), 3.91 – 3.55 (m, 8H). 13C NMR (101 MHz, CDCl3) δ 163.80, 163.09, 160.65, 155.10, 101.89, 65.83, 52.84. HRMS [C13H13ClN3O + H]+: 258.0640 calculated, 258.0638 found.

Sodium (2-chloro-6-morpholinopyrimidine-4-carbonyl) glycinate (128). A round-bottom flask was charged with methyl ester 117h (0.27 g, 0.85 mmol, 1 eq) in 5 mL THF/MeOH (4:1, v/v). A 1.5 M aqueous NaOH solution (0.57 mL, 0.85 mmol, 1 eq) was added together with 0.43 mL H2O. The reaction was stirred overnight at rt after which the solvents were evaporated yielding the product which was used without further purification (0.27 g, 0.85 mmol, quant.). TLC: Rf = 0.2 (5% MeOH/DCM). 1H NMR (400 MHz, MeOD) δ 7.30 (s, 1H), 3.95 – 3.86 (m, 2H), 3.81 – 3.65 (m, 8H). 13C NMR (101 MHz, MeOD) δ 180.70, 159.60, 159.40, 158.60, 152.43, 99.06, 65.99, 43.24. HRMS [C12H14ClN2O + H]+= 258.0638 calculated, 258.0638 found.

(±)-1-Benzyl 4-(tert-butyl) 2-phenylpiperazine-1,4-dicarboxylate (129). A round-bottom flask was charged with tert-butyl 3-phenylpiperazine-1-carboxylate (0.29 g, 1.1 mmol, 1 eq), NaHCO3 (0.46 g, 5.5 mmol, 5 eq) in THF/H2O (8 mL, 1:1). The mixture was cooled to 0 °C and CbzCl (189 μL, 1.3 mmol, 1.2 eq) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The mixture was extracted with EtOAc (3 x 20 mL), the combined organic layers were washed with brine (50 mL), dried (Na2SO4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% → 40% EtOAc/pentane) affording the product (0.40 g, 1.0 mmol, 91%). TLC: Rf = 0.4 (20% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 7.55 – 7.04 (m, 1OH), 5.36 (br s, 1H), 5.27 – 5.12 (m, 2H), 4.50 (d, J = 13.9 Hz, 1H), 4.13 – 3.68 (m, 2H), 3.33 (dd, J = 14.0, 4.3 Hz, 1H), 3.19 – 2.79 (m, 2H), 1.42 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 155.77, 154.43, 138.40, 136.48, 128.66, 128.61, 128.21, 128.00, 127.39, 126.88, 80.32, 67.64, 54.15, 46.04, 42.81, 39.80, 28.42. HRMS [C32H33N2O4 + Na]+= 419.1941 calculated, 419.1934 found.

(±)-Benzyl 2-phenylpiperazine-1-carboxylate hydrochloride (130). A round-bottom flask was charged with Boc-protected amine 129 (103 mg, 0.26 mmol, 1 eq) and HCl (4 M solution in 1,4-dioxane, 1 mL, 4.0 mmol, 15.5 eq) and the reaction was stirred at rt. After 1 h the reaction was concentrated under reduced pressure to afford the product as the hydrochloride salt (87 mg, 0.26 mmol, 99%). TLC: Rf = 0.3 (50% EtOAc/pentane). 1H NMR (400 MHz, CDCl3) δ 10.24 (br s, 1H), 9.33 – 8.80 (m, 1H), 7.51 – 7.02 (m, 1OH), 5.55 (br s, 1H), 5.29 – 4.95 (m, 2H), 4.22 (d, J = 14.1 Hz, 1H), 3.99 – 3.77 (m, 1H), 3.49 – 3.22 (m, 3H), 3.06 (br s, 1H). 13C NMR (101 MHz, CDCl3) δ 155.26, 135.78, 135.54, 129.31, 128.64, 128.42, 128.28, 128.11, 126.34, 68.19, 51.77, 44.38, 42.59, 36.98.

References


**Supplementary Information**

**Supplementary Scheme 1.** Synthesis of pyrimidine regioisomer 4. Reagents and conditions: a) morpholine, DiPEA, MeOH, 0 °C, 5% (+ 89% regioisomer 28); b) N-methylphenethylamine, DiPEA, MeOH, 70 °C, 71%.

**Supplementary Scheme 2.** Synthesis of R_1 cyclopropylmethylamine analogue 5. Reagents and conditions: a) NaH, MeI, DMF, 0 °C to rt, 44%.

**Supplementary Scheme 3.** Synthesis of R_1 cyclopropylmethylamine analogues 18-20. Reagents and conditions: a) NaOH, THF, MeOH, H_2O, rt, 99%; b) N-methylphenethylamine, DiPEA, n-BuOH, 120 °C, 20%; c) EDC-HCl, HOBT, MeOH, DCM, rt, 62%; d) MeNH_2-HCl, PyBOP, DiPEA, DMF, 50%.
**Supplementary Scheme 4.** Synthesis of R₁ cyclopropylmethylamine analogue 22. Reagents and conditions: a) NaOtBu, MeI, DMF, 0 °C to rt, 30%.

**Supplementary Scheme 5.** Synthesis of R₁ cyclopropylmethylamine analogue 27. Reagents and conditions: a) 2-bromocyclopropylethanone, Cs₂CO₃, DMF, rt, 53%; b) NH₄OAc, xylene, 140 °C, 6%.

**Supplementary Scheme 6.** Synthesis of R₂ 3-phenylpiperazine analogues 65-67. Reagents and conditions: a) CbzCl, NaHCO₃, THF, H₂O, 0 °C to rt, 91%; b) 4 M HCl, 1,4-dioxane, rt, 99%; c) 130, DiPEA, n-BuOH, 120 °C, 99%; d) Pd/C, H₂, MeOH, rt, 90%; e) BnBr, DiPEA, CH₃CN, rt, 73%.
Supplementary Scheme 7. Synthesis of R₃ morpholine analogue 74-76. Reagents and conditions: a) Pd/C, H₂, MeOH, AcOH, rt, 64%; b) Ac₂O, DiPEA, DCM, rt, 79%; c) BzCl, Et₃N, DCM, rt, 71%.

Supplementary Scheme 8. Synthesis of R₃ morpholine analogue 89. Reagents and conditions: a) NaH, Mel, DMF, 0 °C to rt, 44%.