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Illuminating N-acylethanolamine biosynthesis with new chemical tools

Mock, E.D.

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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 (CB₁ and CB₂), 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.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.

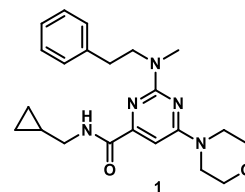


Figure 1. Structure of HTS lead hit **1**.

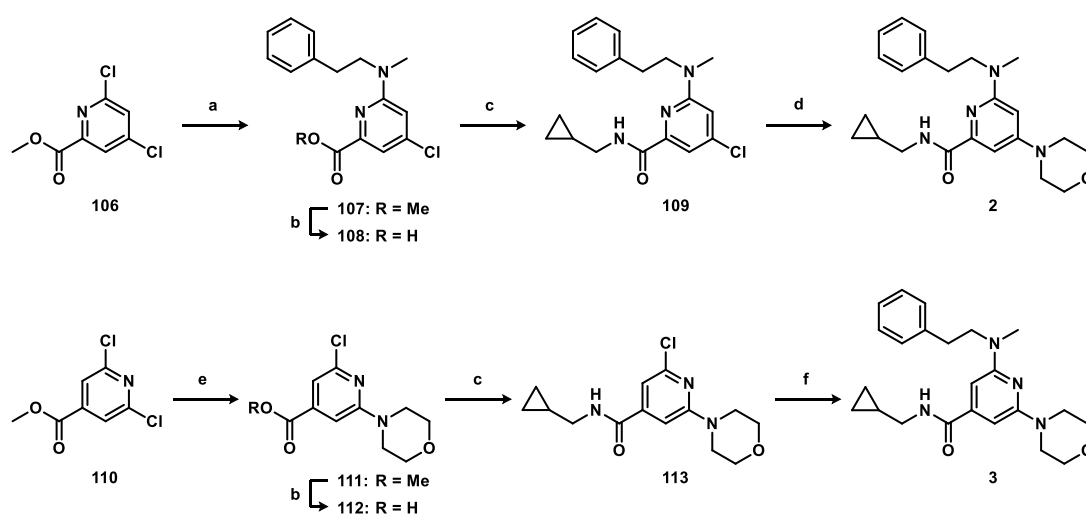
3.2 Results

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**.

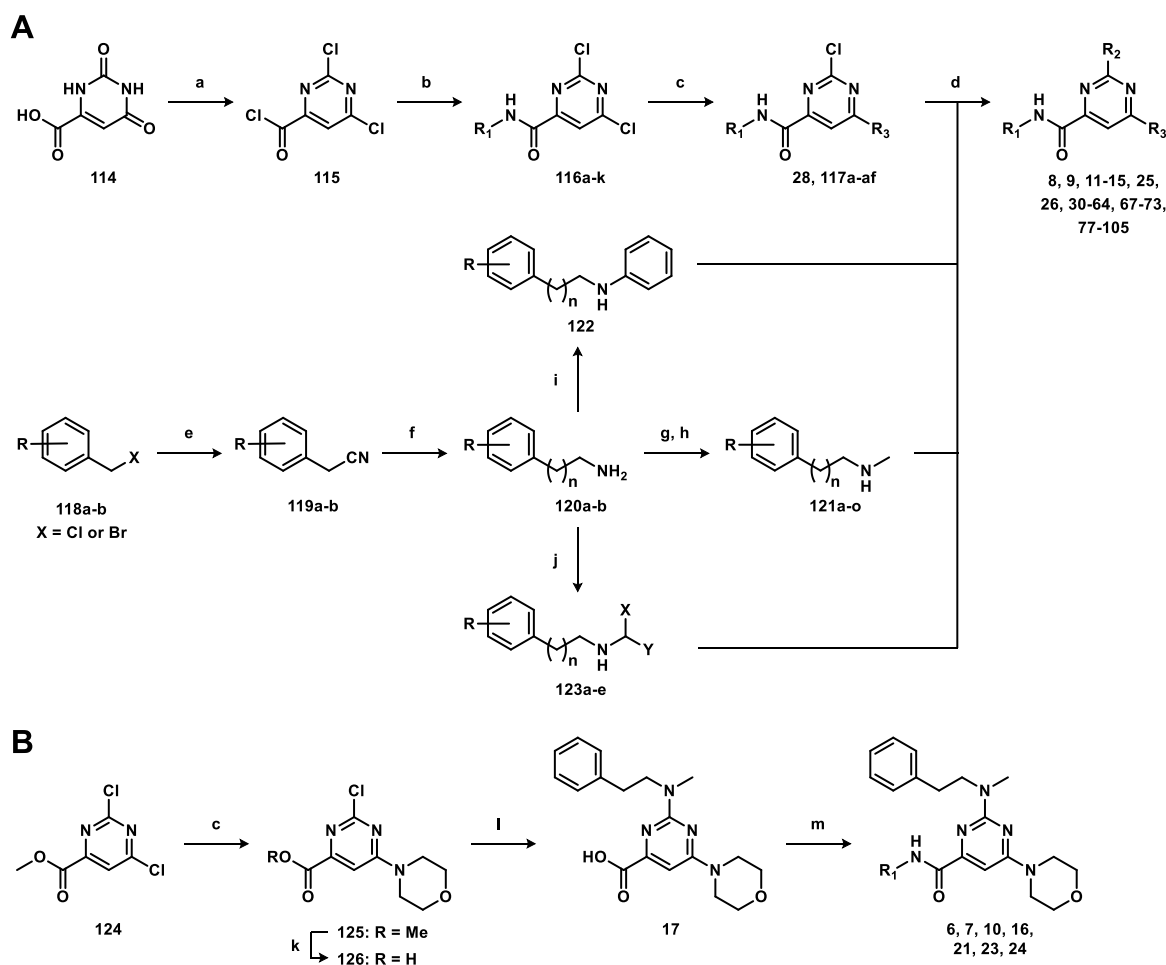
The influence of the nitrogen atoms in the pyrimidyl ring was investigated with pyridyl analogues **2** and **3** (Scheme 1). The synthesis of compound **2** commenced with the regioselective nucleophilic aromatic substitution (S_NAr) of dichloride **106** with *N*-methylphenethylamine, which gave **107** (confirmed by 1H , ^{13}C -HMBC and 1H -NOESY 2D NMR). Subsequent ester hydrolysis and amide coupling afforded **109**, which was converted to **2** with morpholine using Buchwald-Hartwig amination conditions.¹² Isomer **3** was synthesized in four steps from symmetric dichloride **110**: S_NAr 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 $^1\text{H-NOESY}$ 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 benzylic 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 LiAlH_4 reduction, giving the *N*-methylphenethylamines **121a-o**. Alternatively, phenethylamine was converted to the *N*-phenyl analogue **122** via Chan-Lam coupling¹³ 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 1. Synthesis of pyridyl analogues **2** and **3**. Reagents and conditions: a) *N*-methylphenethylamine, DiPEA, MeOH, rt, 40%; b) NaOH, THF, H₂O, rt, for **108**: 90%, for **112**: 99%; c) cyclopropylmethanamine, EDC-HCl, HOBT, DCM, rt, for **109**: 24%, for **113**: 77%; d) morpholine, RuPhos-Pd-G3, NaOtBu, THF, toluene, 110 °C, 37%; e) morpholine, K₂CO₃, CH₃CN, reflux, 65%; f) *N*-methylphenethylamine, RuPhos-Pd-G3, NaOtBu, THF, toluene, 110 °C, 41%.

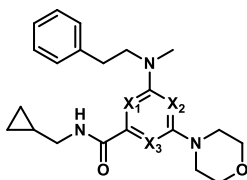


Scheme 2. A) General synthetic route for compound **1** analogues. B) Alternative synthetic route for amide analogues. Reagents and conditions: a) POCl_3 , DMF, reflux, 60%; b) R_1NH_2 , Et_3N , DCM, -78°C to 0°C , 78% – 99%; c) (cyclo)alkylNH, DiPEA, MeOH, 0°C , 32% – 99%, or (hetero)arylOH or heteroarylNH, K_2CO_3 , 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, H_2O , reflux, 84% – 99%; f) H_2 , Pd/C, HCl, EtOH, rt, 98% – 99%; g) methyl chloroformate, DiPEA, DCM, 0°C to rt; h) LiAlH_4 , THF, 0°C to reflux, 40% – 94% over 2 steps; i) phenylboronic acid, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, 4 \AA MS, O_2 , DCE, rt, 32%; j) aldehyde or ketone, $\text{NaB}(\text{OAc})_3\text{H}$, AcOH, DCM, rt, 18% – 63%. k) NaOH, THF, MeOH, H_2O , rt, 99%; l) *N*-methylphenethylamine, DiPEA, *n*-BuOH, 120°C , 51%; m) R_1NH_2 , PyBOP, DiPEA, DMF, 0°C to rt, 43% – 55%.

A fluorescent NAPE-PLD activity assay was performed to measure the half maximum inhibitory concentration (IC_{50}) of inhibitors (**2-105**), as described previously (Chapter 2). The data are reported in Tables 1-7 as the $\text{pIC}_{50} \pm \text{SEM}$ ($N = 2$, $n = 2$). 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 X_2 -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**.



ID	X_1	X_2	X_3	$pIC_{50} \pm SEM$	$cLogP^a$
1	N	N	CH	6.09 ± 0.04	3.84
2	N	CH	CH	4.98 ± 0.03	4.25
3	CH	N	CH	5.84 ± 0.03	3.90
4	CH	N	N	5.39 ± 0.11	3.84

^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 π -character compared to the cyclopropyl moiety.¹⁴ 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).

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**.

ID	R ₁ :	pIC ₅₀ ± SEM	cLogP ^a	ID	R ₁ :	pIC ₅₀ ± SEM	cLogP ^a
1		6.09 ± 0.04	3.84	17		<4.3	3.29
5		<4.3	2.71	18		<4.3	2.66
6		5.43 ± 0.07	3.45	19		6.08 ± 0.03	2.87
7		4.75 ± 0.08	2.52	20		4.77 ± 0.06	2.01
8		4.87 ± 0.07	2.87	21		5.30 ± 0.04	2.31
9		5.34 ± 0.11	3.40	22		4.96 ± 0.03	3.07
10		5.74 ± 0.09	3.93	23		4.51 ± 0.02	2.27
11		5.17 ± 0.08	4.45	24		4.49 ± 0.03	3.18
12		4.46 ± 0.10	5.51	25		4.63 ± 0.07	4.84
13		5.15 ± 0.09	4.32	26		<4.3	6.72
14		4.67 ± 0.08	4.72	27		4.39 ± 0.05	3.94
15		6.04 ± 0.06	3.29				
16		4.48 ± 0.07	3.66				

^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 3. Structure-activity relationship analysis of *N*-methylphenethylamine analogues **28-50**.

ID	R ₂ :	pIC ₅₀ ± SEM	cLogP ^a	ID	R ₂ :	pIC ₅₀ ± SEM	cLogP ^a
1		6.09 ± 0.04	3.84	39		6.05 ± 0.07	4.29
28		<4.3	1.58	40		5.46 ± 0.07	3.76
29		<4.3	0.84	41		6.11 ± 0.04	3.76
30		5.56 ± 0.06	3.76	42		5.21 ± 0.08	4.72
31		5.04 ± 0.08	3.51	43		5.52 ± 0.10	5.94
32		4.64 ± 0.10	3.11	44		5.46 ± 0.08	5.94
33		5.50 ± 0.07	4.22	45		6.22 ± 0.06	5.94
34		5.00 ± 0.04	4.75	46		6.31 ± 0.10	5.43
35		5.20 ± 0.08	4.55	47		4.94 ± 0.07	2.34
36		5.61 ± 0.14	4.55	48		4.97 ± 0.10	2.34
37		6.01 ± 0.07	4.55	49		4.89 ± 0.04	2.34
38		5.74 ± 0.07	4.34	50		5.97 ± 0.03	3.49

^a 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**.

ID	R ₂ :	pIC ₅₀ ± SEM	cLogP ^a
1		6.09 ± 0.04	3.84
51		6.19 ± 0.08	4.37
52		6.55 ± 0.07	4.68
53		5.96 ± 0.07	4.42
54		5.95 ± 0.09	5.61
55		6.13 ± 0.06	4.50
56		6.28 ± 0.16	5.79

^a cLogP was calculated using Chemdraw 15.

Table 5. Structure-activity relationship analysis of *N*-methylphenethylamine analogues **57-67**.

ID	R ₂ :	pIC ₅₀ ± SEM	cLogP ^a	ID	R ₂ :	pIC ₅₀ ± SEM	cLogP ^a
1		6.09 ± 0.04	3.84	62		4.60 ± 0.10	5.59
57		5.65 ± 0.09	3.08	63		5.59 ± 0.09	3.76
58		5.66 ± 0.10	3.42	64		5.91 ± 0.03	2.59
59		6.42 ± 0.11	3.97	65		5.11 ± 0.06	2.58
60		6.42 ± 0.09	3.94	66		6.00 ± 0.12	5.02
61		6.13 ± 0.06	4.50	67		5.49 ± 0.11	5.49

^a cLogP was calculated using Chemdraw 15.

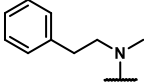

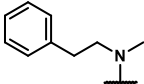

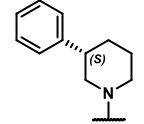

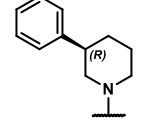

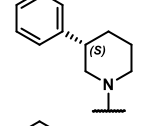

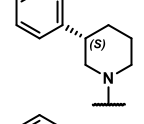
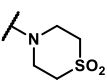
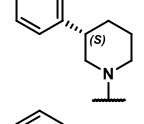
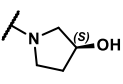
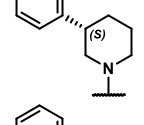
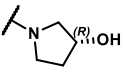
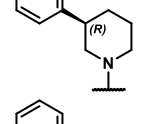
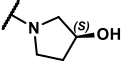
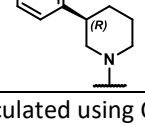
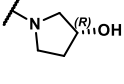
To study the SAR of the R₃-substituent, inhibitors **68-97** were evaluated (Table 6). Substitution of the morpholine for a more hydrophobic piperidine (**68**) was allowed, while the 3,3-difluoropiperidine **69** increased the potency two-fold. The 4-position of the morpholine ring was less favorable for substitution (compounds **70-77**). Replacing the morpholine with a dimethylamine **78** increased the activity two-fold, suggesting that the morpholine **1** 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-hydroxypyrrolidine (**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.

Table 6. Structure-activity relationship analysis of morpholine analogues **68-97**.

ID	R ₃ :	pIC ₅₀ ± SEM	cLogP ^a	ID	R ₃ :	pIC ₅₀ ± SEM	cLogP ^a
1		6.09 ± 0.04	3.84	83		5.78 ± 0.03	3.68
68		6.19 ± 0.08	5.22	84		6.65 ± 0.09	4.66
69		6.41 ± 0.12	5.51	85		5.93 ± 0.10	4.95
70		5.05 ± 0.08	4.61	86		6.65 ± 0.04	3.33
71		5.58 ± 0.08	4.67	87		6.52 ± 0.03	3.33
72		<4.3	2.87	88		6.63 ± 0.05	3.33
73		5.80 ± 0.04	4.40	89		6.15 ± 0.11	4.09
74		5.27 ± 0.07	3.83	90		5.02 ± 0.03	4.28
75		5.92 ± 0.05	4.55	91		5.85 ± 0.08	6.22
76		5.11 ± 0.09	5.01	92		5.96 ± 0.05	6.32
77		4.89 ± 0.09	6.74	93		6.81 ± 0.06	6.65
78		6.54 ± 0.05	4.55	94		5.92 ± 0.08	4.09
79		6.07 ± 0.06	4.47	95		5.65 ± 0.04	3.64
80		6.00 ± 0.03	3.81	96		4.95 ± 0.11	5.74
81		6.30 ± 0.10	5.61	97		5.28 ± 0.05	4.25
82		6.37 ± 0.05	4.10				

^a cLogP was calculated using Chemdraw 15.

Table 7. Structure-activity relationship analysis of optimized analogues **98-105**.

ID	R ₂ :	R ₃ :	pIC ₅₀ ± SEM		cLogP ^a	LipE ^b (hNAPE-PLD)
			hNAPE-PLD	mNAPE-PLD		
1			6.09 ± 0.04	5.48 ± 0.04	3.84	2.31
78			6.54 ± 0.05	n.d.	4.55	1.99
98			6.95 ± 0.10	6.41 ± 0.10	4.68	2.26
99			6.39 ± 0.11	n.d.	4.68	1.71
100			6.68 ± 0.09	6.24 ± 0.09	3.97	2.70
101			4.76 ± 0.08	5.02 ± 0.08	3.01	1.75
102 (LEI-401)			7.14 ± 0.04	6.35 ± 0.04	3.46	3.68
103			6.96 ± 0.04	6.42 ± 0.04	3.46	3.50
104			6.60 ± 0.05	5.74 ± 0.05	3.46	3.13
105			6.49 ± 0.04	5.90 ± 0.04	3.46	3.02

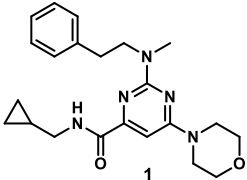
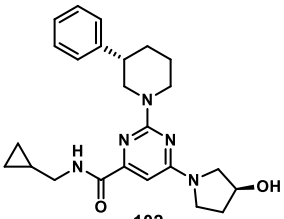
^a cLogP was calculated using Chemdraw 15; ^b Lipophilic efficiency (LipE) = pIC₅₀ – cLogP.

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-hydroxypyrrolidine afforded the most potent compound (**102**, $pIC_{50} = 7.14 \pm 0.04$), 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 ($pIC_{50} = 6.35 \pm 0.04$) 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)**.

Compound	pIC_{50} \pm SEM	K_i (μ M) 95% CI ^a	cLogP ^b	LipE ^c	MW ^d (Da)	tPSA ^b (\AA^2)	HBD ^e	HBA ^f	RB ^g
 1	6.09 \pm 0.04	0.30 0.22-0.38	3.84	2.31	396	69.5	1	6	9
 102 (LEI-401)	7.14 \pm 0.04	0.027 0.021- 0.033	3.46	3.68	422	80.5	2	6	7

^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 Å²; RB < 10).^{15,16} Due to a polar surface area below 90 Å², **LEI-401** is expected to cross the blood-brain barrier (BBB), which will allow targeting of NAPE-PLD in the central nervous system.¹⁷

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.

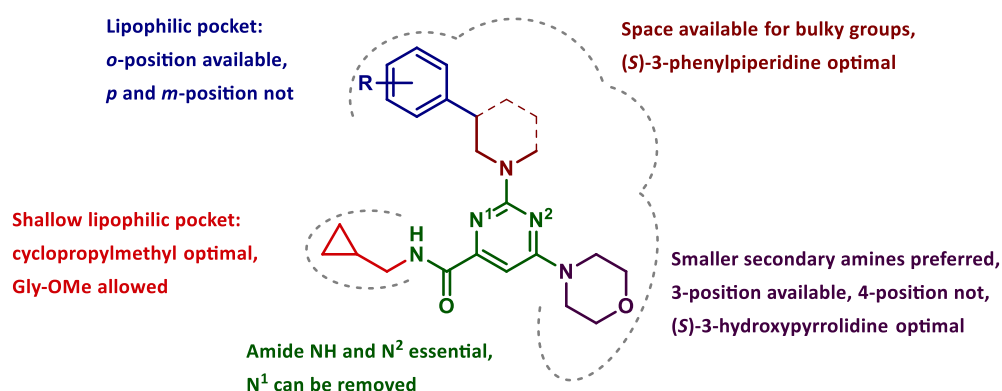


Figure 2. Structure activity map for the pyrimidine-4-carboxamide NAPE-PLD inhibitor library.

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

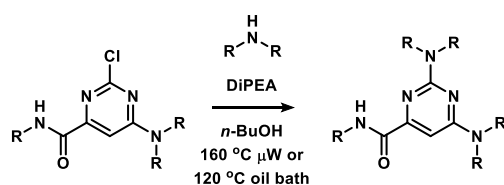
The NAPE-PLD activity assay was performed as described in Chapter 2.

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.

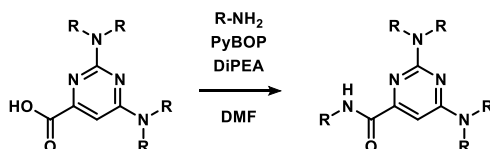
General procedure A:



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

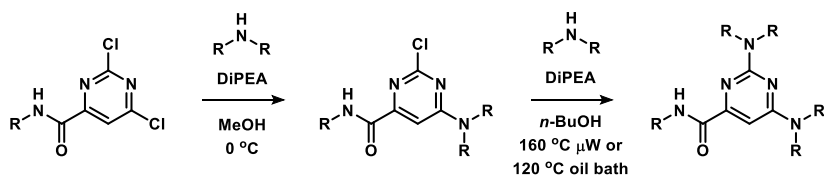
gel column chromatography affording the product, or alternatively by HPLC-MS purification yielding the TFA salt. The free base was generated by dissolving the TFA salt in EtOAc, followed by washing with sat. aq. NaHCO₃ (2x). The organic layer was dried (Na₂SO₄), filtered and concentrated under reduced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

General procedure B:



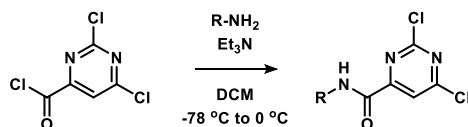
A round-bottom flask was charged with carboxylic acid (1 eq) and dissolved in dry DMF (0.2 M). PyBOP (1.2-1.5 eq), DiPEA (3-5 eq) and the appropriate amine (1.2-5 eq) were added and the mixture was stirred overnight at rt. Work-up involved dilution with EtOAc, washing with H₂O (1x) and brine (2x), drying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

General procedure C:



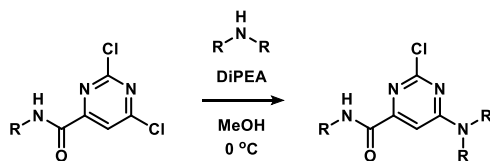
A microwave vial was charged with the dichloropyrimidine (1 eq) and dry MeOH (0.1 M) and cooled to 0 °C. DiPEA (1.5-2.5 eq) and the appropriate amine (1.05 eq) were added and the mixture was stirred for 1-2 h at 0 °C. The solvents were evaporated under reduced pressure. The vial was charged with *n*-BuOH (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:



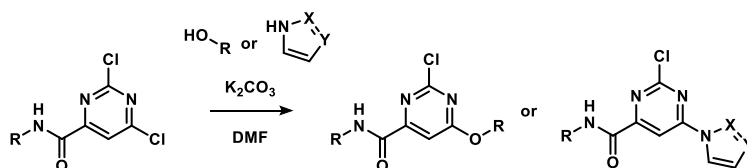
A round-bottom flask with dry DCM (0.1 M) was charged via syringe with 2,6-dichloropyrimidine-4-carbonyl chloride (1 eq) and cooled to -78 °C. Et₃N (1.3-2.3 eq) and the appropriate amine (1.025 eq) were added and the mixture was stirred, while letting the acetone bath warm up to 0 °C (3-4 h). The mixture 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:



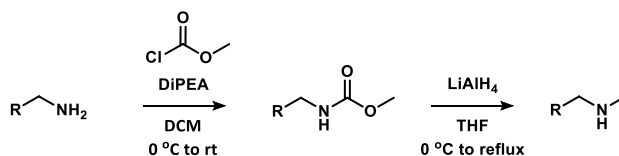
A round-bottom flask was charged with the dichloropyrimidine (1 eq) and dry MeOH (0.1 M) and cooled to 0 °C. DiPEA (1.5-2.5 eq) and the appropriate amine (1.05 eq) were added and the mixture was stirred for 1-2 h at 0 °C. The solvents were evaporated under reduced pressure and the crude material was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

General procedure F:

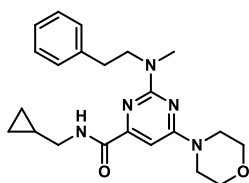


A round-bottom flask was charged with the dichloropyrimidine (1 eq) and dry DMF (0.1 M). K_2CO_3 (1.5 eq) and the appropriate phenol or heteroaryl (1.05 eq) were added and the mixture was stirred overnight at rt. H_2O was added and the mixture was extracted with EtOAc (3x). The organic layers were combined and washed with brine (2x), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, affording the pure product.

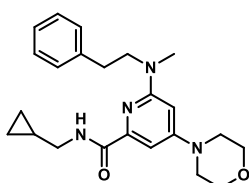
General procedure G:



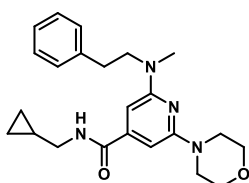
Carbamoylation: a round-bottom flask was charged with the primary amine (1 eq) and dry DCM (0.2 M). The solution was cooled to 0 °C and DiPEA (2 eq) and methylchloroformate (1.5 eq) were added. The reaction was stirred and allowed to warm up to room temperature over 1-2 h. Then the mixture was diluted 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_2O (3x) and cooling to 0 °C, followed by the sequential addition of water (1 μ L for every 1 mg of $LiAlH_4$), $NaOH$ (aq) 15% (1 μ L for every 1 mg of $LiAlH_4$) and water (3 μ L 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.



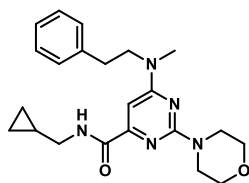
N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-morpholino-pyrimidine-4-carboxamide (1). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (59 mg, 0.20 mmol, 1 eq), *N*-methylphenethylamine HBr salt (66 mg, 0.30 mmol, 1.5 eq) and DiPEA (140 μ L, 0.80 mmol, 4 eq). Total heating time: 8 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (40 mg, 0.10 mmol, 50%). TLC: R_f = 0.3 (40% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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, 35.70, 33.93, 10.88, 3.48. HRMS [$\text{C}_{22}\text{H}_{29}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 396.2394 calculated, 396.2387 found.



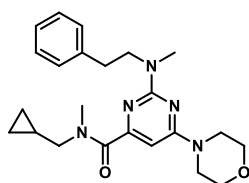
N-(Cyclopropylmethyl)-6-(methyl(phenethyl)amino)-4-morpholino-picolinamide (2). A microwave vial with a magnetic stir bar under N_2 was charged with 4-chloropyridine **109** (30 mg, 87 μ mol, 1 eq), morpholine (9 μ L, 0.10 mmol, 1.2 eq) and dry toluene (87 μ L). The vial was capped and the solution purged with N_2 . This was followed by the addition of RuPhosPd G3 (0.01 M THF solution, 237 μ L, 2.37 μ mol, 0.027 eq) and NaOtBu (2 M THF solution, 97 μ L, 0.19 mmol, 2.2 eq) and the mixture was purged again with N_2 and stirred in a preheated oil bath at 110 $^{\circ}$ 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% \rightarrow 60% EtOAc/pentane) affording the product (5 mg, 13 μ mol, 15%). TLC: R_f = 0.2 (30% EtOAc/pentane) and recovered starting material (11 mg, 32 μ mol, 37%). ^1H NMR (500 MHz, CDCl_3) 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). ^{13}C NMR (126 MHz, CDCl_3) 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 [$\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_2 + \text{H}$] $^+$: 395.2442 calculated, 395.2438 found.



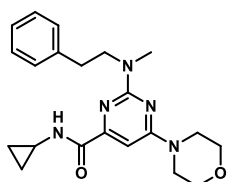
N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-morpholino-isonicotinamide (3). A microwave vial with a magnetic stir bar under N_2 was charged with 2-chloropyridine **113** (31 mg, 0.10 mmol, 1 eq), *N*-methylphenethylamine HBr salt (28 mg, 0.13 mmol, 1.3 eq) and dry toluene (0.1 mL). The vial was capped and the solution purged with N_2 . This was followed by the addition of RuPhosPd G3 (0.01 M THF solution, 100 μ L, 1 μ mol, 0.01 eq) and NaOtBu (2 M THF solution, 120 μ L, 0.24 mmol, 2.4 eq) and the mixture was purged again with N_2 and stirred in a preheated oil bath at 110 $^{\circ}$ 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% \rightarrow 55% $\text{CH}_3\text{CN}/\text{H}_2\text{O} + 0.2\%$ TFA, RT 12.3 min) afforded the product (16 mg, 40 μ mol, 41%). TLC: R_f = 0.5 (60% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_2 + \text{H}$] $^+$: 395.2442 calculated, 395.2434 found.



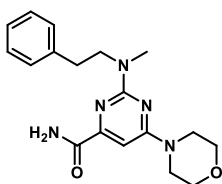
N-(Cyclopropylmethyl)-6-(methyl(phenethyl)amino)-2-morpholinopyrimidine-4-carboxamide (4). The title compound was prepared according to general procedure A using 4-chloropyrimidine **127** (21 mg, 70 μmol , 1.0 eq), *N*-methylphenethylamine HBr salt (16 mg, 70 μmol , 1 eq) and DiPEA (36.6 μL , 0.21 mmol, 3 eq) in MeOH. Total heating time: 6 h at 70 $^{\circ}\text{C}$. Column chromatography (30% \rightarrow 60% EtOAc/pentane) afforded the product (20 mg, 50 μmol , 71%). TLC: R_f = 0.4 (30% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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, 10H), 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). ^{13}C NMR (101 MHz, CDCl_3) δ 162.97, 159.05, 128.91, 128.82, 126.75, 93.22, 66.81, 44.92, 44.69, 10.71, 3.65. HRMS [$\text{C}_{22}\text{H}_{29}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 396.2394 calculated, 396.2385 found.



N-(Cyclopropylmethyl)-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 $^{\circ}\text{C}$. 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 H_2O (20 mL) followed by extraction with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 50 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50 \rightarrow 80% EtOAc/pentane) affording the product (18 mg, 40 μmol , 44%). TLC: R_f = 0.3 (60% EtOAc/pentane). ^1H NMR analysis showed two rotamers in 6:4 ratio in CDCl_3 at 298 K, which was confirmed by high temperature ^1H NMR experiments. ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{23}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 410.2551 calculated, 410.2545 found.

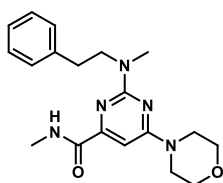


N-Cyclopropyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (6). The title compound was prepared according to general procedure B using carboxylic acid **17** (34 mg, 0.10 mmol, 1 eq), DiPEA (52 μL , 0.30 mmol, 3 eq), PyBOP (78 mg, 0.12 mmol, 1.2 eq) and cyclopropylamine (8.3 μL , 0.12 mmol, 1.2 eq). Column chromatography (50% \rightarrow 80% EtOAc/pentane) afforded the product (8 mg, 21 μmol , 21%). TLC: R_f = 0.3 (60% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{21}\text{H}_{27}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 382.2238 calculated, 382.2241 found.

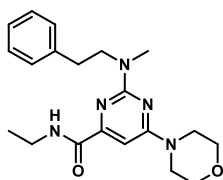


2-(Methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (7). The title compound was prepared according to general procedure B using carboxylic acid **17** (27 mg, 79 μmol , 1 eq), DiPEA (56 μL , 0.32 mmol, 4 eq), PyBOP (62 mg, 0.12 mmol, 1.5 eq), HOBt (16 mg, 0.12 mmol, 1.5 eq) and ammonium chloride (15 mg, 0.32 mmol, 3.5 eq). Column chromatography (80% \rightarrow 100% EtOAc/pentane) afforded the product (20 mg, 59 μmol , 75%). TLC: R_f = 0.5 (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 167.46, 163.96,

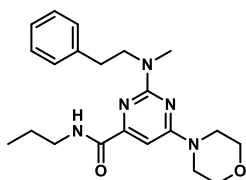
161.04, 156.27, 139.93, 128.86, 128.62, 126.31, 90.17, 66.74, 51.60, 44.50, 35.77, 33.97. HRMS $[C_{18}H_{23}N_5O_2 + H]^+$: 342.1925 calculated, 342.1934 found.



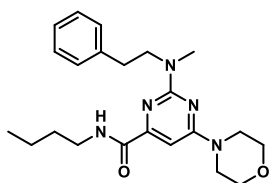
N-Methyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide TFA salt (8). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117a** (8.5:1 mixture of regioisomers) (51 mg, 0.20 mmol, 1 eq), DiPEA (139 μ L, 0.80 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (65 mg, 0.30 mmol, 1.5 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Purification by preparative HPLC (C18 reverse phase, 25% to 35% CH_3CN/H_2O + 0.2% TFA, RT = 8.77) afforded the product as the TFA salt (83 mg, 0.18 mmol, 88%) TLC: R_f = 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). ^{13}C 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 $[C_{19}H_{25}N_5O_2 + H]^+$: 356.2081 calculated, 356.2079 found.



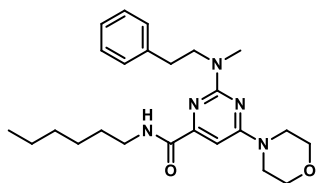
N-Ethyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (9). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117b** (54 mg, 0.20 mmol, 1 eq), DiPEA (139 μ L, 0.80 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (65 mg, 0.30 mmol, 1.5 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (50% -> 70% EtOAc/pentane) afforded the product (64 mg, 0.17 mmol, 86%). TLC: R_f = 0.3 (50% EtOAc/pentane). 1H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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 $[C_{20}H_{27}N_5O_2 + H]^+$: 370.2238 calculated, 370.2236 found.



N-Propyl-2-(methyl(phenethyl)amino)-6-morpholino-pyrimidine-4-carboxamide (10). The title compound was prepared according to general procedure B using carboxylic acid **17** (23 mg, 67 μ mol, 1 eq), DiPEA (60 μ L, 0.34 mmol, 3 eq), PyBOP (52 mg, 0.10 mmol, 1.5 eq) and propylamine HCl salt (8 mg, 80 μ mol, 1.2 eq). Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (17 mg, 44 μ mol, 66%). TLC: R_f = 0.3 (50% EtOAc/pentane). 1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $[C_{21}H_{29}N_5O_2 + H]^+$: 384.2394 calculated, 384.2394 found.

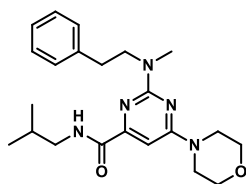


N-Butyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (11). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117c** (30 mg, 0.10 mmol, 1 eq), DiPEA (70 μ L, 0.40 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 45 h at 120 $^{\circ}$ C. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (29 mg, 73 μ mol, 73%). TLC: R_f = 0.6 (50% EtOAc/pentane). 1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $[C_{22}H_{31}N_5O_2 + H]^+$: 398.2551 calculated, 398.2560 found.



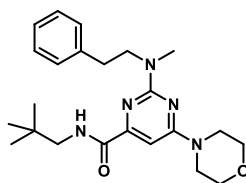
N-Hexyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (12). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117d** (33 mg, 0.10 mmol, 1 eq), DiPEA (70 μ L, 0.40 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 3 d at 120 $^{\circ}$ C. Column chromatography (40% \rightarrow 50% EtOAc/ pentane) afforded the product (36 mg, 85 μ mol, 85%).

TLC: R_f = 0.6 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{24}\text{H}_{35}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 426.2864 calculated, 426.2857 found.



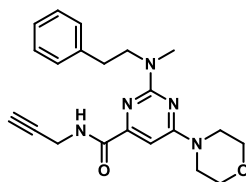
N-Isobutyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (13). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117e** (30 mg, 0.10 mmol, 1 eq), DiPEA (70 μ L, 0.40 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 3 d at 120 $^{\circ}$ C. Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (29 mg, 73 μ mol, 73%). TLC: R_f = 0.7 (50% EtOAc/pentane). ^1H NMR

(400 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{22}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 398.2551 calculated, 398.2552 found.



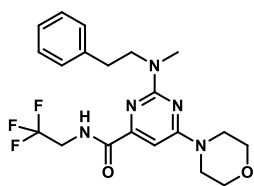
N-Neopentyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (14). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117f** (31 mg, 0.10 mmol, 1 eq), DiPEA (70 μ L, 0.40 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 3 d at 120 $^{\circ}$ C. Column chromatography (20% \rightarrow 50% EtOAc/pentane) afforded the product (30 mg, 73 μ mol, 73%). TLC: R_f = 0.6 (40%

EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{23}\text{H}_{33}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 412.2707 calculated, 412.2710 found.

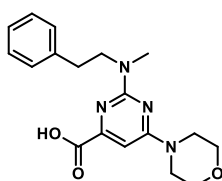


2-(Methyl(phenethyl)amino)-6-morpholino-N-(prop-2-yn-1-yl)pyrimidine-4-carboxamide (15). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117g** (42 mg, 0.15 mmol, 1 eq), DiPEA (105 μ L, 0.60 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (49 mg, 0.225 mmol, 1.5 eq). Total heating time: 45 h at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 50% EtOAc/pentane) afforded the product (43 mg, 0.11 mmol, 73%). TLC: R_f = 0.7 (50%

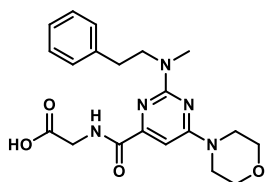
EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 8.03 (br s, 1H), 7.33 – 7.25 (m, 2H), 7.25 – 7.17 (m, 3H), 6.69 (s, 1H), 4.22 (dd, J = 5.6, 2.5 Hz, 2H), 3.86 – 3.72 (m, 6H), 3.72 – 3.60 (m, 4H), 3.11 (s, 3H), 2.96 – 2.85 (m, 2H), 2.29 (t, J = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.60, 163.89, 160.88, 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 [$\text{C}_{21}\text{H}_{25}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 380.2081 calculated, 380.2089 found.



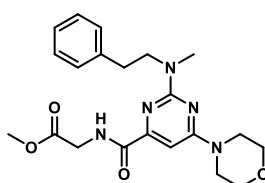
***N*-(2,2-Trifluoroethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (16)**. The title compound was prepared according to general procedure B using carboxylic acid **17** (25 mg, 73 μ mol, 1 eq), DiPEA (51 μ L, 0.29 mmol, 4 eq), PyBOP (57 mg, 0.11 mmol, 1.5 eq) and 2,2,2-trifluoroethylamine HCl salt (12 mg, 88 μ mol, 1.2 eq). Column chromatography (30% \rightarrow 40% EtOAc/pentane) afforded the product (17 mg, 40 μ mol, 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). ^{13}C NMR (126 MHz, CDCl_3) δ 165.31, 163.88, 160.92, 155.42, 139.85, 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 [$\text{C}_{20}\text{H}_{24}\text{F}_3\text{N}_5\text{O}_2 + \text{H}$] $^+$: 424.1955 calculated, 424.1958 found.



2-(Methyl(phenethyl)amino)-6-morpholinopyrimidine-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 together with 0.75 mL H_2O . The reaction was stirred overnight at rt after which the solvents were evaporated yielding the product as the Na^+ salt (**126**) which was used without further purification (779 mg, 2.64 mmol, quant.). *$S_N\text{Ar}$ reaction*: 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 μ L, 1.3 mmol, 1.3 eq). Total heating time: 6 d at 120 $^\circ\text{C}$. Column chromatography (2.5% \rightarrow 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). ^{13}C 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 [$\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_3 + \text{H}$] $^+$: 343.1765 calculated, 343.1772 found.

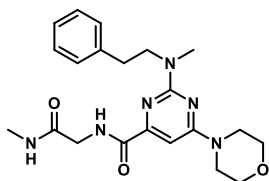


2-(Methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carbonyl)glycine (18). The title compound was prepared according to general procedure A using 2-chloropyrimidine **128** (150 mg, 0.50 mmol, 1 eq), DiPEA (0.43 mL, 2.5 mmol, 5 eq) and *N*-methylphenethylamine HBr salt (162 mg, 0.76 mmol, 1.5 eq). Total heating time: 6 h at 160 $^\circ\text{C}$ with μW irradiation. Purification by HPLC (C18 reverse phase, 10% to 70% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 50 mM NH_4HCO_3) afforded the product (40 mg, 0.10 mmol, 20%). TLC: R_f = 0.3 (5% MeOH/DCM). ^1H NMR (500 MHz, MeOD + CDCl_3) δ 7.32 – 7.14 (m, 5H), 6.65 (s, 1H), 4.01 (s, 2H), 3.83 (t, J = 7.3 Hz, 2H), 3.80 – 3.75 (m, 4H), 3.73 – 3.60 (m, 4H), 3.11 (s, 3H), 2.91 (t, J = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, MeOD + CDCl_3) δ 173.63, 164.96, 163.55, 160.59, 155.89, 139.54, 128.50, 128.00, 125.67, 89.33, 66.26, 51.10, 49.06, 43.96, 42.64, 39.58, 35.05, 33.47, 20.71. HRMS [$\text{C}_{20}\text{H}_{25}\text{N}_5\text{O}_4 + \text{H}$] $^+$: 400.1979 calculated, 400.1984 found.

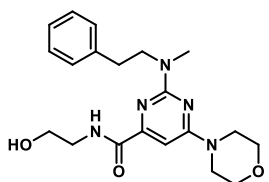


Methyl 2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carbonyl)glycinate (19). A round-bottom flask was charged with carboxylic acid **18** (28 mg, 70 μ mol, 1 eq) in dry DCM (1.5 mL). This was followed by addition of HOBT (15 mg, 0.11 mmol, 1.5 eq), EDC-HCl (20 mg, 0.11 mmol, 1.5 eq). The reaction was stirred for 1 h at rt after which MeOH (11 μ L, 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% \rightarrow 80% EtOAc/pentane) affording the product (18 mg, 44 μ mol, 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,

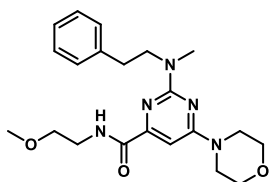
3H), 2.96 – 2.85 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.25, 165.14, 163.91, 160.92, 155.99, 139.96, 128.98, 128.58, 126.27, 90.13, 66.75, 52.52, 51.68, 44.51, 41.37, 35.79, 34.01. HRMS [$\text{C}_{21}\text{H}_{27}\text{N}_5\text{O}_4 + \text{H}$] $^+$: 414.2136 calculated, 414.2144 found.



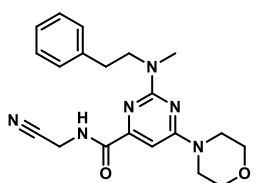
***N*-(2-(Methylamino)-2-oxoethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (20).** The title compound was prepared according to general procedure B using carboxylic acid **18** (12 mg, 30 μmol , 1 eq), DiPEA (21 μL , 120 μmol , 4 eq), PyBOP (19 mg, 45 μmol , 1.5 eq) and methylamine HCl salt (3 mg, 36 μmol , 1.2 eq). Column chromatography (2.5% \rightarrow 10% MeOH/DCM) afforded the product (6 mg, 15 μmol , 50%). TLC: R_f = 0.4 (5% MeOH/DCM). ^1H 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 [$\text{C}_{21}\text{H}_{28}\text{N}_6\text{O}_3 + \text{H}$] $^+$: 413.2296 calculated, 413.2294 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% \rightarrow 100% EtOAc/pentane to 5% MeOH/EtOAc) afforded the product (25 mg, 65 μmol , 59%). TLC: R_f = 0.3 (80% EtOAc/pentane). ^1H 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 [$\text{C}_{20}\text{H}_{27}\text{N}_5\text{O}_3 + \text{H}$] $^+$: 386.2187 calculated, 386.2191 found.

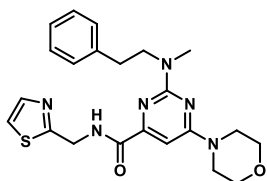


***N*-(2-Methoxyethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (22).** A round-bottom flask was charged with alcohol **21** (17 mg, 44 μmol , 1 eq) in dry DMF (1 mL) and cooled to 0 $^\circ\text{C}$. NaOtBu (2 M in THF, 33 μL , 66 μmol , 1.5 eq) and methyl iodide (3.1 μL , 49 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_2O (1 x 25 mL) and brine (2 x 25 mL), drying (Na_2SO_4), filtering and concentration under reduced pressure. The residue was purified by silica gel column chromatography (70 \rightarrow 80% EtOAc/pentane) affording the product (5 mg, 13 μmol , 30%). TLC: R_f = 0.4 (80% EtOAc/pentane). ^1H 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 [$\text{C}_{21}\text{H}_{29}\text{N}_5\text{O}_3 + \text{H}$] $^+$: 400.2343 calculated, 400.2345 found.

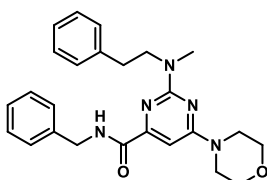


***N*-(Cyanomethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (23).** The title compound was prepared according to general procedure B using carboxylic acid **17** (21 mg, 61 μmol , 1 eq), DiPEA (53 μL , 0.31 mmol, 5 eq), PyBOP (48 mg, 92 μmol , 1.5 eq) and aminoacetonitrile bisulfate (11 mg, 73 μmol , 1.2 eq). Column chromatography (50% \rightarrow 70% EtOAc/pentane) afforded the product (10 mg, 26 μmol , 43%). TLC: R_f = 0.6 (60% EtOAc/pentane). ^1H 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 =

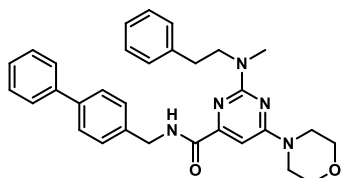
6.1 Hz, 2H), 3.86 – 3.79 (m, 2H), 3.79 – 3.74 (m, 4H), 3.66 (br s, 4H), 3.10 (s, 3H), 2.95 – 2.84 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 165.12, 163.72, 160.92, 154.96, 139.94, 128.88, 128.68, 126.41, 115.95, 90.37, 66.71, 51.58, 44.50, 35.86, 34.05, 27.52. HRMS [$\text{C}_{20}\text{H}_{24}\text{N}_6\text{O}_2 + \text{H}$] $^+$: 381.2034 calculated, 381.2042 found.



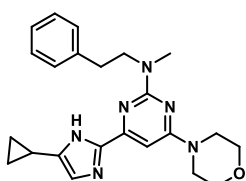
***N*-(Thiazol-2-ylmethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (24)**. The title compound was prepared according to general procedure B using carboxylic acid **17** (27 mg, 79 μmol , 1 eq), DiPEA (82 μL , 0.47 mmol, 6 eq), PyBOP (62 mg, 0.12 mmol, 1.5 eq) and 2-aminomethylthiazole double HCl salt (19 mg, 0.10 mmol, 1.3 eq). Purification by preparative HPLC (C18 reverse phase, 34% to 37% $\text{CH}_3\text{CN}/\text{H}_2\text{O} + 0.2\%$ TFA) afforded the product (11 mg, 25 μmol , 32%). TLC: $R_f = 0.3$ (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 167.81, 165.37, 164.19, 161.18, 156.27, 142.95, 140.22, 129.23, 128.91, 126.61, 120.05, 90.65, 67.07, 51.97, 44.85, 41.38, 36.13, 34.31. HRMS [$\text{C}_{22}\text{H}_{26}\text{N}_6\text{O}_2\text{S} + \text{H}$] $^+$: 439.1911 calculated, 439.1913 found.



***N*-Benzyl-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-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 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 $^\circ\text{C}$ with μW irradiation. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (75 mg, 0.17 mmol, 87%). TLC: $R_f = 0.8$ (60% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{25}\text{H}_{29}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 432.2394 calculated, 432.2390 found.

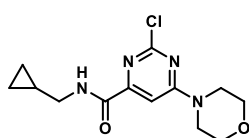


***N*-([1,1'-Biphenyl]-4-ylmethyl)-2-(methyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (26)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117j** (41 mg, 0.10 mmol, 1 eq), DiPEA (70 μL , 0.40 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (40% -> 60% EtOAc/pentane) afforded the product (40 mg, 79 μmol , 79%). TLC: $R_f = 0.5$ (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{31}\text{H}_{33}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 508.2707 calculated, 508.2704 found.



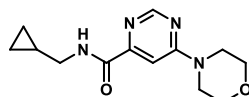
4-(5-Cyclopropyl-1H-imidazol-2-yl)-*N*-methyl-6-morpholino-*N*-phenethylpyrimidin-2-amine (27). *Acyloxymethylketone synthesis*: a round-bottom flask was charged with carboxylic acid **17** (53 mg, 0.15 mmol, 1 eq) in dry DMF (1 mL). Cs_2CO_3 (91 mg, 0.28 mmol, 1.8 eq) and 2-bromocyclopropylethanone (16 μL , 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_2O (1 x 25 mL) and brine (2 x 25 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% -> 50% EtOAc/pentane) affording the

acyloxymethylketone **131** (34 mg, 80 μ mol, 53%). ^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.12 (m, 5H), 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) δ 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. *Imidazole synthesis*: a microwave vial was charged with acyloxymethylketone **131** (34 mg, 80 μ mol, 1 eq) and NH_4OAc (31 mg, 0.40 mmol, 5 eq) in xylene (0.7 mL). The vial was capped and stirred at 140 $^\circ\text{C}$ for 2 h. Purification by preparative HPLC (C18 reverse phase, 35% to 40% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0.2% TFA) afforded the product (2 mg, 5 μ mol, 6%). TLC: R_f = 0.7 (40% EtOAc/pentane). ^1H NMR (850 MHz, CDCl_3) δ 9.89 (br 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) δ 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 [$\text{C}_{23}\text{H}_{28}\text{N}_5\text{O} + \text{H}$] $^+$: 405.2397 calculated, 405.2403 found.



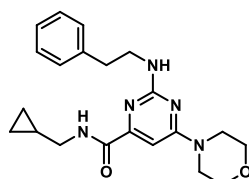
2-Chloro-*N*-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (28).

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. ^1H NMR (400 MHz, CDCl_3) δ 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) δ 163.83, 162.21, 159.84, 157.90, 99.36, 66.35, 44.45, 10.65, 3.64. Regioselectivity was confirmed by ^1H -NOESY NMR analysis. HRMS [$\text{C}_{13}\text{H}_{17}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 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. ^1H NMR (400 MHz, CDCl_3) δ 7.80 – 7.65 (m, 1H), 7.32 (s, 1H), 3.90 – 3.72 (m, 8H), 3.30 (t, J = 6.5 Hz, 2H), 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) δ 163.48, 162.31, 160.68, 158.86, 107.51, 66.64, 44.42, 44.30, 10.80, 3.55.



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

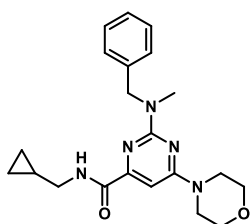
A round-bottom flask was charged with 2-chloropyrimidine **28** (24 mg, 80 μ mol, 1 eq), NaHCO_3 (8 mg, 0.10 mmol, 1.2 eq) and MeOH (0.5 mL). The solution was purged with N_2 followed by addition of Pd/C (10% w/w, 40 mg, 50 μ mol, 5 mol%), purged again with N_2 and then stirred overnight under an H_2 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 μ mol, 95%). TLC: R_f = 0.2 (40% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) δ 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), 1.10 – 1.02 (m, 1H), 0.59 – 0.54 (m, 2H), 0.32 – 0.26 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 163.56, 163.02, 157.44, 155.78, 100.60, 66.59, 44.44, 44.37, 10.79, 3.65. HRMS [$\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_2 + \text{H}$] $^+$: 263.1503 calculated, 263.1502 found.



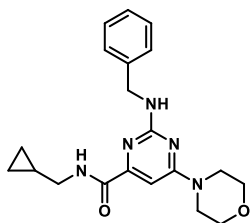
***N*-(Cyclopropylmethyl)-6-morpholino-2-(phenethylamino)pyrimidine-4-carboxamide (30).**

The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (59 mg, 0.20 mmol, 1 eq), 2-phenethylamine (30 μ L, 0.24 mmol, 1.2 eq) and DiPEA (70 μ L, 0.40 mmol, 2 eq). Total heating time: 8 h at 160 $^\circ\text{C}$ 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). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 164.46, 163.98,

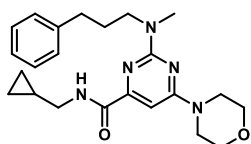
161.46, 156.84, 139.40, 128.89, 128.71, 126.53, 91.72, 66.68, 44.50, 43.00, 36.13, 10.79, 3.63. HRMS $[C_{21}H_{27}N_5O_2 + H]^+$: 382.2238 calculated, 382.2241 found.



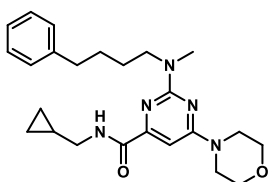
2-(Benzyl(methyl)amino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (31). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (59 mg, 0.20 mmol, 1 eq), *N*-methylbenzylamine (38 μ L, 0.30 mmol, 1.5 eq) and DiPEA (140 μ L, 0.80 mmol, 4 eq). Total heating time: 8 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (2% \rightarrow 5% MeOH/DCM) afforded the product (40 mg, 0.10 mmol, 50%). TLC: R_f = 0.5 (4% MeOH/DCM). 1H NMR (500 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.34 – 7.28 (m, 2H), 7.28 – 7.21 (m, 3H), 6.75 (s, 1H), 4.85 (s, 2H), 3.82 – 3.69 (m, 4H), 3.69 – 3.54 (m, 4H), 3.26 (t, J = 6.5 Hz, 2H), 3.15 (s, 3H), 1.10 – 0.95 (m, 1H), 0.56 – 0.44 (m, 2H), 0.29 – 0.17 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.58, 163.97, 161.35, 156.85, 139.11, 128.56, 127.34, 127.03, 90.41, 66.68, 52.76, 44.47, 44.00, 35.18, 10.85, 3.43. HRMS $[C_{21}H_{27}N_5O_2 + H]^+$: 382.2238 calculated, 382.2241 found.



N-(Cyclopropylmethyl)-2-(benzylamino)-6-morpholinopyrimidine-4-carboxamide (32). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (59 mg, 0.20 mmol, 1 eq), DiPEA (0.14 mL, 0.80 mmol, 4 eq) and benzylamine (33 μ L, 0.30 mmol, 1.5 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (2% \rightarrow 4% MeOH/DCM) afforded the product (19 mg, 50 μ mol, 25%). TLC: R_f = 0.5 (6% MeOH/DCM). 1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.20, 164.03, 161.41, 156.91, 139.73, 128.65, 127.53, 127.27, 91.86, 66.67, 45.79, 44.48, 44.25, 10.78, 3.59. HRMS $[C_{20}H_{25}N_5O_2 + H]^+$: 368.2081 calculated, 368.2081 found.

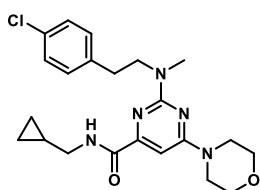


N-(Cyclopropylmethyl)-2-(methyl(3-phenylpropyl)amino)-6-morpholinopyrimidine-4-carboxamide (33). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (39 mg, 0.13 mmol, 1 eq), amine **121b** (30 mg, 0.20 mmol, 1.5 eq) and DiPEA (87 μ L, 0.53 mmol, 4 eq). Total heating time: 48 h at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 60% EtOAc/pentane) afforded the product (38 mg, 93 μ mol, 72%). TLC: R_f = 0.4 (50% EtOAc/pentane). 1H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.32 – 7.22 (m, 2H), 7.22 – 7.14 (m, 3H), 6.69 (s, 1H), 3.76 – 3.68 (m, 4H), 3.65 – 3.59 (m, 2H), 3.59 – 3.51 (m, 4H), 3.28 (t, J = 7.0, 5.9 Hz, 2H), 3.14 (s, 3H), 2.66 (t, J = 7.5 Hz, 2H), 1.95 (p, J = 9.0, 7.5 Hz, 2H), 1.10 – 0.98 (m, 1H), 0.57 – 0.49 (m, 2H), 0.30 – 0.24 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.69, 163.93, 161.04, 156.75, 142.00, 128.49, 128.43, 125.93, 89.96, 66.73, 48.99, 44.42, 43.97, 35.31, 33.52, 28.92, 10.93, 3.43. HRMS $[C_{23}H_{31}N_5O_2 + H]^+$: 410.2551 calculated, 410.2548 found.



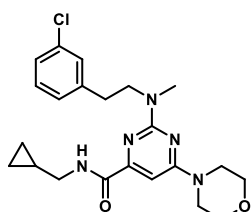
N-(Cyclopropylmethyl)-2-(methyl(4-phenylbutyl)amino)-6-morpholinopyrimidine-4-carboxamide (34). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **121c** (23 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 24 h at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 60% EtOAc/pentane) afforded the product (40 mg, 94 μ mol, 94%). TLC: R_f = 0.5 (50% EtOAc/pentane). 1H NMR (400 MHz, $CDCl_3$) δ 8.03 (t, J = 5.8 Hz, 1H), 7.31 – 7.22 (m, 2H), 7.21 – 7.12 (m, 3H), 6.70 (s, 1H), 3.77 – 3.70 (m, 4H), 3.67 – 3.58 (m, 6H), 3.31 – 3.24 (m, 2H), 3.11 (s, 3H), 2.73 – 2.59 (m, 2H), 1.76 – 1.56 (m, J = 3.5, 2.9 Hz, 4H), 1.11 – 0.95 (m, 1H), 0.56 – 0.44 (m, 2H), 0.28 – 0.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.70, 163.96, 161.10, 156.74, 142.44, 128.42, 128.40, 125.87, 89.89, 66.72,

49.12, 44.47, 44.00, 35.88, 35.32, 29.03, 27.20, 10.86, 3.39. HRMS $[C_{24}H_{33}N_5O_2 + H]^+$: 424.2707 calculated, 424.2706 found.

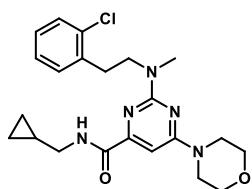


2-((4-Chlorophenethyl)(methyl)amino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (35). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **121d** (34 mg, 0.20 mmol, 2 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 25 h at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 70% EtOAc/pentane) afforded the product (10 mg, 30 μ mol, 30%). TLC:

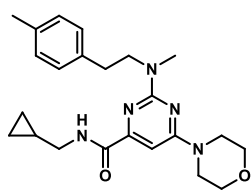
$R_f = 0.4$ (50% EtOAc/pentane). 1H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.28 – 7.23 (m, 2H), 7.17 – 7.09 (m, 2H), 6.73 (s, 1H), 3.82 – 3.72 (m, 6H), 3.65 (t, $J = 4.8$ Hz, 4H), 3.35 – 3.24 (m, 2H), 3.09 (s, 3H), 2.94 – 2.82 (m, 2H), 1.12 – 1.01 (m, 1H), 0.60 – 0.49 (m, 2H), 0.36 – 0.23 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 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 $[C_{22}H_{28}ClN_5O_2 + H]^+$: 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, 70 μ mol, 1 eq), amine **121e** (20 mg, 0.12 mmol, 1.5 eq) and DiPEA (49 μ L, 0.28 mmol, 4 eq). Total heating time: 5 d at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 50% EtOAc/pentane) afforded the product (26 mg, 62 μ mol, 89%). TLC: $R_f = 0.6$ (40% EtOAc/pentane). 1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $[C_{22}H_{28}ClN_5O_2 + H]^+$: 430.2004 calculated, 430.2004 found.



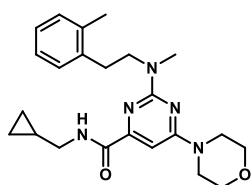
2-((2-Chlorophenethyl)(methyl)amino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (37). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **121f** (28 mg, 0.17 mmol, 1.7 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 3 d at 120 $^{\circ}$ C. Purification by HPLC (C18 reverse phase, 35% \rightarrow 45% $CH_3CN/H_2O + 0.2\%$ TFA, RT 10.8 min) afforded the product (31 mg, 70 μ mol, 70%). TLC: $R_f = 0.7$ (50% EtOAc/pentane). 1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $[C_{22}H_{28}ClN_5O_2 + H]^+$: 430.2004 calculated, 430.2003 found.



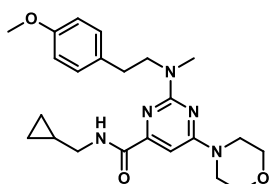
N-(Cyclopropylmethyl)-2-(methyl(4-methylphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (38). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **121g** (23 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 3 d at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 50% EtOAc/pentane) afforded the product (16 mg, 40 μ mol, 40%). TLC: $R_f = 0.8$ (50%

EtOAc/pentane). 1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 164.72, 164.01, 160.89,

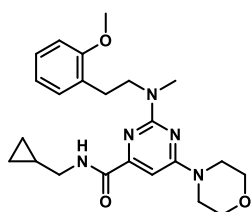
156.79, 136.81, 135.80, 129.28, 128.72, 90.06, 66.76, 51.81, 44.52, 44.12, 35.69, 33.46, 21.16, 10.90, 3.49. HRMS [C₂₃H₃₁N₅O₂ + H]⁺: 410.2551 calculated, 410.2549 found.



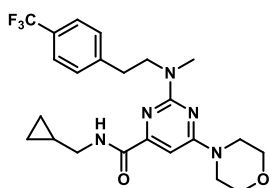
N-(Cyclopropylmethyl)-2-(methyl(2-methylphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (39). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **121h** (23 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 4 d at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 60% EtOAc/pentane) afforded the product (39 mg, 95 μ mol, 95%). TLC: R_f = 0.4 (40% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) 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 [C₂₃H₃₁N₅O₂ + H]⁺: 410.2551 calculated, 410.2546 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 μ L, 0.40 mmol, 4 eq). Total heating time: 7 d at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 70% EtOAc/pentane) afforded the product (38 mg, 90 μ mol, 90%). TLC: R_f = 0.4 (30% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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), 3.30 (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). ¹³C NMR (101 MHz, CDCl₃) 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 [C₂₃H₃₁N₅O₃ + H]⁺: 426.2500 calculated, 426.2497 found.

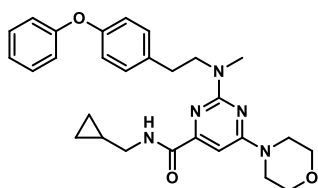


N-(Cyclopropylmethyl)-2-((2-methoxyphenethyl)(methyl)amino)-6-morpholinopyrimidine-4-carboxamide (41). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **121j** (24 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 8 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (30% \rightarrow 70% EtOAc/pentane) afforded the product (42 mg, 0.10 mmol, 99%). TLC: R_f = 0.3 (30% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) 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 [C₂₃H₃₁N₅O₃ + H]⁺: 426.2500 calculated, 426.2496 found.

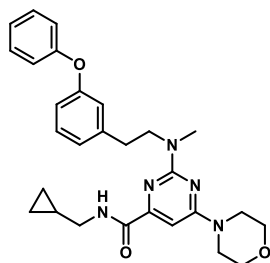


N-(Cyclopropylmethyl)-2-(methyl(4-(trifluoromethyl)phenethyl)amino)-6-morpholino-pyrimidine-4-carboxamide (42) The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (22 mg, 73 μ mol, 1 eq), amine **121k** (29 mg, 0.10 mmol, 1.5 eq) and DiPEA (51 μ L, 0.29 mmol, 4 eq). Total heating time: 25 h at 120 $^{\circ}$ C. Purification by HPLC (C18 reverse phase, 47% \rightarrow 55% CH₃CN/H₂O + 0.2% TFA, RT 12 min) afforded the product (9 mg, 20 μ mol, 27%). TLC: R_f = 0.4 (50% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) δ 164.61, 163.98, 160.88, 156.81, 144.18 (q, *J* = 1.4 Hz), 129.21, 128.89,

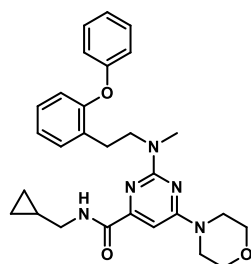
128.57, 125.73, 125.51 (q, $J = 3.7$ Hz), 123.03, 90.37, 66.75, 51.30, 44.51, 44.13, 35.87, 33.91, 10.92, 3.50. HRMS $[C_{23}H_{28}F_3N_5O_2 + H]^+$: 464.2268 calculated, 464.2267 found.



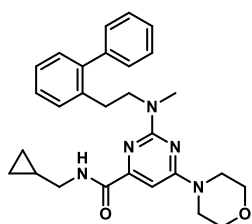
N-(Cyclopropylmethyl)-2-(methyl(4-phenoxyphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (43). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **121l** (34 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 48 h at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 70% EtOAc/pentane) afforded the product (26 mg, 50 μ mol, 50%). TLC: $R_f = 0.4$ (50% EtOAc/pentane). 1H NMR (600 MHz, $CDCl_3$) 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). ^{13}C NMR (151 MHz, $CDCl_3$) 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 $[C_{28}H_{33}N_5O_3 + H]^+$: 488.2656 calculated, 488.2656 found.



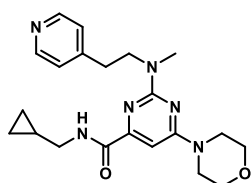
N-(Cyclopropylmethyl)-2-(methyl(3-phenoxyphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (44). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (25 mg, 84 μ mol, 1 eq), amine **121m** (28 mg, 0.12 mmol, 1.5 eq) and DiPEA (60 μ L, 0.34 mmol, 4 eq). Total heating time: 5 d at 120 $^{\circ}$ C. Purification by HPLC (C18 reverse phase, 40% \rightarrow 50% $CH_3CN/H_2O + 0.2\%$ TFA, RT 11.2 min) afforded the product (14 mg, 29 μ mol, 35%). TLC: $R_f = 0.5$ (30% EtOAc/pentane). 1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $[C_{28}H_{33}N_5O_3 + H]^+$: 488.2656 calculated, 488.2653 found.



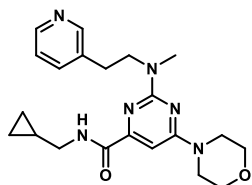
N-(Cyclopropylmethyl)-2-(methyl(2-phenoxyphenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (45). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (34 mg, 0.10 mmol, 1 eq), amine **121n** (37 mg, 0.16 mmol, 1.6 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 3 d at 120 $^{\circ}$ C. Column chromatography (30% \rightarrow 50% EtOAc/pentane) afforded the product (45 mg, 90 μ mol, 90%). TLC: $R_f = 0.5$ (40% EtOAc/pentane). 1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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, 89.98, 66.70, 50.17, 44.44, 44.03, 35.57, 28.69, 10.92, 3.49. HRMS $[C_{28}H_{33}N_5O_3 + H]^+$: 488.2656 calculated, 488.2653 found.



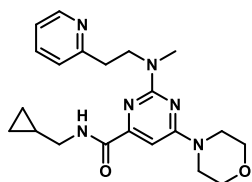
2-((2-([1,1'-Biphenyl]-2-yl)ethyl)(methyl)amino)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (46). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (29 mg, 96 μmol , 1 eq), amine **121o** (31 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μL , 0.40 mmol, 4 eq). Total heating time: 24 h at 160 $^{\circ}\text{C}$ with μW irradiation. Column chromatography (30% \rightarrow 60% EtOAc/pentane) afforded the product (43 mg, 91 μmol , 95%). TLC: R_f = 0.4 (30% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{28}\text{H}_{33}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 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 $^{\circ}\text{C}$. Column chromatography (2% \rightarrow 6% MeOH/DCM) afforded the product (8 mg, 21 μmol , 21%). TLC: R_f = 0.2 (4% MeOH/DCM). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{21}\text{H}_{28}\text{N}_6\text{O}_2 + \text{H}$] $^+$: 397.2347 calculated, 397.2345 found.

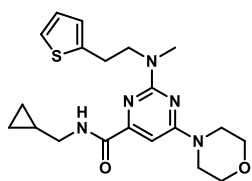


N-(Cyclopropylmethyl)-2-(methyl(2-(pyridin-3-yl)ethyl)amino)-6-morpholinopyrimidine-4-carboxamide (48). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), *N*-methyl-2-(pyridin-3-yl)ethan-1-amine (21 μL , 0.15 mmol, 1.5 eq) and DiPEA (70 μL , 0.40 mmol, 4 eq). Total heating time: 17 h at 120 $^{\circ}\text{C}$. Column chromatography (2% \rightarrow 6% MeOH/DCM) afforded the product (11 mg, 29 μmol , 29%). TLC: R_f = 0.15 (4% MeOH/DCM). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{21}\text{H}_{28}\text{N}_6\text{O}_2 + \text{H}$] $^+$: 397.2347 calculated, 397.2345 found.

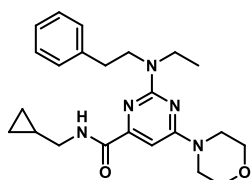


N-(Cyclopropylmethyl)-2-(methyl(2-(pyridin-2-yl)ethyl)amino)-6-morpholinopyrimidine-4-carboxamide (49). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), *N*-methyl-2-(pyridin-2-yl)ethan-1-amine (21 μL , 0.15 mmol, 1.5 eq) and DiPEA (70 μL , 0.40 mmol, 4 eq). Total heating time: 8 h at 160 $^{\circ}\text{C}$ with μW irradiation. Column chromatography (3% \rightarrow 4% MeOH/DCM) afforded the product (26 mg, 66 μmol , 66%). TLC: R_f = 0.3 (3% MeOH/DCM). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 164.62, 163.91, 160.79, 159.86, 156.60, 149.21,

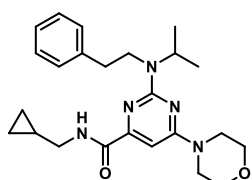
136.68, 123.60, 121.48, 90.12, 66.72, 49.98, 44.48, 44.01, 36.15, 35.62, 10.94, 3.45. HRMS [$C_{21}H_{28}N_6O_2 + H$] $^+$: 397.2347 calculated, 397.2345 found.



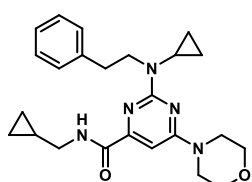
***N*-(Cyclopropylmethyl)-2-(methyl(2-(thiophen-2-yl)ethyl)amino)-6-morpholinopyrimidine-4-carboxamide (50).** The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), DiPEA (52 μ L, 0.30 mmol, 3 eq) and *N*-methyl-2-thiopheneethylamine (18 μ L, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (16 mg, 40 μ mol, 40%). TLC: R_f = 0.4 (50% EtOAc/pentane). 1 H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (101 MHz, $CDCl_3$) δ 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 [$C_{20}H_{27}N_5O_2S + H$] $^+$: 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 μ mol, 1 eq), amine **123a** (21 mg, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 12 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (20% \rightarrow 50% EtOAc/pentane) afforded the product (15 mg, 40 μ mol, 43%). TLC: R_f = 0.3 (30% EtOAc/pentane). 1 H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (101 MHz, $CDCl_3$) δ 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 [$C_{23}H_{31}N_5O_2 + H$] $^+$: 410.2551 calculated, 410.2549 found.

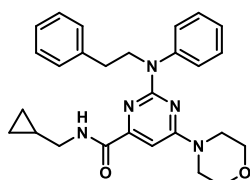


***N*-(Cyclopropylmethyl)-2-(isopropyl(phenethyl)amino)-6-morpholinopyrimidine-4-carboxamide (52).** The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (59 mg, 0.20 mmol, 1 eq), amine **123b** (50 mg, 0.30 mmol, 1.5 eq) and DiPEA (140 μ L, 0.80 mmol, 4 eq). Total heating time: 12 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (50% \rightarrow 60% EtOAc/pentane) afforded the product (19 mg, 40 μ mol, 20%). TLC: R_f = 0.4 (50% EtOAc/pentane). 1 H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (101 MHz, $CDCl_3$) δ 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 [$C_{24}H_{33}N_5O_2 + H$] $^+$: 424.2707 calculated, 424.2705 found.



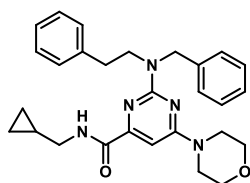
2-(Cyclopropyl(phenethyl)amino)-*N*-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (53). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **123c** (25 mg, 0.16 mmol, 1.6 eq) and DiPEA (115 μ L, 0.60 mmol, 6 eq). Total heating time: 36 h at 160 $^{\circ}$ C with μ W irradiation. Purification by HPLC (C18 reverse phase, 37% \rightarrow 47% $CH_3CN/H_2O + 0.2\%$ TFA) afforded the product (7 mg, 20 μ mol, 20%). TLC: R_f = 0.4 (40% EtOAc/pentane). 1 H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.34 – 7.24 (m, 3H),

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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 422.2551 calculated, 422.2549 found.



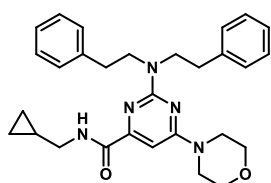
***N*-(Cyclopropylmethyl)-6-morpholino-2-(phenethyl(phenyl)amino)pyrimidine-4-carboxamide (54).**

A microwave vial with a magnetic stir bar under N_2 was charged with 2-chloropyrimidine **28** (29 mg, 98 μmol , 1 eq), 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 N_2 . 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 N_2 and stirred in a preheated oil bath at 110 $^\circ\text{C}$. 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% \rightarrow 50% $\text{CH}_3\text{CN}/\text{H}_2\text{O} + 0.2\%$ TFA, RT 12.0 min) afforded the product (12 mg, 26 μmol , 27%). TLC: $R_f = 0.4$ (40% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 164.24, 163.97, 160.50, 156.64, 144.67, 139.63, 128.84, 128.62, 127.72, 126.40, 125.73, 91.42, 66.71, 52.33, 44.51, 43.96, 34.64, 10.70, 3.34. HRMS [$\text{C}_{27}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 458.2551 calculated, 458.2547 found.



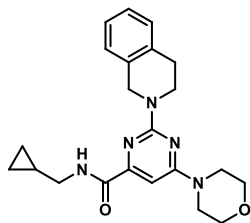
2-(Benzyl(phenethyl)amino)-*N*-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (55).

The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (26 mg, 88 μmol , 1 eq), amine **123d** (28 mg, 0.13 mmol, 1.5 eq) and DiPEA (44 μL , 0.25 mmol, 3 eq). Total heating time: 7 d at 120 $^\circ\text{C}$. Column chromatography (30% \rightarrow 50% EtOAc/pentane) afforded the product (20 mg, 40 μmol , 45%). TLC: $R_f = 0.6$ (40% EtOAc/pentane). ^1H NMR (400 MHz, MeOD + CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{28}\text{H}_{33}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 472.2707 calculated, 472.2704 found.

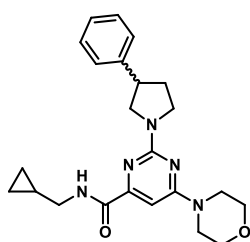


***N*-(Cyclopropylmethyl)-2-(diphenethylamino)-6-morpholinopyrimidine-4-carboxamide (56).**

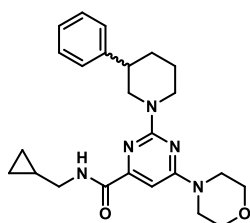
The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **123e** (37 mg, 0.16 mmol, 1.6 eq) and DiPEA (70 μL , 0.40 mmol, 4 eq). Total heating time: 12 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (20% \rightarrow 50% EtOAc/pentane) afforded the product (24 mg, 50 μmol , 50%). TLC: $R_f = 0.5$ (30% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{29}\text{H}_{35}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 486.2864 calculated, 486.2861 found.



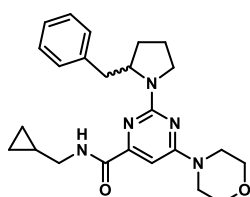
***N*-(Cyclopropylmethyl)-2-(3,4-dihydroisoquinolin-2(1H)-yl)-6-morpholinopyrimidine-4-carboxamide (57).** The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (29 mg, 97 μ mol, 1 eq), 1,2,3,4-tetrahydroisoquinoline (19 μ L, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 18 h at 120 $^{\circ}$ C. Column chromatography (20% \rightarrow 60% EtOAc/pentane) afforded the product (34 mg, 90 μ mol, 93%). TLC: R_f = 0.5 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 164.61, 163.99, 160.78, 156.88, 135.40, 134.49, 128.77, 126.58, 126.40, 126.23, 90.80, 66.76, 46.46, 44.54, 44.10, 41.63, 29.14, 10.99, 3.54. HRMS [$\text{C}_{22}\text{H}_{27}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 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 μ L, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (30% \rightarrow 70% EtOAc/pentane) afforded the product (39 mg, 95 μ mol, 95%). TLC: R_f = 0.4 (40% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{23}\text{H}_{29}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 408.2394 calculated, 408.2391 found.

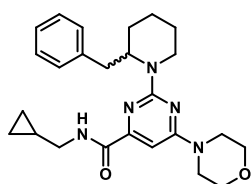


(±)-*N*-(Cyclopropylmethyl)-6-morpholino-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (59). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), (±)-3-phenylpiperidine (24 μ L, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (40% \rightarrow 70% EtOAc/pentane) afforded the product (37 mg, 88 μ mol, 88%). TLC: R_f = 0.3 (40% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 422.2551 calculated, 422.2548 found.

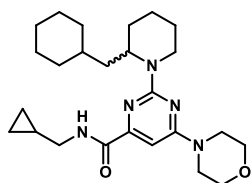


(±)-2-(2-Benzylpyrrolidin-1-yl)-*N*-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (60). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), (±)-2-benzylpyrrolidine (24 μ L, 0.15 mmol, 1.5 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 3 d at 120 $^{\circ}$ C. Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (42 mg, 0.10 mmol, 99%). TLC: R_f = 0.5 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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

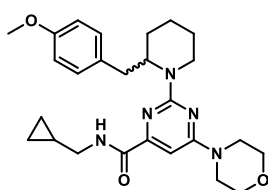
(m, 2H), 0.37 – 0.21 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.71, 164.02, 159.56, 156.78, 139.83, 129.39, 128.49, 126.24, 90.22, 66.76, 59.06, 47.38, 44.54, 44.18, 39.30, 29.42, 23.16, 10.87, 3.51. HRMS [$\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 422.2551 calculated, 422.2549 found.



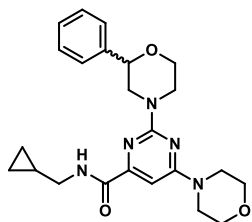
(±)-2-(2-Benzylpiperidin-1-yl)-N-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (61). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), (±)-2-benzylpiperidine hydrochloride (52 mg, 0.24 mmol, 2.4 eq) and DiPEA (104 μL , 0.60 mmol, 6 eq). Total heating time: 6 d at 120 $^\circ\text{C}$. Column chromatography (30% \rightarrow 60% EtOAc/pentane) afforded the product (12 mg, 27 μmol , 27%). TLC: R_f = 0.4 (50% EtOAc/pentane). ^1H NMR (600 MHz, CDCl_3) 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), 0.31 (q, J = 4.7 Hz, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 164.75, 163.97, 160.84, 156.81, 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 [$\text{C}_{25}\text{H}_{33}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 436.2707 calculated, 436.2706 found.



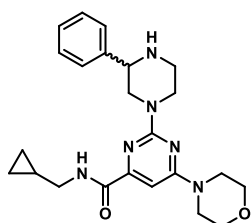
(±)-N-(Cyclopropylmethyl)-2-(2-(cyclohexylmethyl)piperidin-1-yl)-6-morpholinopyrimidine-4-carboxamide. The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (24 mg, 80 μmol , 1 eq), DiPEA (70 μL , 0.4 mmol, 5 eq) and (±)-2-(cyclohexylmethyl)piperidine (22 mg, 0.12 mmol, 1.5 eq). Total heating time: 24 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (10% \rightarrow 60% EtOAc/pentane) afforded the product (6 mg, 14 μmol , 18%). TLC: R_f = 0.6 (50% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) 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). ^{13}C NMR (126 MHz, CDCl_3) 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 [$\text{C}_{25}\text{H}_{39}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 442.3177 calculated, 442.3174 found.



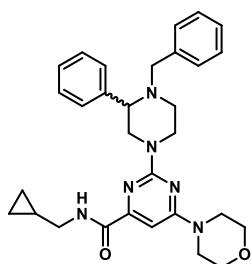
(±)-N-(Cyclopropylmethyl)-2-(2-(4-methoxybenzyl)piperidin-1-yl)-6-morpholinopyrimidine-4-carboxamide (63). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), (±)-2-(4-methoxybenzyl)piperidine (46 mg, 0.22 mmol, 2.2 eq) and DiPEA (70 μL , 0.40 mmol, 4 eq). Total heating time: 28 h at 160 $^\circ\text{C}$ with μW irradiation. Purification by HPLC (C18 reverse phase, 5% \rightarrow 90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0.2% TFA, RT 9.3 min) afforded the product (13 mg, 29 μmol , 29%). TLC: R_f = 0.3 (40% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{26}\text{H}_{35}\text{N}_5\text{O}_3 + \text{H}$] $^+$: 466.2813 calculated, 466.2809 found.



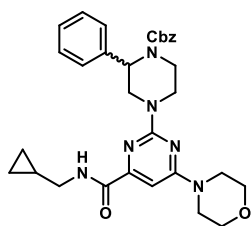
(±)-*N*-(Cyclopropylmethyl)-6-morpholino-2-(2-phenylmorpholino)pyrimidine-4-carboxamide (64). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), DIPEA (52 μ L, 0.30 mmol, 3 eq) and (±)-2-phenylmorpholine (21 μ L, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with μ W irradiation. Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (37 mg, 87 μ mol, 87%). TLC: R_f = 0.4 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 $[\text{C}_{23}\text{H}_{29}\text{N}_5\text{O}_3 + \text{H}]^+$: 424.2343 calculated, 424.2340 found.



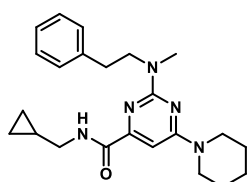
(±)-*N*-(Cyclopropylmethyl)-6-morpholino-2-(3-phenylpiperazin-1-yl)pyrimidine-4-carboxamide (65). A round-bottom flask was charged with Cbz-protected amine **67** (56 mg, 0.10 mmol, 1 eq) and MeOH (0.5 mL). The solution was purged with N_2 and Pd/C (10% w/w, 50 mg, 50 μ mol, 0.5 eq) was added. The mixture was purged with N_2 and then with H_2 and stirred for 2 h under an H_2 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% \rightarrow 4% MeOH/DCM) to afford the product (38 mg, 90 μ mol, 90%). TLC: R_f = 0.3 (2% MeOH/DCM). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 $[\text{C}_{23}\text{H}_{30}\text{N}_6\text{O}_2 + \text{H}]^+$: 423.2503 calculated, 423.2501 found.



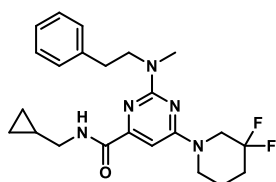
(±)-2-(4-Benzyl-3-phenylpiperazin-1-yl)-*N*-(cyclopropylmethyl)-6-morpholinopyrimidine-4-carboxamide (66). A round-bottom flask was charged with amine **65** (19 mg, 45 μ mol, 1 eq) in dry CH_3CN (0.5 mL). This was followed by DIPEA (16 μ L, 90 μ mol, 2 eq) and benzyl bromide (6.4 μ L, 54 μ mol, 1.2 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 \rightarrow 5% MeOH/DCM) affording the product (17 mg, 33 μ mol, 73%). TLC: R_f = 0.5 (2% MeOH/DCM). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 $[\text{C}_{30}\text{H}_{36}\text{N}_6\text{O}_2 + \text{H}]^+$: 513.2973 calculated, 513.2973 found.



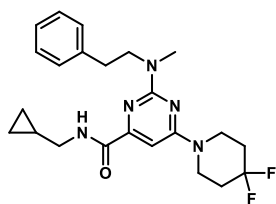
(±)-Benzyl 4-(4-((cyclopropylmethyl)carbamoyl)-6-morpholinopyrimidin-2-yl)-2-phenylpiperazine-1-carboxylate (67). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), amine **130** (45 mg, 0.12 mmol, 1.2 eq) and DiPEA (70 μ L, 0.40 mmol, 4 eq). Total heating time: 41 h at 120 $^{\circ}$ C. Column chromatography (40% \rightarrow 70% EtOAc/pentane) afforded the product (56 mg, 0.10 mmol, 99%). TLC: R_f = 0.3 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{31}\text{H}_{36}\text{N}_6\text{O}_4 + \text{H}$] $^+$: 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 μ L, 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 $^{\circ}$ C with μ W irradiation. Column chromatography (20% \rightarrow 50% EtOAc/pentane) afforded the product (37 mg, 94 μ mol, 63%). TLC: R_f = 0.4 (20% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{23}\text{H}_{31}\text{N}_5\text{O} + \text{H}$] $^+$: 394.2601 calculated, 394.2592 found.

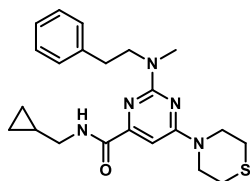


N-(Cyclopropylmethyl)-6-(3,3-difluoropiperidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (69). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117l** (50 mg, 0.15 mmol, 1 eq), DiPEA (78 μ L, 0.45 mmol, 3 eq) and *N*-methylphenethylamine (33 μ L, 0.27 mmol, 1.5 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (10% \rightarrow 30% EtOAc/pentane) afforded the product (10 mg, 23 μ mol, 15%). TLC: R_f = 0.5 (20% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{23}\text{H}_{29}\text{F}_2\text{N}_5\text{O} + \text{H}$] $^+$: 430.2413 calculated, 430.2419 found.

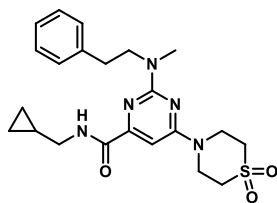


N-(Cyclopropylmethyl)-6-(4,4-difluoropiperidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (70). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117m** (45 mg, 0.14 mmol, 1 eq), DiPEA (73 μ L, 0.42 mmol, 3 eq) and *N*-methylphenethylamine (31 μ L, 0.21 mmol, 1.5 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (5% \rightarrow 30% EtOAc/pentane) afforded the product (27 mg, 63 μ mol, 45%). TLC: R_f = 0.5 (15% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C

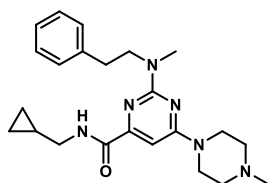
NMR (101 MHz, CDCl₃) δ 164.58, 163.23, 160.99, 157.16, 139.85, 128.83, 128.62, 126.35, 122.10 (t, J = 242.0 Hz), 90.06, 51.73, 44.13, 41.27, 35.74, 33.95, 33.84 (t, J = 23.0 Hz), 10.89, 3.49. HRMS [C₂₃H₂₉F₂N₅O + H]⁺: 430.2413 calculated, 430.2422 found.



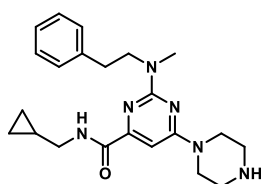
***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-thiomorpholinopyrimidine-4-carboxamide (71)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117n** (41 mg, 0.13 mmol, 1 eq), DiPEA (91 μ L, 0.52 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (43 mg, 0.20 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μ W irradiation. Column chromatography (10% \rightarrow 40% EtOAc/pentane) afforded the product (51 mg, 0.12 mmol, 92%). TLC: R_f = 0.4 (25% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 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). ¹³C NMR (101 MHz, CDCl₃) δ 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 [C₂₂H₂₉N₅OS + H]⁺: 412.2166 calculated, 412.2159 found.



***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 μ L, 0.40 mmol, 4 eq) and *N*-methylphenethylamine HBr salt (32 mg, 0.15 mmol, 1.5 eq). Total heating time: 2 d at 120 °C. Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (35 mg, 79 μ mol, 79%). TLC: R_f = 0.6 (60% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 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). ¹³C NMR (101 MHz, CDCl₃) δ 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 [C₂₂H₂₉N₅O₃S + H]⁺: 444.2064 calculated, 444.2074 found.

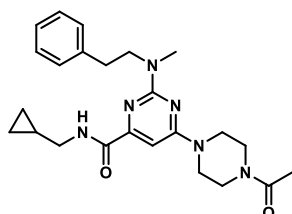


***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(4-methylpiperazin-1-yl)pyrimidine-4-carboxamide (73)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117p** (42 mg, 0.14 mmol, 1 eq), DiPEA (98 μ L, 0.56 mmol, 4 eq) and *N*-methylphenethylamine HBr 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% CH₃CN/H₂O + 0.2% TFA, RT 8.98 min) afforded the product (21 mg, 51 μ mol, 36%). TLC: R_f = 0.3 (5% MeOH/DCM). ¹H NMR (400 MHz, CDCl₃) δ 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). ¹³C NMR (101 MHz, CDCl₃) δ 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 [C₂₃H₃₂N₆O + H]⁺: 409.2710 calculated, 409.2708 found.



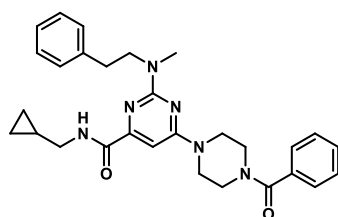
***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(piperazin-1-yl)pyrimidine-4-carboxamide (74)**. A round-bottom flask was charged with Cbz-protected amine **77** (175 mg, 0.33 mmol, 1 eq), dry MeOH (3 mL) and AcOH (0.3 mL). The flask was purged with N₂, followed by addition of Pd/C (10% w/w, 18 mg, 0.02 mmol, 5 mol%) and then purging with H₂ (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 [C₂₂H₃₀N₆O + H]⁺: 395.2554 calculated, 395.2558 found.



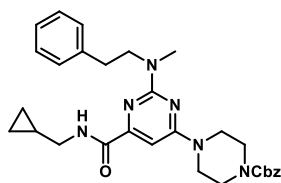
6-(4-Acetylpiperazin-1-yl)-N-(cyclopropylmethyl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (75). A round-bottom flask was charged with amine **74** (22 mg, 56 μmol, 1 eq) in dry DCM (1.5 mL). This was followed by addition of DiPEA (49 μL, 0.28 mmol, 5 eq) and Ac₂O (10.5 μL, 0.11 mmol, 2 eq). 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: R_f = 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, 41.12, 35.73, 33.92, 21.57, 10.87, 3.48. HRMS [C₂₄H₃₂N₆O₂ + 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

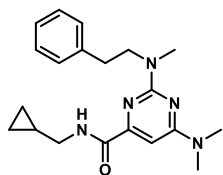
concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60 → 80% EtOAc/pentane) affording the product (20 mg, 40 μmol, 71%). TLC: R_f = 0.3 (60% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.03 (br s, 1H), 7.49 – 7.40 (m, 5H), 7.32 – 7.25 (m, 2H), 7.25 – 7.17 (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 [C₂₉H₃₄N₆O₂ + H]⁺: 499.2816 calculated, 499.2825 found.



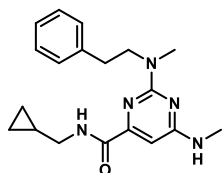
Benzyl 4-(6-((cyclopropylmethyl)carbamoyl)-2-(methyl(phenethyl)amino)pyrimidin-4-yl)piperazine-1-carboxylate (77). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117q** (202 mg, 0.47 mmol, 1 eq), DiPEA (0.40 mL, 2.28 mmol, 5 eq) and *N*-methylphenethylamine 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: R_f = 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,

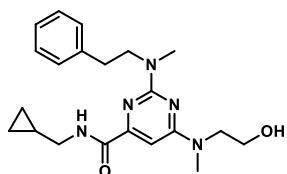
67.46, 51.66, 44.07, 43.86, 43.53, 35.67, 33.91, 10.85, 3.44. HRMS [C₃₀H₃₆N₆O₃ + H]⁺: 529.2922 calculated, 529.2933 found.



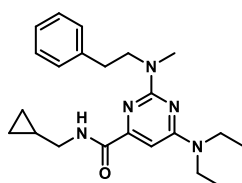
N-(Cyclopropylmethyl)-6-(dimethylamino)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (78). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117r** (27 mg, 0.11 mmol, 1 eq), *N*-methylphenethylamine HBr salt (35 mg, 0.16 mmol, 1.6 eq) and DiPEA (92 μ L, 0.53 mmol, 5 eq). Total heating time: 8 h at 160 °C with μ W irradiation. Column chromatography (20% \rightarrow 50% EtOAc/pentane) afforded the product (32 mg, 90 μ mol, 82%). TLC: R_f = 0.6 (40% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) 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 [C₂₀H₂₇N₅O + H]⁺: 354.2288 calculated, 354.2290 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 μ L, 0.30 mmol, 3 eq) and *N*-methylphenethylamine (22 μ L, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μ W irradiation. Column chromatography (50% \rightarrow 70% EtOAc/pentane) afforded the product (26 mg, 77 μ mol, 77%). TLC: R_f = 0.5 (50% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) 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 [C₁₉H₂₅N₅O + H]⁺: 340.2132 calculated, 340.2138 found.

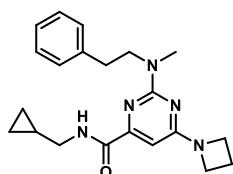


N-(Cyclopropylmethyl)-6-((2-hydroxyethyl)(methyl)amino)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (80). The title compound was prepared according to general procedure C using dichloropyrimidine **116a** (39 mg, 0.16 mmol, 1 eq), DiPEA (43 μ L, 0.24 mmol, 1.5 eq) and *N*-methylethanolamine (13 μ L, 0.16 mmol, 1.0 eq) in MeOH (1.6 mL), followed by concentration and addition of DiPEA (84 μ L, 0.48 mmol, 3 eq), *N*-methylphenethylamine (35 μ L, 0.24 mmol, 1.5 eq) and *n*-BuOH (0.75 mL). Total heating time: 4 h at 160 °C with μ W irradiation. Column chromatography (20% \rightarrow 40% EtOAc/pentane) afforded the product (15 mg, 33 μ mol, 21%). TLC: R_f = 0.4 (80% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) 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 [C₂₁H₂₉N₅O₂ + H]⁺: 384.2394 calculated, 384.2399 found.

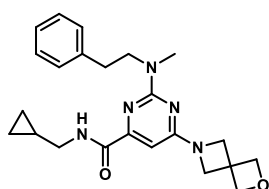


N-(Cyclopropylmethyl)-6-(diethylamino)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (81). The title compound was prepared according to general procedure A using 2-chloropyrimidine **177t** (37 mg, 0.13 mmol, 1 eq), DiPEA (68 μ L, 0.39 mmol, 3 eq) and *N*-methylphenethylamine (28 μ L, 0.20 mmol, 1.5 eq). Total heating time: 4 h at 160 °C with μ W irradiation. Column chromatography (20% \rightarrow 40% EtOAc/pentane) afforded the product (30 mg, 79 μ mol, 61%). TLC: R_f = 0.8 (50% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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),

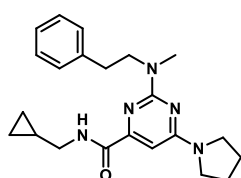
1.13 – 0.99 (m, 1H), 0.64 – 0.46 (m, 2H), 0.37 – 0.21 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 165.05, 162.59, 160.96, 155.94, 140.12, 128.87, 128.55, 126.21, 90.19, 51.79, 44.03, 42.44, 35.60, 34.04, 13.26, 10.92, 3.46. HRMS [$\text{C}_{22}\text{H}_{31}\text{N}_5\text{O} + \text{H}$] $^+$: 382.2601 calculated, 382.2599 found.



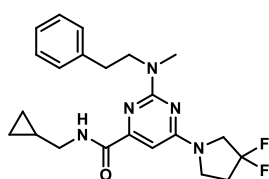
***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(azetidin-1-yl)pyrimidine-4-carboxamide (82)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117u** (27 mg, 0.10 mmol, 1 eq), DiPEA (52 μL , 0.30 mmol, 3 eq) and *N*-methylphenethylamine (22 μL , 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (25 mg, 68 μmol , 68%). TLC: R_f = 0.6 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{21}\text{H}_{27}\text{N}_5\text{O} + \text{H}$] $^+$: 366.2288 calculated, 366.2296 found.



***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidine-4-carboxamide (83)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117v** (31 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 $^\circ\text{C}$ with μW irradiation. Column chromatography (70% \rightarrow 90% EtOAc/pentane) afforded the product (7 mg, 17 μmol , 17%). TLC: R_f = 0.4 (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{23}\text{H}_{29}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 408.2394 calculated, 408.2396 found.

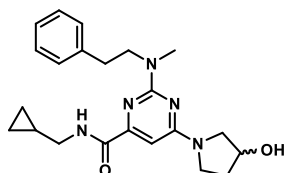


***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(pyrrolidin-1-yl)pyrimidine-4-carboxamide (84)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117w** (28 mg, 0.10 mmol, 1 eq), DiPEA (52 μL , 0.30 mmol, 3 eq) and *N*-methylphenethylamine (22 μL , 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (30% \rightarrow 50% EtOAc/pentane) afforded the product (26 mg, 69 μmol , 69%). TLC: R_f = 0.7 (40% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{22}\text{H}_{29}\text{N}_5\text{O} + \text{H}$] $^+$: 380.2445 calculated, 380.2452 found.

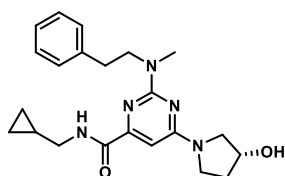


***N*-(Cyclopropylmethyl)-6-(3,3-difluoropyrrolidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (85)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117x** (32 mg, 0.10 mmol, 1 eq), DiPEA (52 μL , 0.30 mmol, 3 eq) and *N*-methylphenethylamine (22 μL , 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (20% \rightarrow 40% EtOAc/pentane) afforded the product (34 mg, 82 μmol , 82%). TLC: R_f = 0.8 (40% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 8.03 (br s, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m,

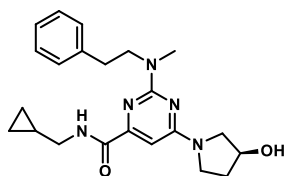
3H), 6.52 (br s, 1H), 3.89 (br s, 2H), 3.84 – 3.78 (m, 2H), 3.74 (br s, 2H), 3.37 – 3.22 (m, 2H), 3.13 (s, 3H), 2.97 – 2.83 (m, 2H), 2.56 – 2.37 (m, 2H), 1.14 – 1.00 (m, 1H), 0.64 – 0.47 (m, 2H), 0.29 (q, $J = 4.7$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.50, 162.05, 160.76, 156.36, 139.91, 128.86, 128.61, 127.48 (t, $J = 247.3$ Hz), 126.31, 90.39, 53.35 (t, $J = 32.2$ Hz), 51.68, 44.12, 43.95, 35.66, 33.94 (t, $J = 22.8$ Hz), 10.88, 3.50. HRMS [$\text{C}_{22}\text{H}_{27}\text{F}_2\text{N}_5\text{O} + \text{H}$] $^+$: 416.2256 calculated, 416.2260 found.



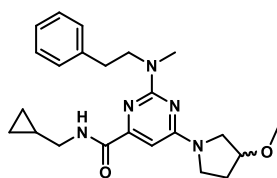
(±)-*N*-(Cyclopropylmethyl)-6-(3-hydroxypyrrolidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (86). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117y** (65 mg, 0.22 mmol, 1 eq), DiPEA (115 μL , 0.66 mmol, 3 eq) and *N*-methylphenethylamine (48 μL , 0.33 mmol, 1.5 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (70% \rightarrow 100% EtOAc/pentane) afforded the product (60 mg, 0.15 mmol, 68%). TLC: $R_f = 0.4$ (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 165.08, 162.07, 160.78, 155.35, 140.10, 128.87, 128.54, 126.19, 91.26, 54.89, 51.73, 44.36, 44.10, 35.57, 33.91, 10.83, 3.48. HRMS [$\text{C}_{22}\text{H}_{29}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 396.2394 calculated, 396.2400 found.



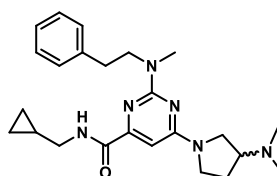
(*R*)-*N*-(Cyclopropylmethyl)-6-(3-hydroxypyrrolidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (87). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117z** (38 mg, 0.13 mmol, 1 eq), DiPEA (67 μL , 0.38 mmol, 3 eq) and *N*-methylphenethylamine (28 μL , 0.19 mmol, 1.5 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (80% \rightarrow 100% EtOAc/pentane) afforded the product (37 mg, 94 μmol , 72%). *ee*: >99% (as determined by chiral HPLC using 75:25 hexane/ethanol, Chiralcell OD). TLC: $R_f = 0.3$ (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{22}\text{H}_{29}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 396.2394 calculated, 396.2394 found.



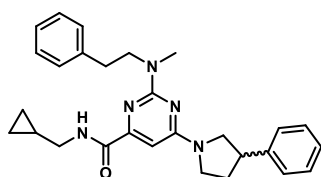
(*S*)-*N*-(Cyclopropylmethyl)-6-(3-hydroxypyrrolidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (88). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117aa** (36 mg, 0.12 mmol, 1 eq), DiPEA (63 μL , 0.36 mmol, 3 eq) and *N*-methylphenethylamine (27 μL , 0.18 mmol, 1.5 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (80% \rightarrow 100% EtOAc/pentane) afforded the product (36 mg, 91 μmol , 76%). *ee*: 97% (as determined by chiral HPLC using 75:25 hexane/ethanol, Chiralcell OD). TLC: $R_f = 0.3$ (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{22}\text{H}_{29}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 396.2394 calculated, 396.2398 found.



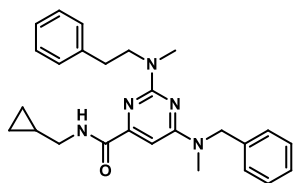
(±)-N-(Cyclopropylmethyl)-6-(3-methoxypyrrolidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (89). A round-bottom flask was charged with alcohol **86** (35 mg, 88 μmol , 1 eq) in dry DMF (0.5 mL) and cooled to 0 °C. NaH (60% in mineral oil, 4 mg, 106 μmol , 1.2 eq) was added and the mixture 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 x 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: R_f = 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, *J* = 4.7 Hz, 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 [C₂₃H₃₁N₅O₂ + H]⁺: 410.2551 calculated, 410.2549 found.



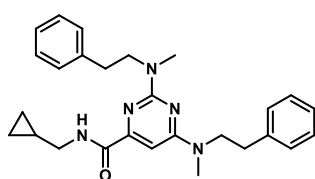
(±)-N-(Cyclopropylmethyl)-6-(3-(dimethylamino)pyrrolidin-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (90). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117ab** (50 mg, 0.15 mmol, 1 eq), DiPEA (78 μL , 0.60 mmol, 4 eq) and *N*-methylphenethylamine (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: R_f = 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 [C₂₄H₃₄N₆O + H]⁺: 423.2867 calculated, 423.2868 found.



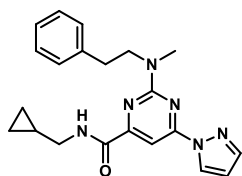
(±)-N-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(3-phenylpyrrolidin-1-yl)pyrimidine-4-carboxamide (91). The title compound was prepared according to general procedure C using dichloropyrimidine **116a** (40 mg, 0.16 mmol, 1 eq), DiPEA (43 μL , 0.24 mmol, 1.5 eq) and (±)-3-phenylpyrrolidine (24 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: R_f = 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 [C₂₈H₃₃N₅O + H]⁺: 456.2758 calculated, 456.2757 found.



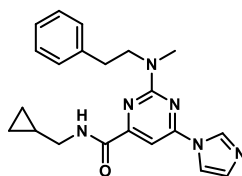
***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(benzyl(methyl)amino)pyrimidine-4-carboxamide (92).** The title compound was prepared according to general procedure C using dichloropyrimidine **116a** (37 mg, 0.15 mmol, 1 eq), DiPEA (39 μ L, 0.23 mmol, 1.5 eq) and *N*-methylbenzylamine (19 μ L, 0.15 mmol, 1.0 eq) in MeOH (1.5 mL), followed by concentration and addition of DiPEA (78 μ L, 0.45 mmol, 3 eq), *N*-methylphenethylamine (33 μ L, 0.23 mmol, 1.5 eq) and *n*-BuOH (0.75 mL). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Purification by HPLC (C18 reverse phase, 43% to 49% CH₃CN/H₂O + 0.2% TFA) afforded the product (47 mg, 0.11 mmol, 73%). TLC: R_f = 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, 8H), 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 [C₂₆H₃₁N₅O + H]⁺: 430.2601 calculated, 430.2604 found.



***N*-(Cyclopropylmethyl)-2,6-bis(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 μ L, 0.46 mmol, 4 eq) and *N*-methylphenethylamine (41 μ L, 0.28 mmol, 2.5 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (20% -> 40% EtOAc/pentane) afforded the product (30 mg, 68 μ mol, 62%). TLC: R_f = 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 [C₂₇H₃₃N₅O + H]⁺: 444.2758 calculated, 444.2765 found.

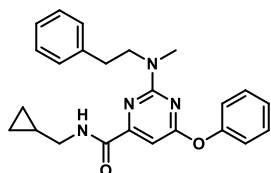


***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(1H-pyrazol-1-yl)pyrimidine-4-carboxamide (94).** The title compound was prepared according to general procedure A using 2-chloropyrimidine **117ac** (28 mg, 0.10 mmol, 1 eq), DiPEA (52 μ L, 0.30 mmol, 3 eq) and *N*-methylphenethylamine (22 μ L, 0.15 mmol, 1.5 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Column chromatography (20% -> 40% EtOAc/pentane) afforded the product (30 mg, 80 μ mol, 80%). TLC: R_f = 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 [C₂₁H₂₄N₆O + H]⁺: 377.2084 calculated, 377.2088 found.

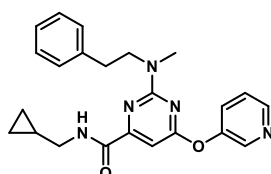


***N*-(Cyclopropylmethyl)-6-(1H-imidazol-1-yl)-2-(methyl(phenethyl)amino)pyrimidine-4-carboxamide (95).** The title compound was prepared according to general procedure A using 2-chloropyrimidine **117ad** (42 mg, 0.15 mmol, 1 eq), DiPEA (78 μ L, 0.45 mmol, 3 eq) and *N*-methylphenethylamine (33 μ L, 0.23 mmol, 1.5 eq). Total heating time: 4 h at 160 $^{\circ}$ C with μ W irradiation. Purification by preparative HPLC (C18 reverse phase, 35% to 45% CH₃CN/H₂O + 0.2% TFA, RT 8.87 min) afforded the product (27 mg, 72 μ mol, 48%). TLC: R_f = 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,

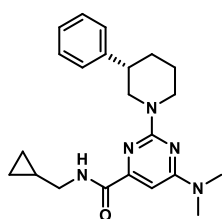
1H), 0.69 – 0.51 (m, 2H), 0.32 (q, $J = 4.9$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.88, 160.89, 160.19, 157.03, 139.14, 135.37, 131.10, 128.82, 128.73, 126.61, 116.00, 93.80, 51.89, 44.36, 36.06, 33.78, 10.84, 3.56. HRMS $[\text{C}_{21}\text{H}_{24}\text{N}_6\text{O} + \text{H}]^+$: 377.2084 calculated, 377.2087 found.



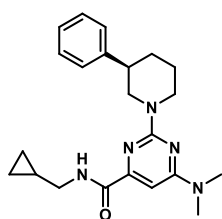
***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-phenoxy pyrimidine-4-carboxamide (96)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117ae** (49 mg, 0.16 mmol, 1 eq), DiPEA (84 μL , 0.48 mmol, 3 eq) and *N*-methylphenethylamine (35 μL , 0.24 mmol, 1.5 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (5% \rightarrow 25% EtOAc/pentane) afforded the product (40 mg, 99 μmol , 62%). TLC: $R_f = 0.5$ (20% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 $[\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_2 + \text{H}]^+$: 403.2129 calculated, 403.2137 found.



***N*-(Cyclopropylmethyl)-2-(methyl(phenethyl)amino)-6-(pyridin-3-yloxy) 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 $^\circ\text{C}$ with μW irradiation. Column chromatography (60% \rightarrow 100% EtOAc/pentane) afforded the product (26 mg, 64 μmol , 53%). TLC: $R_f = 0.5$ (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 8.66 – 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). ^{13}C NMR (101 MHz, CDCl_3) 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 $[\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}_2 + \text{H}]^+$: 404.2081 calculated, 404.2088 found.

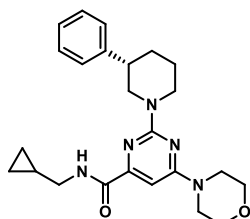


(*S*)-*N*-(Cyclopropylmethyl)-6-(dimethylamino)-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (98). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117r** (25 mg, 0.10 mmol, 1 eq), DiPEA (52 μL , 0.30 mmol, 3 eq) and (*S*)-3-phenylpiperidine (21 mg, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (30% \rightarrow 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). ^1H NMR (400 MHz, CDCl_3) δ 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), 0.63 – 0.44 (m, 2H), 0.36 – 0.20 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) 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 $[\text{C}_{22}\text{H}_{29}\text{N}_5\text{O} + \text{H}]^+$: 380.2445 calculated, 380.2452 found.

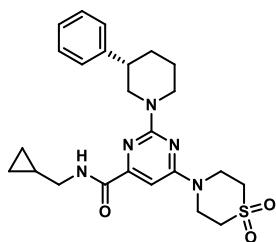


(*R*)-*N*-(Cyclopropylmethyl)-6-(dimethylamino)-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (99). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117r** (25 mg, 0.10 mmol, 1 eq), DiPEA (52 μL , 0.30 mmol, 3 eq) and (*R*)-3-phenylpiperidine (21 mg, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (30% \rightarrow 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%

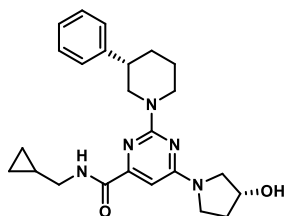
EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 8.01 (t, $J = 5.4$ Hz, 1H), 7.39 – 7.28 (m, 4H), 7.28 – 7.21 (m, 1H), 6.70 (s, 1H), 4.95 – 4.74 (m, 2H), 3.40 – 3.18 (m, 2H), 3.10 (s, 6H), 2.96 – 2.83 (m, 2H), 2.83 – 2.70 (m, 1H), 2.07 (d, $J = 13.9$ Hz, 1H), 1.90 – 1.81 (m, 1H), 1.81 – 1.62 (m, 2H), 1.11 – 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) δ 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 [$\text{C}_{22}\text{H}_{29}\text{N}_5\text{O} + \text{H}$] $^+$: 380.2445 calculated, 380.2452 found.



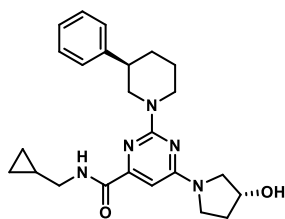
(S)-N-(Cyclopropylmethyl)-6-morpholino-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (100). The title compound was prepared according to general procedure A using 2-chloropyrimidine **28** (30 mg, 0.10 mmol, 1 eq), DiPEA (52 μL , 0.30 mmol, 3 eq) and (*S*)-3-phenylpiperidine (21 mg, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (41 mg, 97 μmol , 97%). TLC: $R_f = 0.6$ (50% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) δ 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) δ 164.63, 164.11, 160.97, 156.96, 144.30, 128.66, 127.30, 126.67, 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 [$\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 422.2551 calculated, 422.2549 found.



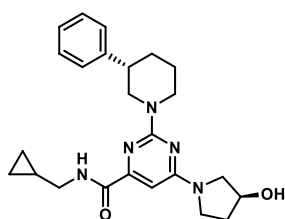
(S)-N-(Cyclopropylmethyl)-6-(1,1-dioxidothiomorpholino)-2-(3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (101). The title compound was prepared according to general procedure A using 2-chloropyrimidine **117o** (4:1 mixture of regioisomers) (35 mg, 0.10 mmol, 1 eq), DiPEA (53 μL , 0.30 mmol, 3 eq) and (*S*)-3-phenylpiperidine (21 mg, 0.13 mmol, 1.3 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Purification by preparative HPLC (C18 reverse phase, 45% to 55% $\text{CH}_3\text{CN}/\text{H}_2\text{O} + 0.2\%$ TFA, RT 12.52 min) afforded the product (27 mg, 57 μmol , 57%). TLC: $R_f = 0.5$ (60% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_3\text{S} + \text{H}$] $^+$: 470.2220 calculated, 470.2223 found.



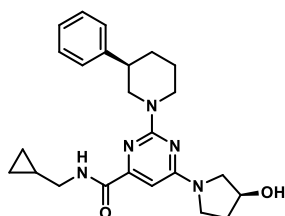
N-(Cyclopropylmethyl)-6-((R)-3-hydroxypyrrolidin-1-yl)-2-((S)-3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (102, LEI-401) The title compound was prepared according to general procedure A using 2-chloropyrimidine **117z** (24 mg, 81 μmol , 1 eq), DiPEA (42 μL , 0.24 mmol, 3 eq) and (*S*)-3-phenylpiperidine (17 mg, 0.11 mmol, 1.3 eq). Total heating time: 4 h at 160 $^\circ\text{C}$ with μW irradiation. Column chromatography (70% \rightarrow 90% EtOAc/pentane) afforded the product (23 mg, 55 μmol , 68%). TLC: $R_f = 0.4$ (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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 [$\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 422.2551 calculated, 422.2551 found.



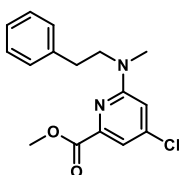
***N*-(Cyclopropylmethyl)-6-((*R*)-3-hydroxypiperidin-1-yl)-2-((*R*)-3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (**103**)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117z** (22 mg, 74 μ mol, 1 eq), DiPEA (39 μ L, 0.22 mmol, 3 eq) and (*R*)-3-phenylpiperidine (16 mg, 96 μ mol, 1.3 eq). Total heating time: 4 h at 160 °C with μ W irradiation. Column chromatography (70% -> 90% EtOAc/pentane) afforded the product (23 mg, 55 μ mol, 74%). TLC: R_f = 0.4 (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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), 2.56 (s, 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). ^{13}C NMR (101 MHz, CDCl_3) δ 164.96, 162.19, 160.91, 155.67, 144.43, 128.62, 127.32, 126.59, 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 [$\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 422.2551 calculated, 422.2552 found.



***N*-(Cyclopropylmethyl)-6-((*S*)-3-hydroxypiperidin-1-yl)-2-((*S*)-3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (**104**)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117aa** (37 mg, 0.12 mmol, 1 eq), DiPEA (65 μ 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 μ W irradiation. Column chromatography (70% -> 100% EtOAc/pentane) afforded the product (26 mg, 62 μ mol, 52%). TLC: R_f = 0.4 (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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). ^{13}C NMR (101 MHz, CDCl_3) δ 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 [$\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 422.2551 calculated, 422.2555 found.

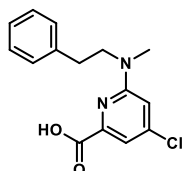


***N*-(Cyclopropylmethyl)-6-((*S*)-3-hydroxypiperidin-1-yl)-2-((*R*)-3-phenylpiperidin-1-yl)pyrimidine-4-carboxamide (**105**)**. The title compound was prepared according to general procedure A using 2-chloropyrimidine **117aa** (32 mg, 0.11 mmol, 1 eq), DiPEA (56 μ L, 0.32 mmol, 3 eq) and (*R*)-3-phenylpiperidine (23 mg, 0.14 mmol, 1.3 eq). Total heating time: 4 h at 160 °C with μ W irradiation. Column chromatography (70% -> 100% EtOAc/pentane) afforded the product (26 mg, 56 μ mol, 51%). TLC: R_f = 0.4 (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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). ^{13}C NMR (101 MHz, CDCl_3) δ 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 [$\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_2 + \text{H}$] $^+$: 422.2551 calculated, 422.2552 found.

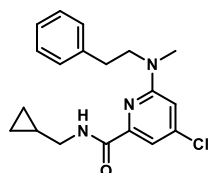


Methyl 4-chloro-6-(methyl(phenethyl)amino)picolinate (107**)**. A round-bottom flask was charged with methyl 4,6-dichloropicolinate (**106**) (206 mg, 0.99 mmol, 1 eq), *N*-methylphenethylamine HBr salt (218 mg, 1.01 mmol, 1.02 eq), DiPEA (436 μ L, 2.5 mmol, 2.5 eq) and dry MeOH (2 mL). The solution 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: R_f = 0.2 (5% EtOAc/pentane). ^1H NMR

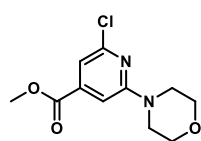
(400 MHz, CDCl₃) δ 7.35 – 7.26 (m, 3H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 6.56 (d, *J* = 2.3 Hz, 1H), 3.96 (s, 3H), 3.63 (t, *J* = 7.3 Hz, 2H), 2.93 – 2.81 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 165.68, 155.45, 152.41, 147.85, 138.19, 128.84, 128.80, 126.84, 107.83, 107.79, 53.84, 53.05, 38.50, 33.14. Regioselectivity was confirmed by ¹H, ¹³C-HMBC and ¹H-NOESY 2D NMR. HRMS [C₁₆H₁₇ClN₂O₂ + H]⁺: 305.1051 calculated, 305.1054 found.



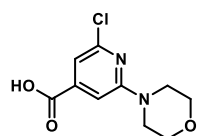
4-Chloro-6-(methyl(phenethyl)amino)picolinic acid (108). A round-bottom flask was charged with methyl ester **107** (122 mg, 0.4 mmol, 1 eq) and THF (2 mL). An aqueous 1.5 M NaOH solution (0.53 mL, 0.8 mmol, 2 eq) was added dropwise and the reaction was stirred for 1.5 h at rt. The mixture was cooled 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 washed with brine (1 x 15 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to afford the product (104 mg, 0.36 mmol, 90%). TLC R_f = 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, 108.27, 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%), R_f = 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.

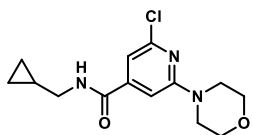


Methyl 2-chloro-6-morpholinoisonicotinate (110). A round-bottom flask was charged with methyl-2,6-dichloroisonicotinate (**110**) (0.41 g, 2.0 mmol, 1 eq), K₂CO₃ (0.55 g, 4.0 mmol, 2 eq) morpholine (0.26 mL, 3.0 mmol, 1.5 eq) and dry CH₃CN (10 mL). The mixture was heated to reflux. After 45 h the reaction 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: R_f = 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 [C₁₁H₁₃ClN₂O₃ + H]⁺: 257.0688 calculated, 257.0690 found.

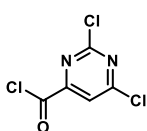


2-Chloro-6-morpholinoisonicotinic acid (112). A round-bottom flask was charged with methyl ester **111** (0.32 g, 1.3 mmol, 1 eq) and THF (5 mL). A 1 M aqueous solution of NaOH (2.5 mL, 2.5 mmol, 2 eq) was added dropwise. After stirring 20 minutes at room temperature the reaction mixture was acidified 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: R_f = 0.2

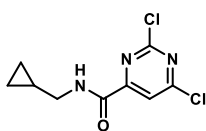
(30% EtOAc/pentane with 3 drops of AcOH). ^1H NMR (400 MHz, MeOD + CDCl_3) δ 7.12 (s, 1H), 7.09 (s, 1H), 3.78 (t, $J = 4.9$ Hz, 4H), 3.54 (t, $J = 4.9$ Hz, 4H). ^{13}C NMR (101 MHz, MeOD + CDCl_3) δ 167.10, 160.29, 150.79, 143.21, 112.56, 105.74, 67.18, 45.94. HRMS [$\text{C}_{10}\text{H}_{11}\text{ClN}_2\text{O}_3 + \text{H}$] $^+$: 243.0531 calculated, 243.0533 found.



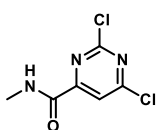
2-Chloro-*N*-(cyclopropylmethyl)-6-morpholinoisonicotinamide (113). A round-bottom flask was charged with carboxylic acid **112** (0.33 g, 1.3 mmol, 1 eq), EDC hydrochloride (0.30 g, 2.0 mmol, 1.5 eq) and HOBT (0.30 g, 2.0 mmol, 1.5 eq) and dry DCM (7 mL). The suspension was stirred for 1 h at room temperature 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 dried (MgSO_4), filtered and concentrated under reduced pressure. The resulting crude material was purified by silica gel column chromatography (30% \rightarrow 60% EtOAc/pentane) affording the product (0.30 g, 1.0 mmol, 77%). TLC: $R_f = 0.3$ (40% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 6.91 (s, 1H), 6.81 (s, 1H), 6.45 – 6.31 (m, 1H), 3.84 – 3.73 (m, 4H), 3.66 – 3.51 (m, 4H), 3.28 (dd, $J = 7.2, 5.4$ Hz, 2H), 1.12 – 0.98 (m, 1H), 0.64 – 0.52 (m, 2H), 0.38 – 0.21 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 165.28, 159.52, 150.25, 146.27, 109.10, 103.25, 66.61, 45.27, 45.25, 10.68, 3.73. HRMS [$\text{C}_{14}\text{H}_{18}\text{ClN}_3\text{O}_2 + \text{H}$] $^+$: 296.1160 calculated, 296.1158 found.



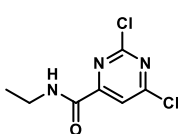
2,6-Dichloropyrimidine-4-carbonyl chloride (115). In a 500 mL round-bottom flask orotic acid (**114**) (15.6 g, 100 mmol, 1 equiv.) was dissolved in phosphorous oxychloride (46 mL, 500 mmol, 5 equiv.) and 10 drops of DMF were added. The mixture was heated to reflux and stirred for 19 h. *n*-Hexane (250 mL) was added and the mixture was stirred vigorously for 10 min and then transferred to a separatory funnel containing 100 mL H_2O . 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 (MgSO_4) and concentrated under reduced pressure to yield the product (12.8 g, 60.4 mmol, 60%). ^1H NMR (500 MHz, CDCl_3) δ 8.00 (s, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 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-carbonyl chloride **115** (0.63 mL, 5.0 mmol, 1 eq), Et_3N (0.91 mL, 6.5 mmol, 1.3 eq) and cyclopropylmethanamine (444 μL , 5.13 mmol, 1.025 eq). Column chromatography (5% \rightarrow 20% EtOAc/pentane) afforded the product (0.99 g, 4.0 mmol, 80%). TLC: $R_f = 0.8$ (20% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 8.11 (s, 1H), 7.96 (br s, 1H), 3.44 – 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) δ 164.74, 160.44, 160.04, 159.77, 118.22, 44.72, 10.57, 3.67. HRMS [$\text{C}_9\text{H}_9\text{Cl}_2\text{N}_3\text{O} + \text{H}$] $^+$: 246.0195 calculated, 246.0196 found.

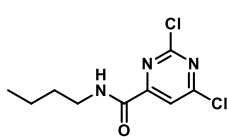


2,6-Dichloro-*N*-methylpyrimidine-4-carboxamide (116b). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.63 mL, 5.0 mmol, 1 eq), Et_3N (1.6 mL, 11.5 mmol, 2.3 eq) and methylamine HCl salt (0.35 g, 5.13 mmol, 1.025 eq). Column chromatography (10% \rightarrow 30% EtOAc/pentane) afforded the product (0.97 g, 4.7 mmol, 94%). TLC: $R_f = 0.3$ (20% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 7.90 (br s, 1H), 3.08 (d, $J = 5.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.84, 160.85, 160.25, 159.82, 118.11, 26.51. HRMS [$\text{C}_6\text{H}_5\text{Cl}_2\text{N}_3\text{O} + \text{H}$] $^+$: 205.9882 calculated, 205.9884 found.

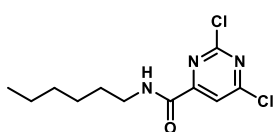


2,6-Dichloro-*N*-ethylpyrimidine-4-carboxamide (116c). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.63 mL, 5.0 mmol, 1 eq), Et_3N (1.6 mL, 11.5 mmol, 2.3 eq) and ethylamine HCl salt (0.42 g, 5.13 mmol, 1.025 eq). Column chromatography (5% \rightarrow 20% EtOAc/pentane) afforded the product (0.88 g, 4.0 mmol, 80%). TLC: $R_f = 0.6$ (20% EtOAc/pentane). ^1H NMR

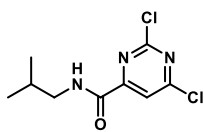
(400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.83 (br s, 1H), 3.65 – 3.38 (m, 2H), 1.30 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.84, 160.47, 160.06, 159.83, 118.18, 34.86, 14.63. HRMS [C₇H₇Cl₂N₃O + H]⁺: 220.0039 calculated, 220.0040 found.



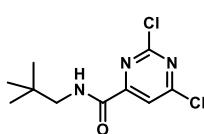
2,6-Dichloro-*N*-butylpyrimidine-4-carboxamide (116d). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.60 mmol, 1.3 eq) and *n*-butylamine (0.20 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% → 20% EtOAc/pentane) afforded the product (0.50 g, 2.0 mmol, 99%). TLC: R_f = 0.7 (20% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.85 (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 [C₉H₁₁Cl₂N₃O + H]⁺: 248.0352 calculated, 248.0354 found.



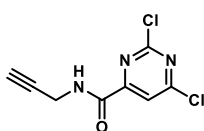
2,6-Dichloro-*N*-hexylpyrimidine-4-carboxamide (116e). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.6 mmol, 1.3 eq) and *n*-hexylamine (0.27 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% → 20% EtOAc/pentane) afforded the product (0.58 g, 2.0 mmol, 99%). TLC: R_f = 0.6 (10% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.89 (br s, 1H), 3.48 (q, *J* = 7.0 Hz, 2H), 1.66 (p, *J* = 7.8, 7.4 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 [C₁₁H₁₅Cl₂N₃O + H]⁺: 276.0665 calculated, 276.0668 found.



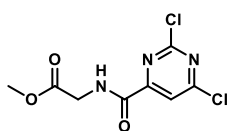
2,6-Dichloro-*N*-isobutylpyrimidine-4-carboxamide (116f). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.60 mmol, 1.3 eq) and isobutylamine (0.20 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% → 20% EtOAc/pentane) afforded the product (0.50 g, 2.0 mmol, 99%). TLC: R_f = 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 [C₉H₁₁Cl₂N₃O + H]⁺: 248.0352 calculated, 248.0354 found.



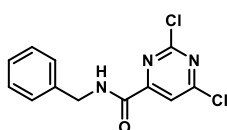
2,6-Dichloro-*N*-neopentylpyrimidine-4-carboxamide (116g). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.6 mmol, 1.3 eq) and neopentylamine (0.24 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% → 20% EtOAc/pentane) afforded the product (0.58 g, 2.0 mmol, 99%). TLC: R_f = 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 [C₁₀H₁₃Cl₂N₃O + H]⁺: 262.0508 calculated, 262.0510 found.



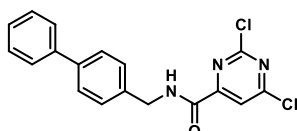
2,6-Dichloro-*N*-(prop-2-yn-1-yl)pyrimidine-4-carboxamide (116h). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.25 mL, 2.0 mmol, 1 eq), Et₃N (0.36 mL, 2.60 mmol, 1.3 eq) and propargylamine (0.13 mL, 2.05 mmol, 1.025 eq). Column chromatography (5% → 20% EtOAc/pentane) afforded the product (0.44 g, 1.9 mmol, 95%). TLC: R_f = 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 [C₈H₅Cl₂N₃O + H]⁺: 229.9882 calculated, 229.9884 found.



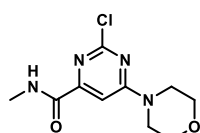
Methyl (2,6-dichloropyrimidine-4-carbonyl)glycinate (116i). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.32 mL, 2.5 mmol, 1 eq), Et₃N (0.80 mL, 5.75 mmol, 2.3 eq) and glycine methylester HCl salt (0.32 g, 2.56 mmol, 1.025 eq). Column chromatography (5% -> 20% EtOAc/pentane) afforded the product (0.51 g, 1.95 mmol, 78%). TLC: R_f = 0.5 (30% EtOAc/pentane). ¹H NMR (500 MHz, CDCl₃) δ 8.31 (br s, 1H), 8.09 (s, 1H), 4.28 (d, *J* = 5.8 Hz, 2H), 3.81 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 169.30, 164.89, 160.65, 160.02, 159.55, 118.31, 52.66, 41.35. HRMS [C₈H₇Cl₂N₃O₃ + H]⁺: 263.9937 calculated, 263.9939 found.



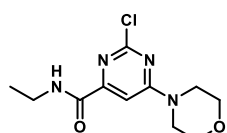
2,6-Dichloropyrimidine-N-benzyl-4-carboxamide (116j). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.63 mL, 5.0 mmol, 1 eq), Et₃N (0.91 mL, 6.5 mmol, 1.3 eq) and benzylamine (0.56 mL, 5.13 mmol, 1.025 eq). Column chromatography (10% -> 25% EtOAc/pentane) afforded the product (1.38 g, 4.9 mmol, 98%). TLC: R_f = 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 [C₁₂H₉Cl₂N₃O + H]⁺: 282.0195 calculated, 282.0197 found.



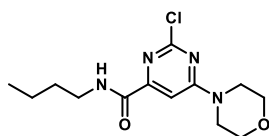
2,6-Dichloropyrimidine-N-([1,1'-biphenyl]-4-ylmethyl)-4-carboxamide (116k). The title compound was prepared according to general procedure D using 2,6-dichloropyrimidine-4-carbonyl chloride **115** (0.63 mL, 5.0 mmol, 1 eq), Et₃N (0.91 mL, 6.5 mmol, 1.3 eq) and 4-phenylbenzylamine (0.94 g, 5.13 mmol, 1.025 eq). Column chromatography (10% -> 30% EtOAc/pentane) afforded the product (1.46 g, 4.1 mmol, 82%). TLC: R_f = 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: R_f = 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 [C₁₀H₁₃ClN₄O₂ + H]⁺: 257.0800 calculated, 257.0800 found.

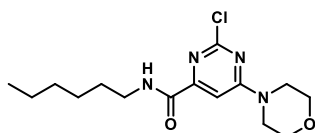


2-Chloro-N-ethyl-6-morpholinopyrimidine-4-carboxamide (117b). The title compound was prepared according to general procedure E using dichloropyrimidine **116c** (0.42 g, 1.9 mmol, 1 eq), DiPEA (0.49 mL, 2.8 mmol, 1.5 eq) and morpholine (0.17 mL, 2.0 mmol, 1.05 eq). Column chromatography (50% -> 70% EtOAc/pentane) afforded the product (0.48 g, 1.8 mmol, 95%). TLC: R_f = 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 [C₁₁H₁₅ClN₄O₂ + H]⁺: 271.0956 calculated, 271.0957 found.



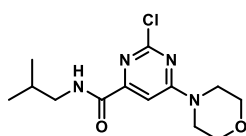
2-Chloro-*N*-butyl-6-morpholinopyrimidine-4-carboxamide (117c). The title compound was prepared according to general procedure E using dichloropyrimidine **116d** (193 mg, 0.78 mmol, 1 eq), DiPEA (203 μ L, 1.17 mmol, 1.5 eq) and morpholine (71 μ L, 0.82 mmol, 1.05 eq). Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (212 mg, 0.71 mmol, 91%).

TLC: R_f = 0.4 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 163.79, 162.19, 159.75, 157.88, 99.21, 66.31, 44.57, 39.29, 31.48, 20.07, 13.72. HRMS [$\text{C}_{13}\text{H}_{19}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 299.1269 calculated, 299.1269 found.



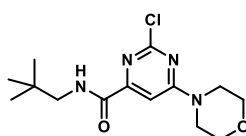
2-Chloro-*N*-hexyl-6-morpholinopyrimidine-4-carboxamide (117d). The title compound was prepared according to general procedure E using dichloropyrimidine **116e** (0.28 g, 1.02 mmol, 1 eq), DiPEA (0.27 mL, 1.54 mmol, 1.5 eq) and morpholine (94 μ L, 1.08 mmol, 1.05 eq). Column chromatography (40% \rightarrow 70% EtOAc/pentane) afforded the product (0.31 g, 0.95 mmol, 93%).

TLC: R_f = 0.5 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{15}\text{H}_{23}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 327.1582 calculated, 327.1582 found.



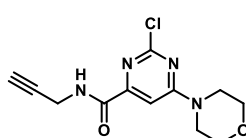
2-Chloro-*N*-isobutyl-6-morpholinopyrimidine-4-carboxamide (117e). The title compound was prepared according to general procedure E using dichloropyrimidine **116f** (0.28 g, 1.11 mmol, 1 eq), DiPEA (0.29 mL, 1.66 mmol, 1.5 eq) and morpholine (101 μ L, 1.16 mmol, 1.05 eq). Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (0.33 g, 1.11 mmol, 99%).

TLC: R_f = 0.5 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.91 (t, J = 5.8 Hz, 1H), 7.28 (s, 1H), 4.01 – 3.52 (m, 8H), 3.26 (t, J = 6.7 Hz, 2H), 2.00 – 1.81 (m, 1H), 0.97 (d, J = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.75, 162.25, 159.71, 157.83, 99.23, 66.26, 46.82, 44.56, 28.58, 20.11. HRMS [$\text{C}_{13}\text{H}_{19}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 299.1269 calculated, 299.1270 found.



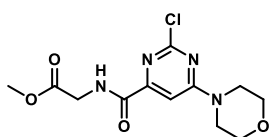
2-Chloro-6-morpholino-*N*-neopentylpyrimidine-4-carboxamide (117f). The title compound was prepared according to general procedure E using dichloropyrimidine **116g** (0.25 g, 0.96 mmol, 1 eq), DiPEA (0.25 mL, 1.44 mmol, 1.5 eq) and morpholine (88 μ L, 1.01 mmol, 1.05 eq). Column chromatography (30% \rightarrow 60% EtOAc/pentane) afforded the product (0.30 g, 0.96 mmol, 99%).

TLC: R_f = 0.5 (40% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 163.77, 162.36, 159.74, 157.82, 99.30, 66.27, 50.64, 44.60, 32.34, 27.23. HRMS [$\text{C}_{14}\text{H}_{21}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 313.1426 calculated, 313.1424 found.



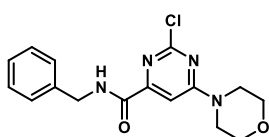
2-Chloro-6-morpholino-*N*-(prop-2-yn-1-yl)pyrimidine-4-carboxamide (117g). The title compound was prepared according to general procedure E using dichloropyrimidine **116h** (221 mg, 0.96 mmol, 1 eq), DiPEA (251 μ L, 1.44 mmol, 1.5 eq) and morpholine (88 μ L, 1.01 mmol, 1.05 eq). Column chromatography (40% \rightarrow 60% EtOAc/pentane) afforded the product (249 mg, 0.89 mmol, 93%).

TLC: R_f = 0.5 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 163.84, 162.23, 160.04, 157.20, 99.53, 78.84, 72.05, 66.41, 29.32. HRMS [$\text{C}_{12}\text{H}_{13}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 281.0800 calculated, 281.0800 found.



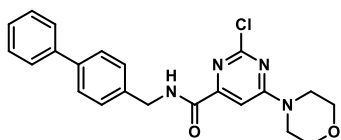
Methyl (2-chloro-6-morpholinopyrimidine-4-carbonyl)glycinate (117h). The title compound was prepared according to general procedure E using dichloropyrimidine **116i** (0.40 g, 1.50 mmol, 1 eq), DiPEA (0.39 mL, 2.25 mmol, 1.5 eq) and morpholine (137 μ L, 1.58 mmol, 1.05 eq). Column chromatography (60% \rightarrow 80% EtOAc/pentane) afforded the product (0.30 g, 0.95 mmol, 63%).

TLC: R_f = 0.5 (70% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 169.59, 163.83, 162.85, 160.06, 157.09, 99.50, 66.39, 52.51, 44.69, 41.29. HRMS [$\text{C}_{12}\text{H}_{15}\text{ClN}_4\text{O}_4 + \text{H}$] $^+$: 315.0855 calculated, 315.0851 found.



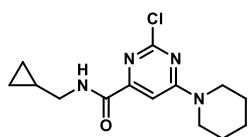
2-Chloro-N-benzyl-6-morpholinopyrimidine-4-carboxamide (117i) The title compound was prepared according to general procedure E using dichloropyrimidine **116j** (0.71 g, 2.50 mmol, 1 eq), DiPEA (0.65 mL, 3.75 mmol, 1.5 eq) and morpholine (0.23 mL, 2.63 mmol, 1.05 eq). Column chromatography (30% \rightarrow 60% EtOAc/pentane) afforded the product (0.68 g, 2.03 mmol, 81%).

TLC: R_f = 0.6 (60% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{16}\text{H}_{17}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 333.1113 calculated, 333.1112 found.



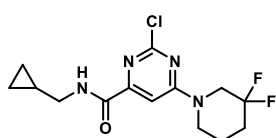
2-Chloro-N-([1,1'-biphenyl]-4-ylmethyl)-6-morpholinopyrimidine-4-carboxamide (117j). The title compound was prepared according to general procedure E using dichloropyrimidine **116k** (0.31 g, 1.0 mmol, 1 eq), DiPEA (0.26 mL, 1.5 mmol, 1.5 eq) and morpholine (91 μ L, 1.05 mmol, 1.05 eq). Column chromatography (20% \rightarrow 50% EtOAc/pentane) afforded the product (0.38 g, 0.94 mmol, 94%).

TLC: R_f = 0.4 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 163.79, 162.44, 159.91, 157.63, 140.62, 136.62, 128.86, 128.43, 127.48, 127.11, 99.53, 66.37, 44.65, 43.36. HRMS [$\text{C}_{22}\text{H}_{21}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 409.1426 calculated, 409.1421 found.



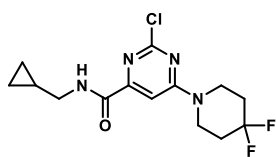
2-Chloro-N-(cyclopropylmethyl)-6-(piperidin-1-yl)pyrimidine-4-carboxamide (117k). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (0.26 g, 1.05 mmol, 1 eq), DiPEA (0.27 mL, 1.58 mmol, 1.5 eq) and piperidine (109 μ L, 1.10 mmol, 1.05 eq). Column chromatography (10% \rightarrow 40% EtOAc/pentane) afforded the product (0.29 g, 0.99 mmol, 94%).

TLC: R_f = 0.2 (20% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 163.12, 162.45, 159.77, 157.35, 99.29, 44.31, 25.55, 24.31, 10.61, 3.58. HRMS [$\text{C}_{14}\text{H}_{19}\text{ClN}_4\text{O} + \text{H}$] $^+$: 295.1320 calculated, 295.1321 found.

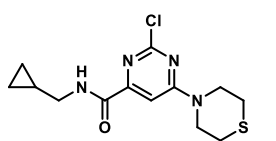


2-Chloro-N-(cyclopropylmethyl)-6-(3,3-difluoropiperidin-1-yl)pyrimidine-4-carboxamide (117l). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (0.10 g, 0.41 mmol, 1 eq), DiPEA (100 μ L, 0.57 mmol, 2.4 eq) and 3,3-difluoropiperidine HCl salt (68 mg, 0.43 mmol, 1.05 eq). Column chromatography (10% \rightarrow 40% EtOAc/pentane) afforded the product (88 mg, 0.26 mmol, 63%).

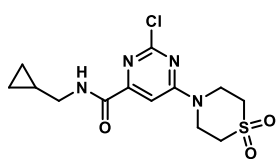
TLC: R_f = 0.4 (20% EtOAc/pentane). ^1H NMR (300 MHz, CDCl_3) δ 7.91 (br s, 1H), 7.35 (s, 1H), 3.99 (br s, 2H), 3.74 (br s, 2H), 3.29 (t, J = 6.5 Hz, 2H), 2.13 (tt, J = 13.3, 6.3 Hz, 2H), 2.02 – 1.74 (m, 2H), 1.17 – 0.95 (m, 1H), 0.67 – 0.44 (m, 2H), 0.28 (q, J = 5.1 Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3) 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 [$\text{C}_{14}\text{H}_{17}\text{ClF}_2\text{N}_4\text{O} + \text{H}$] $^+$: 331.1132 calculated, 331.1127 found.



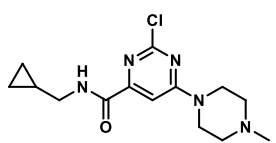
2-Chloro-*N*-(cyclopropylmethyl)-6-(4,4-difluoropiperidin-1-yl)pyrimidine-4-carboxamide (117m). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (0.12 g, 0.49 mmol, 1 eq), DiPEA (0.21 mL, 1.23 mmol, 2.5 eq) and 4,4-difluoropiperidine HCl salt (86 mg, 0.52 mmol, 1.05 eq). Column chromatography (5% → 25% EtOAc/pentane) afforded the product (90 mg, 0.27 mmol, 55%). TLC: $R_f = 0.4$ (15% EtOAc/pentane). $^1\text{H NMR}$ (300 MHz, CDCl_3) 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). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) 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 [$\text{C}_{14}\text{H}_{17}\text{ClF}_2\text{N}_4\text{O} + \text{H}$] $^+$: 331.1132 calculated, 331.1127 found.



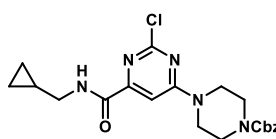
2-Chloro-*N*-(cyclopropylmethyl)-6-thiomorpholinopyrimidine-4-carboxamide (117n). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (0.12 g, 0.48 mmol, 1 eq), DiPEA (0.12 mL, 0.71 mmol, 1.5 eq) and thiomorpholine (51 μL , 0.50 mmol, 1.05 eq). Column chromatography (20% → 50% EtOAc/pentane) afforded the product (48 mg, 0.15 mmol, 31%). TLC: $R_f = 0.2$ (20% EtOAc/pentane). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.91 (br s, 1H), 7.28 (s, 1H), 4.07 (br s, 4H), 3.36 – 3.23 (m, 2H), 2.74 – 2.63 (m, 4H), 1.12 – 0.99 (m, 1H), 0.65 – 0.48 (m, 2H), 0.29 (q, $J = 4.8$ Hz, 2H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 163.33, 162.30, 160.04, 158.07, 99.66, 44.55, 27.05, 10.73, 3.74. HRMS [$\text{C}_{13}\text{H}_{17}\text{ClN}_4\text{OS} + \text{H}$] $^+$: 313.0884 calculated, 313.0884 found.



2-Chloro-*N*-(cyclopropylmethyl)-6-(1,1-dioxidothiomorpholino)pyrimidine-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: $R_f = 0.5$ (60% EtOAc/pentane). Major regioisomer: $^1\text{H NMR}$ (500 MHz, $\text{CDCl}_3 + \text{MeOD}$) 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). $^{13}\text{C NMR}$ (126 MHz, $\text{CDCl}_3 + \text{MeOD}$) δ 163.16, 162.11, 159.92, 158.47, 99.62, 51.14, 44.23, 42.86, 42.43, 10.18, 3.19. HRMS [$\text{C}_{13}\text{H}_{17}\text{ClN}_4\text{O}_3\text{S} + \text{H}$] $^+$: 345.0783 calculated, 345.0782 found.

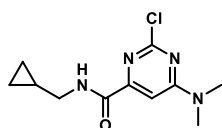


2-Chloro-*N*-(cyclopropylmethyl)-6-(4-methylpiperazin-1-yl)pyrimidine-4-carboxamide (117p). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (96 mg, 0.39 mmol, 1 eq), DiPEA (102 μL , 0.59 mmol, 1.5 eq) and 1-methylpiperazine (45 μL , 0.41 mmol, 1.05 eq). Column chromatography (5% → 10% MeOH/DCM) afforded the product (77 mg, 0.25 mmol, 64%). TLC: $R_f = 0.4$ (5% MeOH/DCM). $^1\text{H NMR}$ (500 MHz, CDCl_3) 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). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 163.61, 162.39, 159.88, 157.74, 99.52, 54.50, 46.06, 44.49, 43.44, 10.70, 3.71. HRMS [$\text{C}_{14}\text{H}_{20}\text{ClN}_5\text{O} + \text{H}$] $^+$: 310.1429 calculated, 310.1429 found.

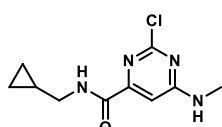


Benzyl-4-(2-chloro-6-((cyclopropylmethyl)carbamoyl)pyrimidin-4-yl)piperazine-1-carboxylate (117q). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (181 mg, 0.74 mmol, 1 eq), DiPEA (193 μL , 1.11 mmol, 1.5 eq) and 1-Cbz-piperazine (149 μL , 0.77 mmol, 1.05 eq). Column chromatography (30% → 60% EtOAc/pentane) afforded the product (290 mg, 0.67 mmol, 91%). TLC: $R_f = 0.5$ (50% EtOAc/pentane). $^1\text{H NMR}$ (400 MHz, CDCl_3) 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). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ

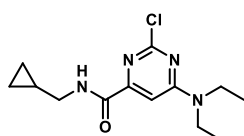
163.64, 162.10, 159.81, 158.01, 155.01, 136.26, 128.54, 128.20, 128.00, 99.44, 67.50, 44.40, 43.17, 10.63, 3.61.



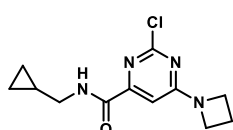
2-Chloro-*N*-(cyclopropylmethyl)-6-(dimethylamino)pyrimidine-4-carboxamide (117r). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (0.25 g, 1.0 mmol, 1 eq), DiPEA (0.26 mL, 1.5 mmol, 1.5 eq) and dimethylamine (2 M in THF, 0.53 mL, 1.05 mmol, 1.05 eq). Column chromatography (40% → 60% EtOAc/pentane) afforded the product (225 mg, 0.88 mmol, 88%). TLC: R_f = 0.5 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.97 (br s, 1H), 7.19 (s, 1H), 3.33 – 3.27 (m, 2H), 3.27 – 3.06 (m, 6H), 1.13 – 0.99 (m, 1H), 0.62 – 0.49 (m, 2H), 0.29 (q, J = 4.8 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.03, 162.29, 159.36, 156.93, 99.19, 44.26, 37.76, 37.29, 10.56, 3.53. HRMS [$\text{C}_{11}\text{H}_{15}\text{ClN}_4\text{O} + \text{H}$] $^+$: 255.1007 calculated, 255.1005 found.



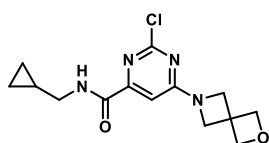
2-Chloro-*N*-(cyclopropylmethyl)-6-(methylamino)pyrimidine-4-carboxamide (117s). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (123 mg, 0.50 mmol, 1 eq), DiPEA (218 μL , 1.25 mmol, 2.5 eq) and methylamine HCl salt (35 mg, 0.53 mmol, 1.05 eq). Column chromatography (50% → 70% EtOAc/pentane) afforded the product (77 mg, 0.32 mmol, 64%). TLC: R_f = 0.4 (60% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) δ 7.93 (br s, 1H), 7.40 – 7.04 (m, 1H), 6.62 – 6.20 (m, 1H), 3.29 (br s, 2H), 3.04 (br s, 3H), 1.13 – 1.00 (m, 1H), 0.65 – 0.50 (m, 2H), 0.29 (q, J = 4.9 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.67, 166.23, 165.44, 162.63, 162.22, 160.34, 158.43, 155.80, 103.55, 98.02, 44.55, 29.81, 29.06, 28.22, 3.76. HRMS [$\text{C}_{10}\text{H}_{13}\text{ClN}_4\text{O} + \text{H}$] $^+$: 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: R_f = 0.7 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.94 (br s, 1H), 7.16 (s, 1H), 3.77 – 3.37 (m, 4H), 3.34 – 3.24 (m, 2H), 1.22 (t, J = 7.0 Hz, 6H), 1.12 – 1.00 (m, 1H), 0.61 – 0.51 (m, 2H), 0.29 (q, J = 4.8 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.96, 162.57, 159.79, 157.11, 99.29, 44.41, 42.96, 42.73, 12.64, 10.69, 3.67. HRMS [$\text{C}_{13}\text{H}_{19}\text{ClN}_4\text{O} + \text{H}$] $^+$: 283.1320 calculated, 283.1319 found.

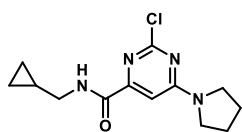


2-Chloro-*N*-(cyclopropylmethyl)-6-(azetidin-1-yl)pyrimidine-4-carboxamide (117u). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (98 mg, 0.40 mmol, 1 eq), DiPEA (174 μL , 1.0 mmol, 2.5 eq) and azetidine HCl salt (39 mg, 0.42 mmol, 1.05 eq). Column chromatography (30% → 50% EtOAc/pentane) afforded the product (79 mg, 0.30 mmol, 75%). TLC: R_f = 0.3 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.90 (br s, 1H), 6.88 (s, 1H), 4.44 – 4.07 (m, 4H), 3.28 (dd, J = 7.0, 6.0 Hz, 2H), 2.49 (p, J = 7.6 Hz, 2H), 1.14 – 0.99 (m, 1H), 0.62 – 0.51 (m, 2H), 0.28 (q, J = 4.7 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.91, 162.30, 159.95, 156.54, 98.54, 50.20, 44.44, 16.51, 10.69, 3.69. HRMS [$\text{C}_{12}\text{H}_{15}\text{ClN}_4\text{O} + \text{H}$] $^+$: 267.1007 calculated, 267.1005 found.

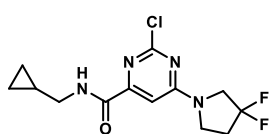


2-Chloro-*N*-(cyclopropylmethyl)-6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidine-4-carboxamide (117v). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (98 mg, 0.40 mmol, 1 eq), DiPEA (174 μL , 1.0 mmol, 2.5 eq) and 2-oxa-6-azaspiro[3.3]heptane hemioxalate salt (61 mg, 0.42 mmol, 1.05 eq). Column chromatography (40% → 100% EtOAc/pentane) afforded the product (96 mg, 0.31 mmol, 78%). TLC: R_f = 0.2 (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.88 (br s, 1H), 6.92 (s, 1H), 4.86 (br s, 4H), 4.35 (s, 4H), 3.28 (dd, J = 7.0, 6.0 Hz,

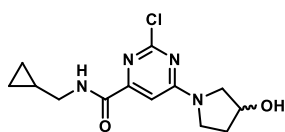
2H), 1.11 – 0.98 (m, 1H), 0.63 – 0.50 (m, 2H), 0.34 – 0.23 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.01, 162.11, 160.06, 157.10, 98.96, 80.71, 59.73, 44.56, 39.16, 10.72, 3.76. HRMS [$\text{C}_{14}\text{H}_{17}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 309.1113 calculated, 309.1110 found.



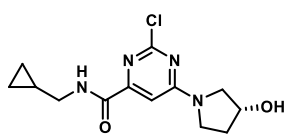
2-Chloro-*N*-(cyclopropylmethyl)-6-(pyrrolidin-1-yl)pyrimidine-4-carboxamide (117w). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (123 mg, 0.50 mmol, 1 eq), DiPEA (131 μL , 0.75 mmol, 1.5 eq) and pyrrolidine (43 μL , 0.53 mmol, 1.05 eq). Column chromatography (30% -> 60% EtOAc/pentane) afforded the product (150 mg, 0.40 mmol, 80%). TLC: R_f = 0.5 (40% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 162.52, 161.97, 159.61, 156.52, 100.53, 47.23, 46.98, 44.43, 25.52, 24.82, 10.69, 3.69. HRMS [$\text{C}_{13}\text{H}_{17}\text{ClN}_4\text{O} + \text{H}$] $^+$: 281.1164 calculated, 281.1160 found.



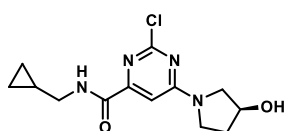
2-Chloro-*N*-(cyclopropylmethyl)-6-(3,3-difluoropyrrolidin-1-yl)pyrimidine-4-carboxamide (117x). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (98 mg, 0.40 mmol, 1 eq), DiPEA (174 μL , 1.0 mmol, 2.5 eq) and 3,3-difluoropyrrolidine HCl salt (60 mg, 0.42 mmol, 1.05 eq). Column chromatography (20% -> 40% EtOAc/pentane) afforded the product (108 mg, 0.34 mmol, 85%). TLC: R_f = 0.6 (40% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) 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). ^{13}C NMR (126 MHz, CDCl_3) δ 162.52, 162.11, 159.90, 157.70, 100.24, 99.83, 53.66 (t, J = 32.9 Hz), 44.62, 33.91, 3.78. HRMS [$\text{C}_{13}\text{H}_{15}\text{ClF}_2\text{N}_4\text{O} + \text{H}$] $^+$: 317.0975 calculated, 317.0974 found.



(±)-2-Chloro-*N*-(cyclopropylmethyl)-6-(3-hydroxypyrrolidin-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 (±)-3-hydroxypyrrolidine 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: R_f = 0.2 (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{13}\text{H}_{17}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 297.1113 calculated, 297.1110 found.

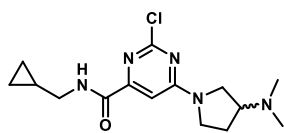


(*R*)-2-Chloro-*N*-(cyclopropylmethyl)-6-(3-hydroxypyrrolidin-1-yl)pyrimidine-4-carboxamide (117z). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (98 mg, 0.40 mmol, 1 eq), DiPEA (174 μL , 1.0 mmol, 2.5 eq) and (*R*)-3-hydroxypyrrolidine HCl salt (52 mg, 0.42 mmol, 1.05 eq). Column chromatography (70% -> 100% EtOAc/pentane) afforded the product (105 mg, 0.35 mmol, 88%). TLC: R_f = 0.2 (80% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{13}\text{H}_{17}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 297.1113 calculated, 297.1110 found.

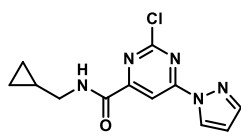


(*S*)-2-Chloro-*N*-(cyclopropylmethyl)-6-(3-hydroxypyrrolidin-1-yl)pyrimidine-4-carboxamide (117aa). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (98 mg, 0.40 mmol, 1 eq), DiPEA (174 μL , 1.0 mmol, 2.5 eq) and (*S*)-3-hydroxypyrrolidine HCl salt (52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

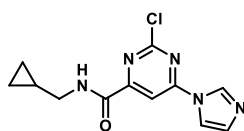
mmol, 1.05 eq). Column chromatography (70% → 100% EtOAc/pentane) afforded the product (97 mg, 0.33 mmol, 83%). TLC: $R_f = 0.2$ (80% EtOAc/pentane). ^1H NMR (300 MHz, CDCl_3) δ 7.98 (t, $J = 5.2$ Hz, 1H), 7.11 – 6.86 (m, 1H), 4.81 – 4.47 (m, 1H), 3.93 – 3.35 (m, 5H), 3.33 – 3.21 (m, 2H), 2.25 – 2.06 (m, 2H), 1.16 – 0.96 (m, 1H), 0.57 (q, $J = 5.5$ Hz, 2H), 0.29 (q, $J = 4.7$ Hz, 2H). ^{13}C 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 [$\text{C}_{13}\text{H}_{17}\text{ClN}_4\text{O}_2 + \text{H}$] $^+$: 297.1113 calculated, 297.1110 found.



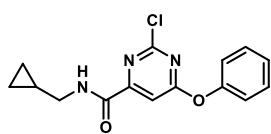
(±)-2-Chloro-*N*-(cyclopropylmethyl)-6-(3-(dimethylamino)pyrrolidin-1-yl)pyrimidine-4-carboxamide (117ab). The title compound was prepared according to general procedure E using dichloropyrimidine **116a** (98 mg, 0.40 mmol, 1 eq), DIPEA (244 μL , 1.4 mmol, 3.5 eq) and (±)-3-(dimethylamino)pyrrolidine 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: $R_f = 0.4$ (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 – 3.25 (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). ^{13}C 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, 156.79, 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, 44.22, 44.02, 30.41, 29.81, 10.90, 10.85, 10.74, 3.76, 3.51, 3.47. HRMS [$\text{C}_{15}\text{H}_{22}\text{ClN}_5\text{O} + \text{H}$] $^+$: 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_2CO_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: $R_f = 0.8$ (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). ^{13}C 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 [$\text{C}_{12}\text{H}_{12}\text{ClN}_5\text{O} + \text{H}$] $^+$: 278.0803 calculated, 278.0802 found.

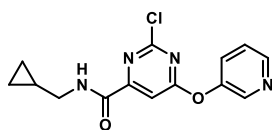


2-Chloro-*N*-(cyclopropylmethyl)-6-(1H-imidazol-1-yl)pyrimidine-4-carboxamide (117ad). The title compound was prepared according to general procedure F using dichloropyrimidine **116a** (123 mg, 0.50 mmol, 1 eq), K_2CO_3 (104 mg, 0.75 mmol, 1.5 eq) and imidazole (36 mg, 0.53 mmol, 1.05 eq). Column chromatography (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: $R_f = 0.4$ (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). ^{13}C 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 [$\text{C}_{12}\text{H}_{12}\text{ClN}_5\text{O} + \text{H}$] $^+$: 278.0803 calculated, 278.0800 found.



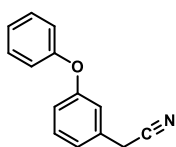
2-Chloro-*N*-(cyclopropylmethyl)-6-phenoxy pyrimidine-4-carboxamide (117ae). The title compound was prepared according to general procedure F using dichloropyrimidine **116a** (100 mg, 0.41 mmol, 1 eq), K_2CO_3 (86 mg, 0.62 mmol, 1.5 eq) and phenol (44 mg, 0.43 mmol, 1.05 eq). Column chromatography (5% → 30% EtOAc/pentane) afforded the product (100 mg, 0.33 mmol, 80%). TLC: $R_f = 0.4$ (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). ^{13}C NMR (75 MHz,

CDCl_3) δ 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 $[\text{C}_{15}\text{H}_{14}\text{ClN}_3\text{O}_2 + \text{H}]^+$: 304.0847 calculated, 304.0845 found.



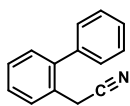
2-Chloro-*N*-(cyclopropylmethyl)-6-(pyridin-3-yloxy)pyrimidine-4-carboxamide (117af). The title compound was prepared according to general procedure F

using dichloropyrimidine **116a** (0.11 g, 0.45 mmol, 1 eq), K_2CO_3 (93 mg, 0.68 mmol, 1.5 eq) and pyridine-3-ol (45 mg, 0.47 mmol, 1.05 eq). Column chromatography (60% \rightarrow 100% EtOAc/pentane) afforded the product (70 mg, 0.23 mmol, 51%). TLC: R_f = 0.4 (80% EtOAc/pentane). ^1H NMR (300 MHz, CDCl_3) δ 8.56 (dd, J = 9.3, 3.2 Hz, 2H), 7.94 (br s, 1H), 7.69 (s, 1H), 7.63 – 7.50 (m, 1H), 7.43 (dd, J = 8.3, 4.7 Hz, 1H), 3.46 – 3.19 (m, 2H), 1.17 – 0.99 (m, 1H), 0.66 – 0.51 (m, 2H), 0.31 (q, J = 4.8 Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 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 $[\text{C}_{14}\text{H}_{13}\text{ClN}_4\text{O}_2 + \text{H}]^+$: 305.0800 calculated, 305.0796 found.



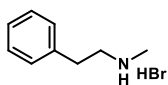
2-(3-Phenoxyphenyl)acetonitrile (119a). A round-bottom flask was charged with 1-(chloromethyl)-3-phenoxybenzene (**118a**) (0.37 mL, 2.0 mmol, 1 eq) in dioxane/EtOH/ H_2O (2:2:1, 6 mL) and KCN (0.26 g, 4.0 mmol, 2 eq). The reaction mixture was stirred overnight at reflux. The mixture was diluted with water and extracted with EtOAc (3x). The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced

pressure. The crude material was purified by silica gel column chromatography (5% \rightarrow 7% EtOAc/pentane) to provide the product (0.35 g, 1.7 mmol, 85%). TLC: R_f = 0.6 (10% EtOAc/pentane). ^1H NMR (500 MHz, CDCl_3) δ 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}C NMR (126 MHz, CDCl_3) δ 157.73, 156.32, 131.81, 130.23, 129.71, 123.58, 122.34, 118.97, 117.96, 117.78, 117.51, 23.00.



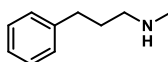
2-([1,1'-Biphenyl]-2-yl)acetonitrile (119b). A round-bottom flask was charged with 2-(bromomethyl)-1,1'-biphenyl (**118b**) (0.37 mL, 2.0 mmol, 1 eq), solvent mixture dioxane/EtOH/ H_2O (2:2:1, 6 mL) and KCN (0.26 g, 4.0 mmol, 2 eq). The reaction mixture was stirred overnight at reflux. The mixture was diluted with water and extracted with EtOAc (3x).

The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (0.5% \rightarrow 5% EtOAc/pentane) to provide the product (0.40 g, 2.0 mmol, 99%). TLC: R_f = 0.6 (3% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.59 – 7.12 (m, 9H), 3.57 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 141.72, 139.78, 130.35, 128.86, 128.84, 128.59, 128.12, 127.68, 118.23, 21.92.



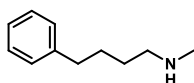
***N*-Methylphenethylamine HBr salt (121a).** A round-bottom flask was charged with methylamine (33 wt% in ethanol, 8.83 mL, 73.0 mmol, 10 eq) and cooled to 0 °C. (2-bromoethyl)benzene (1.0 mL, 7.3 mmol, 1 eq) was added and the reaction was stirred and

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 di-substituted by product, *N*-methyl-*N*-phenethyl-2-phenylethan-1-amine (9:1) and used without further purification (1.4 g, 6.6 mmol, 90%). TLC: R_f = 0.35 (6% MeOH/DCM). ^1H NMR (400 MHz, MeOD) δ 7.52 – 6.99 (m, 5H), 3.42 – 3.10 (m, 2H), 3.10 – 2.85 (m, 2H), 2.67 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 137.75, 129.86, 129.78, 128.10, 51.50, 33.92, 33.31.



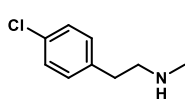
***N*-Methyl-3-phenylpropan-1-amine (121b).** *Carbamoylation:* The methyl carbamate was prepared according to general procedure G using 3-phenylpropan-1-amine (71 μL , 0.50 mmol, 1 eq), methylchloroformate (58 μL , 0.75 mmol, 1.5 eq) and DiPEA (174 μL , 1.0 mmol, 2 eq). Column chromatography (20% \rightarrow 50% EtOAc/pentane) afforded the product (91 mg, 0.47 mmol, 94%). TLC: R_f = 0.7 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 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). ^{13}C NMR (101 MHz, CDCl_3) δ 157.18, 141.47, 128.49, 128.40, 126.02, 52.08, 40.68, 33.06, 31.68. HRMS [$\text{C}_{11}\text{H}_{15}\text{NO}_2 + \text{H}$] $^+$: 194.1176 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), LiAlH_4 (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: $R_f = 0.1$ (5% MeOH/DCM). ^1H NMR (500 MHz, CDCl_3) 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 [$\text{C}_{10}\text{H}_{15}\text{N} + \text{H}$] $^+$: 150.1277 calculated, 150.1278 found.



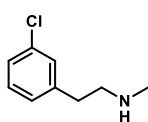
N-Methyl-4-phenylbutan-1-amine (121c). *Carbamoylation*: the methyl carbamate was

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: $R_f = 0.6$ (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 157.15, 142.15, 128.42, 128.37, 125.84, 52.01, 40.93, 35.54, 29.65, 28.55. HRMS [$\text{C}_{12}\text{H}_{17}\text{NO}_2 + \text{H}$] $^+$: 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), LiAlH_4 (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: $R_f = 0.1$ (5% MeOH/DCM). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 142.51, 128.45, 128.31, 125.73, 52.05, 36.57, 35.90, 29.61, 29.24. HRMS [$\text{C}_{11}\text{H}_{17}\text{N} + \text{H}$] $^+$: 164.1434 calculated, 164.1433 found.



2-(4-Chlorophenyl)-N-methylethan-1-amine (121d). *Carbamoylation*: the methyl

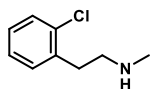
carbamate was prepared according to general procedure G using 2-(4-chlorophenyl)ethan-1-amine (70 μL , 0.50 mmol, 1 eq), methylchloroformate (58 μL , 0.75 mmol, 1.5 eq) and DiPEA (174 μL , 1.0 mmol, 2 eq). Column chromatography (10% -> 50% EtOAc/pentane) afforded the product (104 mg, 0.50 mmol, 99%). TLC: $R_f = 0.7$ (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 157.04, 137.32, 132.39, 130.22, 128.80, 52.20, 42.17, 35.62. HRMS [$\text{C}_{10}\text{H}_{12}\text{ClNO}_2 + \text{H}$] $^+$: 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), LiAlH_4 (2 M THF solution, 0.39 mL, 0.77 mmol, 1.6 eq). Column chromatography (isocratic, 5% MeOH/DCM + 0.5% Et_3N) afforded the product (36 mg, 0.21 mmol, 44%). TLC: $R_f = 0.1$ (2% MeOH/DCM with 3 drops of Et_3N). ^1H NMR (500 MHz, CDCl_3) 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). ^{13}C NMR (126 MHz, CDCl_3) δ 138.30, 132.03, 130.14, 128.66, 52.87, 36.12, 35.26. HRMS [$\text{C}_9\text{H}_{12}\text{ClN} + \text{H}$] $^+$: 170.0731 calculated, 170.0732 found.



2-(3-Chlorophenyl)-N-methylethan-1-amine (121e). *Carbamoylation*: the methyl

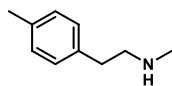
carbamate was prepared according to general procedure G using 2-(3-chlorophenyl)ethan-1-amine (70 μL , 0.40 mmol, 1 eq), methylchloroformate (58 μL , 0.75 mmol, 1.5 eq) and DiPEA (174 μL , 2.0 mmol, 2 eq). Column chromatography (20% -> 40% EtOAc/pentane) afforded the product (67 mg, 0.31 mmol, 78%). TLC: $R_f = 0.7$ (30% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 157.05, 140.94, 134.37, 129.90, 128.93, 127.04, 126.75, 52.15, 42.04, 35.90. HRMS [$\text{C}_{10}\text{H}_{12}\text{ClNO}_2 + \text{H}$] $^+$: 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), LiAlH_4 (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%). $R_f = 0.15$ (6% MeOH/DCM). $^1\text{H NMR}$ (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). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 141.75, 134.40, 129.90, 128.92, 127.06, 126.63, 52.69, 36.06, 35.51. HRMS [$\text{C}_9\text{H}_{12}\text{ClN} + \text{H}$] $^+$: 170.0731 calculated, 170.0730 found.



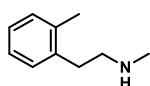
2-(2-Chlorophenyl)-N-methylethan-1-amine (121f). *Carbamoylation:* the methyl carbamate

was prepared according to general procedure G using 2-(2-chlorophenyl)ethan-1-amine (141 μL , 1.0 mmol, 1 eq), methylchloroformate (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, 85%). TLC: $R_f = 0.7$ (50% EtOAc/pentane). $^1\text{H NMR}$ (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). $^{13}\text{C NMR}$ (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 [$\text{C}_{10}\text{H}_{12}\text{ClNO}_2 + \text{H}$] $^+$: 214.0629 calculated, 214.0630 found ($\Delta = 0.14$ ppm). *Carbamate reduction:* 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: $R_f = 0.1$ (6% MeOH/DCM). $^1\text{H NMR}$ (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). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 137.55, 134.08, 130.82, 129.58, 127.67, 126.81, 51.32, 36.18, 33.82. HRMS [$\text{C}_9\text{H}_{12}\text{ClN} + \text{H}$] $^+$: 170.0731 calculated, 170.0732 found.



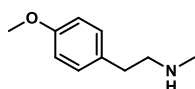
N-Methyl-2-(p-tolyl)ethan-1-amine (121g). *Carbamoylation:* the methyl carbamate was

prepared according to general procedure G using 2-(p-tolyl)ethan-1-amine (145 μL , 1.0 mmol, 1 eq), methylchloroformate (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: $R_f = 0.7$ (50% EtOAc/pentane). $^1\text{H NMR}$ (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). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 157.00, 135.82, 135.66, 129.18, 128.55, 51.85, 42.26, 35.60, 20.91. HRMS [$\text{C}_{11}\text{H}_{15}\text{NO}_2 + \text{H}$] $^+$: 194.1176 calculated, 194.1176 found. *Carbamate reduction:* the title compound was prepared according to general procedure G using the methyl carbamate (198 mg, 1.0 mmol, 1 eq), LiAlH_4 (2 M THF solution, 0.80 mL, 1.0 mmol, 1.6 eq) and was used without further purification (130 mg, 0.87 mmol, 87%). TLC: $R_f = 0.2$ (5% MeOH/DCM). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.11 – 7.07 (m, 4H), 2.83 – 2.72 (m, 4H), 2.41 (s, 3H), 2.33 – 2.28 (m, 4H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 136.87, 135.59, 129.17, 128.60, 80.66, 53.26, 36.28, 35.65, 21.02. HRMS [$\text{C}_{10}\text{H}_{15}\text{N} + \text{H}$] $^+$: 150.1277 calculated, 150.1277 found.



N-Methyl-2-(o-tolyl)ethan-1-amine (121h). *Carbamoylation:* the methyl carbamate was

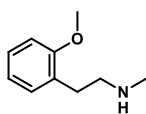
prepared according to general procedure G using 2-(o-tolyl)ethan-1-amine (70 μL , 0.50 mmol, 1 eq), methylchloroformate (58 μL , 0.75 mmol, 1.5 eq) and DiPEA (174 μL , 1.0 mmol, 2 eq). Column chromatography (30% -> 50% EtOAc/pentane) afforded the product (102 mg, 0.50 mmol, 99%). TLC: $R_f = 0.7$ (50% EtOAc/pentane). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.19 – 7.07 (m, 4H), 5.00 – 4.79 (m, 1H), 3.65 (s, 3H), 3.37 (q, $J = 6.9$ Hz, 2H), 2.81 (t, $J = 7.4$ Hz, 2H), 2.32 (s, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 157.12, 136.93, 136.37, 130.44, 129.34, 126.62, 126.11, 52.03, 41.16, 33.59, 19.29. HRMS [$\text{C}_{11}\text{H}_{15}\text{NO}_2 + \text{H}$] $^+$: 194.1176 calculated, 194.1176 found. *Carbamate reduction:* the title compound was prepared according to general procedure G using the methyl carbamate (102 mg, 0.50 mmol, 1 eq), LiAlH_4 (1 M THF solution, 0.85 mL, 0.85 mmol, 1.6 eq) and was used without further purification (74 mg, 0.50 mmol, 99%). TLC: $R_f = 0.1$ (6% MeOH/DCM). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.21 – 7.02 (m, 4H), 2.80 (s, 4H), 2.45 (s, 3H), 2.32 (s, 3H), 1.71 (br s, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 138.15, 136.21, 130.34, 129.25, 126.29, 126.01, 52.11, 36.44, 33.56, 19.42. HRMS [$\text{C}_{10}\text{H}_{15}\text{N} + \text{H}$] $^+$: 150.1277 calculated, 150.1277 found.



2-(4-Methoxyphenyl)-N-methylethan-1-amine (121i). *Carbamoylation:* the methyl

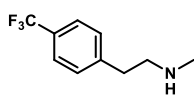
carbamate was prepared according to general procedure G using 2-(4-methoxyphenyl)ethan-1-amine (73 μL , 0.50 mmol, 1 eq), methylchloroformate (58 μL ,

0.75 mmol, 1.5 eq) and DiPEA (174 μ L, 1.0 mmol, 2 eq). Column chromatography (10% \rightarrow 40% EtOAc/pentane) afforded the product (108 mg, 0.50 mmol, 99%). TLC: R_f = 0.6 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 158.21, 157.04, 130.80, 129.69, 113.99, 55.21, 51.96, 42.42, 35.21. HRMS [$\text{C}_{11}\text{H}_{15}\text{NO}_3 + \text{H}$] $^+$: 210.1125 calculated, 210.1125 found. *Carbamate reduction*: the title compound was prepared according to general procedure G using the methyl carbamate (105 mg, 0.50 mmol, 1 eq), LiAlH_4 (2 M THF solution, 0.40 mL, 0.80 mmol, 1.6 eq) and was used without further purification (78 mg, 0.47 mmol, 94%). TLC: R_f = 0.1 (5% MeOH/DCM with 3 drops of Et_3N). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 158.08, 132.00, 129.68, 113.96, 55.30, 53.37, 36.29, 35.18. HRMS [$\text{C}_{10}\text{H}_{15}\text{NO} + \text{H}$] $^+$: 166.1226 calculated, 166.1226 found.



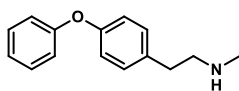
2-(2-Methoxyphenyl)-N-methylethan-1-amine (121j). *Carbamoylation*: the methyl carbamate was prepared according to general procedure G using 2-(2-methoxyphenyl)ethan-1-amine (145 μ L, 1.0 mmol, 1 eq), methylchloroformate (116 μ L, 1.5 mmol, 1.5 eq) and DiPEA (348 μ L, 2.0 mmol, 2 eq). Column chromatography (20% \rightarrow 40%

EtOAc/pentane) afforded the product (230 mg, 1.0 mmol, 99%). TLC: R_f = 0.5 (30% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 157.48, 157.04, 130.51, 127.75, 127.20, 120.51, 110.27, 55.14, 51.81, 41.08, 30.65. HRMS [$\text{C}_{11}\text{H}_{15}\text{NO}_3 + \text{H}$] $^+$: 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), LiAlH_4 (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: R_f = 0.3 (2% MeOH/DCM with 3 drops of Et_3N). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 157.59, 130.33, 128.44, 127.36, 120.39, 110.30, 55.20, 51.85, 36.37, 30.70. HRMS [$\text{C}_{10}\text{H}_{15}\text{NO} + \text{H}$] $^+$: 166.1226 calculated, 166.1225 found.



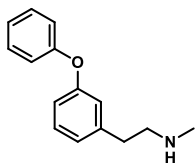
N-Methyl-2-(4-(trifluoromethyl)phenyl)ethan-1-amine (121k). *Carbamoylation*: the methyl carbamate was prepared according to general procedure G using 2-(4-(trifluoromethyl)phenyl)ethan-1-amine (80 μ L, 0.50 mmol, 1 eq), methylchloroformate

(58 μ L, 0.75 mmol, 1.5 eq) and DiPEA (174 μ L, 1.0 mmol, 2 eq). Column chromatography (5% \rightarrow 40% EtOAc/pentane) afforded the product (113 mg, 0.45 mmol, 90%). TLC: R_f = 0.7 (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (101 MHz, CDCl_3) δ 157.06, 143.06, 129.25, 128.82, 128.37, 125.62 (q, J = 3.8 Hz), 122.97, 52.25, 42.03, 36.14. HRMS [$\text{C}_{11}\text{H}_{12}\text{F}_3\text{NO}_2 + \text{H}$] $^+$: 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), LiAlH_4 (2 M THF solution, 0.36 mL, 0.72 mmol, 1.6 eq). Column chromatography (isocratic, 5% MeOH/DCM + 0.5% Et_3N) afforded the product (40 mg, 0.20 mmol, 44%). TLC: R_f = 0.3 (2% MeOH/DCM with 3 drops of Et_3N). ^1H NMR (500 MHz, CDCl_3) 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). ^{13}C NMR (126 MHz, CDCl_3) δ 143.51, 129.13, 125.57 (q, J = 3.7 Hz), 125.41, 123.25, 52.36, 35.73, 35.29. HRMS [$\text{C}_{10}\text{H}_{12}\text{F}_3\text{N} + \text{H}$] $^+$: 204.0995 calculated, 204.0996 found.

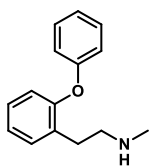


N-Methyl-2-(4-phenoxyphenyl)ethan-1-amine (121l). *Carbamoylation*: the methyl carbamate was prepared according to general procedure G using 2-(4-phenoxyphenyl)ethan-1-amine TFA salt (211 mg, 0.64 mmol, 1 eq), methylchloroformate (74 μ L, 0.96 mmol, 1.5 eq) and DiPEA (245 μ L, 1.41 mmol, 2.2 eq). Column chromatography (10% \rightarrow 40% EtOAc/pentane) afforded the product (145 mg, 0.53 mmol, 83%). TLC: R_f = 0.8

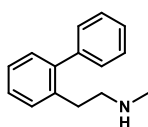
(100% EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.27 (m, 2H), 7.22 – 7.04 (m, 3H), 7.03 – 6.89 (m, 4H), 4.96 – 4.65 (m, 1H), 3.65 (s, 3H), 3.51 – 3.29 (m, 2H), 2.77 (t, $J = 7.1$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.36, 157.05, 155.85, 133.69, 130.06, 129.77, 123.20, 119.12, 118.76, 52.08, 42.36, 35.48. HRMS [$\text{C}_{16}\text{H}_{17}\text{NO}_3 + \text{H}$] $^+$: 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_3N) afforded the product (65 mg, 0.29 mmol, 55%). TLC: $R_f = 0.1$ (5% MeOH/DCM with 3 drops of Et_3N). ^1H 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 [$\text{C}_{15}\text{H}_{17}\text{NO} + \text{H}$] $^+$: 228.1383 calculated, 228.1385 found.



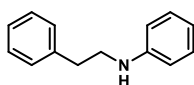
N-Methyl-2-(3-phenoxyphenyl)ethan-1-amine (121m). *Nitrile reduction*: A round-bottom flask was charged with nitrile **119a** (211 mg, 1.0 mmol, 1 eq), EtOH (5 mL) and 37% w/w aqueous HCl (0.16 mL, 2.0 mmol, 2 eq). N_2 was bubbled through the solution for 5 min and Pd/C (10% w/w, 52 mg, 50 μmol , 5 mol%) 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). ^1H 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 157.45, 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 [$\text{C}_{15}\text{H}_{17}\text{NO} + \text{H}$] $^+$: 228.1383 calculated, 228.1384 found.



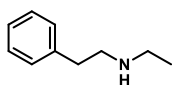
N-Methyl-2-(2-phenoxyphenyl)ethan-1-amine (121n). *Carbamoylation*: the methyl carbamate was prepared according to general procedure G using 2-(2-phenoxyphenyl)ethan-1-amine (99 μL , 0.50 mmol, 1 eq), methylchloroformate (58 μL , 0.75 mmol, 1.5 eq) and DiPEA (174 μL , 1.0 mmol, 2 eq). Column chromatography (20% -> 40% EtOAc/pentane) afforded the product (115 mg, 0.42 mmol, 84%). TLC: $R_f = 0.7$ (30% EtOAc/pentane). ^1H 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 [$\text{C}_{16}\text{H}_{17}\text{NO}_3 + \text{H}$] $^+$: 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_3N) afforded the product (72 mg, 0.32 mmol, 76%). TLC: $R_f = 0.3$ (4% MeOH/DCM with 3 drops of Et_3N). ^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.23 (m, 3H), 7.18 (td, $J = 7.8, 1.7$ 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 [$\text{C}_{15}\text{H}_{17}\text{NO} + \text{H}$] $^+$: 228.1383 calculated, 228.1383 found.



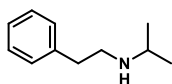
2-([1,1'-Biphenyl]-2-yl)-N-methylethan-1-amine (121o). *Nitrile reduction:* a round-bottom flask was charged with nitrile **119b** (195 mg, 1.0 mmol, 1 eq), EtOH (5 mL) and 37% w/w aqueous HCl (0.16 mL, 2.0 mmol, 2 eq). N₂ was bubbled through the solution for 5 min and Pd/C (10% w/w, 52 mg, 50 μmol, 5 mol%) was added. The mixture was purged with N₂ and then with H₂ and was kept under an H₂ 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_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_f = 0.5 (20% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) 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 [C₁₆H₁₇NO₂ + H]⁺: 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), LiAlH₄ (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_f = 0.3 (6% MeOH/DCM). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) 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 [C₁₅H₁₇N + H]⁺: 212.1434 calculated, 212.1434 found.



N-Phenethylamine (122). A round-bottom flask under N₂ atmosphere was charged with phenylboronic acid (0.49 g, 4.0 mmol, 2 eq), Cu(OAc)₂·H₂O (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 O₂ causing a color shift to purple and stirred under an O₂ 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_f = 0.6 (5% EtOAc/pentane). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) δ 148.06, 139.38, 129.35, 128.86, 128.67, 126.48, 117.50, 113.04, 45.08, 35.55. HRMS [C₁₄H₁₅N + H]⁺: 198.1277 calculated, 198.1275 found.

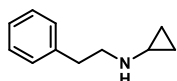


N-Ethyl-2-phenylethan-1-amine (123a). A round-bottom flask was charged with acetaldehyde (56 μL, 1.0 mmol, 1 eq), 2-phenethylamine (189 μL, 1.5 mmol, 1.5 eq) and dry DCM (10 mL). The solution was stirred at room temperature for 10 minutes and then NaBH(OAc)₃ (424 mg, 2 mmol, 2 eq) was added. After 16 h the reaction was complete as judged by TLC. The mixture was diluted with DCM (20 mL), washed with sat. aq. NaHCO₃ (1 x 30 mL), brine (1 x 30 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% → 7% MeOH/DCM with 0.5% Et₃N) affording the product (27 mg, 0.18 mmol, 18%). TLC: R_f = 0.3 (6% MeOH/DCM). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) δ 140.14, 128.83, 128.59, 126.27, 51.11, 46.98, 44.09, 15.24. HRMS [C₁₀H₁₅N + H]⁺: 150.1277 calculated, 150.1277 found.

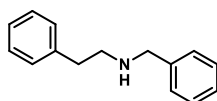


N-phenethylpropan-2-amine (123b). A round-bottom flask was charged with NaBH₄ (218 mg, 5.8 mmol, 1.9 eq) and dry DCM (5 mL). The solution was stirred in an ice bath for 3 minutes and glacial acetic acid (1 mL, 14.4 mmol, 5.8 eq) was added. The mixture was stirred for 1 h at 0 °C and 30 minutes at room temperature. Separately, a solution of 2-phenethylamine

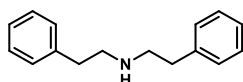
(0.38 mL, 3.0 mmol, 1 eq) was prepared in dry DCM (2.5 mL) and acetone (198 μ L, 2.7 mmol, 0.9 eq). This solution was added dropwise to the NaBH(OAc)₃ mixture and was stirred at rt overnight. After 20 hours the reaction mixture was acidified to pH 2 with 0.1 M HCl (aq.) and washed with DCM (2 x 30 mL) 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% Et₃N/EtOAc) to provide the product (277 mg, 1.7 mmol, 57%). TLC: R_f = 0.3 (100% EtOAc with 3 drops of Et₃N). 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 [C₁₁H₁₇N + H]⁺: 164.1434 calculated, 164.1434 found.



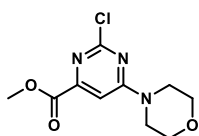
N-Phenethylcyclopropanamine (123c). A round-bottom flask was charged with phenylacetaldehyde (125 μ L, 1.0 mmol, 1 eq), cyclopropanamine (139 μ L, 2.0 mmol, 2 eq) and dry DCM (5 mL). The solution was stirred at room temperature for 10 minutes and then NaHB(OAc)₃ (0.43 g, 2.0 mmol, 2 eq) and glacial AcOH (114 μ L, 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% Et₃N) affording the product (85 mg, 0.53 mmol, 53%), R_f = 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 [C₁₁H₁₅N + H]⁺: 162.1277 calculated, 162.1277 found.



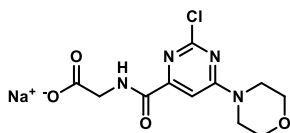
N-Benzyl-2-phenylethan-1-amine (123d). A round-bottom flask was charged with phenylacetaldehyde (125 μ L, 1.0 mmol, 1 eq), benzylamine (218 μ L, 2.0 mmol, 2 eq) and DCM (10 mL). The solution was stirred at room temperature for 3 minutes and then NaHB(OAc)₃ (0.42 g, 2.0 mmol, 2 eq) and glacial AcOH (114 μ L, 2 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 silica gel column chromatography with (4% -> 5% MeOH/DCM with 0.5% Et₃N) affording the product (125 mg, 0.59 mmol, 59%). TLC: R_f = 0.4 (5% MeOH/DCM with 3 drops of Et₃N). 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, 128.15, 126.98, 126.20, 53.88, 50.57, 36.36.



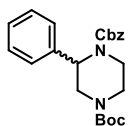
Diphenethylamine (123e). A round-bottom flask was charged with phenylacetaldehyde (125 μ L, 1.0 mmol, 1 eq), 2-phenethylamine (251 μ L, 2.0 mmol, 2 eq) and dry DCM (5 mL). The solution was stirred for 10 minutes and then NaHB(OAc)₃ (0.43 g, 2.0 mmol, 2 eq) and glacial AcOH (114 μ L, 2.0 mmol, 2 eq) were 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% Et₃N) affording the product (128 mg, 0.57 mmol, 57%). TLC: R_f = 0.3 (6% MeOH/DCM with 3 drops of Et₃N). 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 [C₁₆H₁₉N + H]⁺: 226.1590 calculated, 226.1591 found.



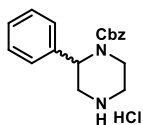
Methyl 2-chloro-6-morpholinopyrimidine-4-carboxylate (125). The title compound was prepared according to general procedure E using methyl 2,6-dichloropyrimidine-4-carboxylate (**124**) (0.62 g, 3.0 mmol, 1 eq), DiPEA (0.78 mL, 4.5 mmol, 1.5 eq) and morpholine (0.27 mL, 3.15 mmol, 1.05 eq). Column chromatography (40% → 60% EtOAc/pentane) afforded the product (0.69 g, 2.7 mmol, 90%). TLC: $R_f = 0.3$ (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.19 (s, 1H), 3.96 (s, 3H), 3.91 – 3.55 (m, 8H). ^{13}C NMR (101 MHz,) δ 163.80, 163.09, 160.65, 155.10, 101.89, 65.83, 52.84, 44.18. HRMS [$\text{C}_{10}\text{H}_{12}\text{ClN}_3\text{O}_3 + \text{H}$] $^+$: 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 H_2O . 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: $R_f = 0.2$ (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). ^{13}C NMR (101 MHz, MeOD) δ 180.70, 159.60, 159.40, 158.60, 152.43, 99.06, 65.99, 43.24. HRMS [$\text{C}_{11}\text{H}_{13}\text{ClN}_4\text{O}_4 + \text{H}$] $^+$: 301.0698 calculated, 301.0696 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), NaHCO_3 (0.46 g, 5.5 mmol, 5 eq) in THF/ H_2O (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 allowed to warm 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 (Na_2SO_4), 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: $R_f = 0.4$ (20% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.55 – 7.04 (m, 10H), 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). ^{13}C NMR (101 MHz, CDCl_3) 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 [$\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_4 + \text{Na}$] $^+$: 419.1941 calculated, 419.1934 found.

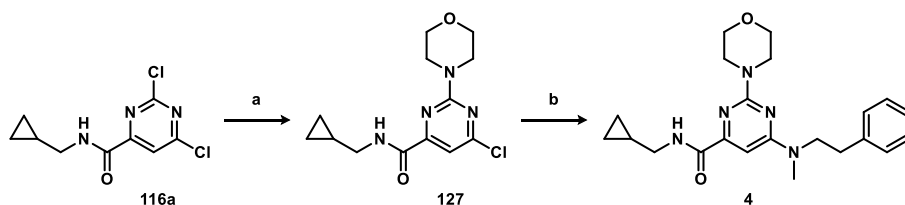


(±)-Benzyl 2-phenylpiperazine-1-carboxylate hydrochloride (130). A round-bottom flask was charged with Boc-protected amine **129** (103 mg, 0.26 mmol, 1 eq) and HCl (4 M solution in 1,4-dioxane, 1 mL, 4.0 mmol, 15.5 eq) and the reaction was stirred at rt. After 1 h the reaction was concentrated under reduced pressure to afford the product as the hydrochloride salt (87 mg, 0.26 mmol, 99%). TLC: $R_f = 0.3$ (50% EtOAc/pentane). ^1H NMR (400 MHz, CDCl_3) δ 10.24 (br s, 1H), 9.33 – 8.80 (m, 1H), 7.51 – 7.02 (m, 10H), 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). ^{13}C NMR (101 MHz, CDCl_3) 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.

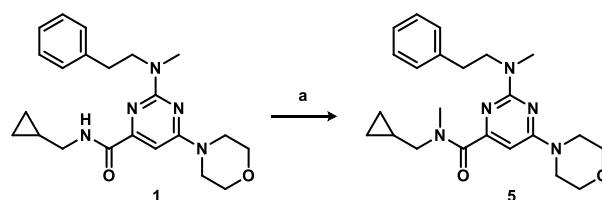
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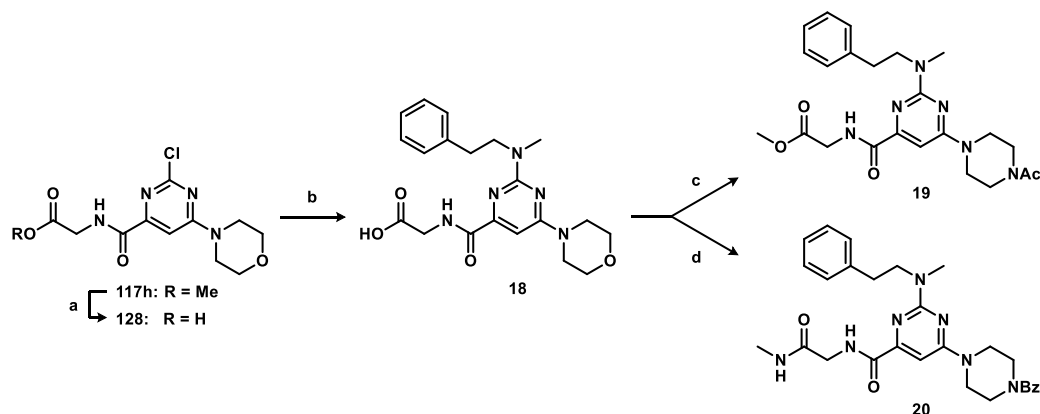
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Supplementary Information


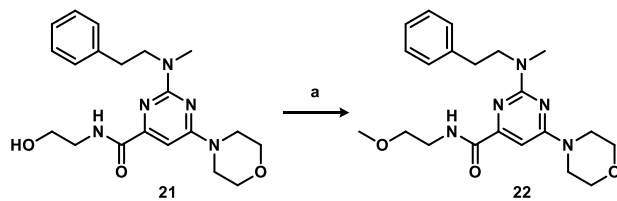
Supplementary Scheme 1. Synthesis of pyrimidine regioisomer **4**. Reagents and conditions: a) morpholine, DiPEA, MeOH, 0 °C, 5% (+ 89% regioisomer **28**); b) *N*-methylphenethylamine, DiPEA, MeOH, 70 °C, 71%.



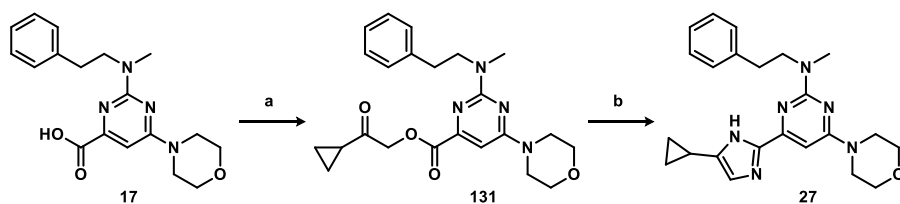
Supplementary Scheme 2. Synthesis of R₁ cyclopropylmethylamine analogue **5**. Reagents and conditions: a) NaH, MeI, DMF, 0 °C to rt, 44%.



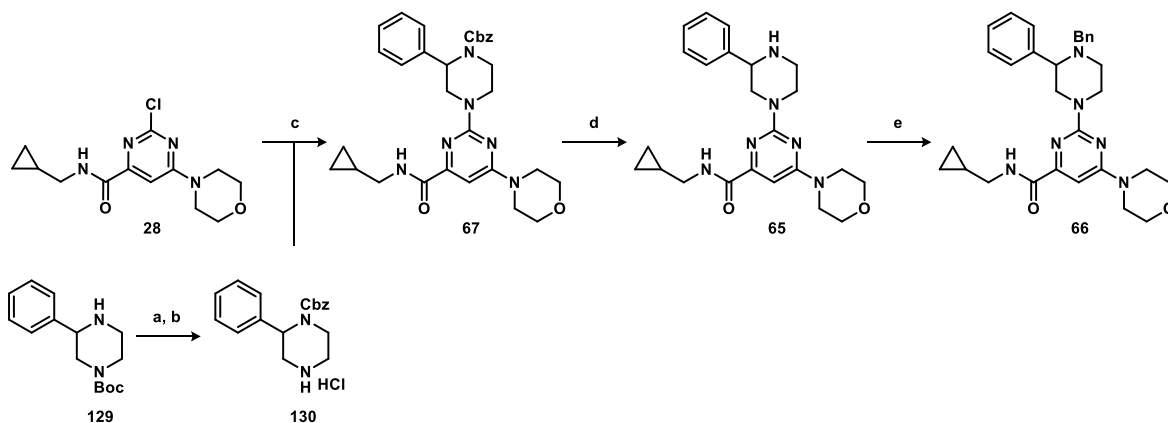
Supplementary Scheme 3. Synthesis of R₁ cyclopropylmethylamine analogues **18-20**. Reagents and conditions: a) NaOH, THF, MeOH, H₂O, rt, 99%; b) *N*-methylphenethylamine, DiPEA, *n*-BuOH, 120 °C, 20%; c) EDC·HCl, HOBt, MeOH, DCM, rt, 62%; d) MeNH₂·HCl, PyBOP, DiPEA, DMF, 50%.



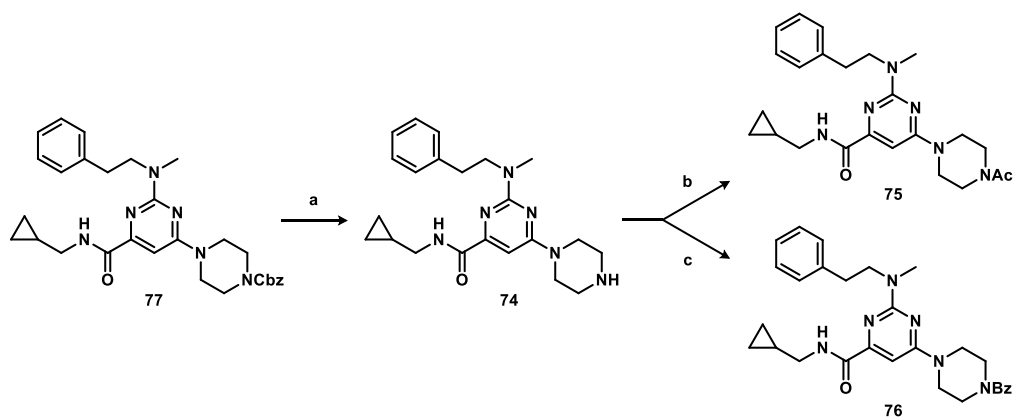
Supplementary Scheme 4. Synthesis of R₁ cyclopropylmethylamine analogue **22**. Reagents and conditions: a) NaOtBu, MeI, DMF, 0 °C to rt, 30%.



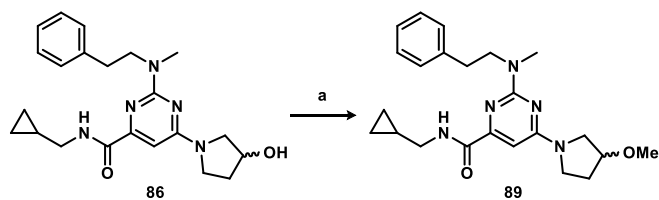
Supplementary Scheme 5. Synthesis of R₁ cyclopropylmethylamine analogue **27**. Reagents and conditions: a) 2-bromocyclopropylethanone, Cs₂CO₃, DMF, rt, 53%; b) NH₄OAc, xylene, 140 °C, 6%.



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, MeI, DMF, 0 °C to rt, 44%.

