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Synthesis of pyrimidinyl arylglycines through subsequent Mitsunobu and Petasis reactions

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ABSTRACT

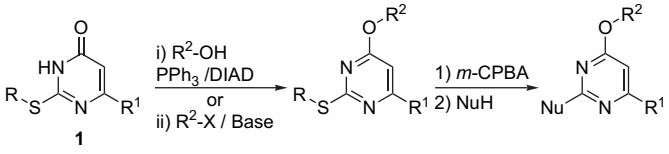
The synthesis of highly functionalized pyrimidinyl arylglycines is presented. The highlight in our synthetic sequence includes selective O-alkylation of 2-(benzylsulfanyl)-4(3*H*)-pyrimidinones with *N*-Boc β-aminoalcohols under Mitsunobu conditions, Petasis reaction with glyoxylic acid and phenylboronic acid and nucleophilic *ipso*-substitution of the activated sulfur with morpholine. The unexpected spontaneous Smiles rearrangement of several pyrimidinyl amines is also discussed.

1. Introduction

In drug discovery, interest in non-proteinogenic α-amino acids[1] is continuously increasing as a result of their potential pharmacological properties and their utility as building blocks in the synthesis of peptidic and non-peptidic compounds.[2] Arylglycines constitute a particularly important class of non-proteinogenic α-amino acids. In fact, arylglycine residues are found in the structure of glycopeptide antibiotics, such as vancomycin and teicoplanin.[3] Nocardicins a type of monocyclic β-lactam antibiotics, also contain the arylglycine moiety.[4] In addition, it was recently discovered that some arylglycines could selectively modulate the activity of metabotronic glutamate receptors (mGluRs), and are used to develop new drugs for the treatment of various neurodegenerative diseases.[5] Owing to this range of potent biological activities, intense research has been undertaken to obtain new arylglycines derivatives.[6]

The Petasis reaction, or boronic Mannich reaction, involves the three-component coupling of an amine, an aldehyde and an organoboron compound. One of the most important uses of the Petasis reaction is the synthesis of arylglycines employing glyoxylic acid as the aldehyde component and an arylboronic acid as the organoboron derivative.[7] This reaction is ideally suited for combinatorial chemistry[8] because: (i) it is a multi-component condensation; (ii) an increasing variety of boronic acids and amines are commercially available and (iii) it proceeds at room temperature in a wide range of solvents. In general, this reaction is more efficient with secondary amines and sterically hindered primary amines.[9]

Our ongoing research is based on the development of efficient methodologies for the preparation of libraries of relevant core structures with a high degree of molecular diversity through combinatorial chemistry.[10] In this way, we have recently described the solution and solid-phase synthesis of 2,6-disubstituted 4-alkoxypyrimidines.[10b] Our synthetic approach is based on the selective O-alkylation of 2-(alkylsulfanyl)-4(3*H*)pyrimidinones **1** with alkyl halides under basic conditions or with alcohols under Mitsunobu conditions, followed by a nucleophilic *ipso*-substitution of the corresponding activated sulfur with a variety of nucleophiles (phenoxides, Grignard reagents, and primary and secondary amines). This last step is useful not only for introducing molecular diversity but also as cleavage reaction on solid-phase synthesis (Scheme 1).



Scheme 1. Synthesis of 2,6-disubstituted 4-alkoxypyrimidines.

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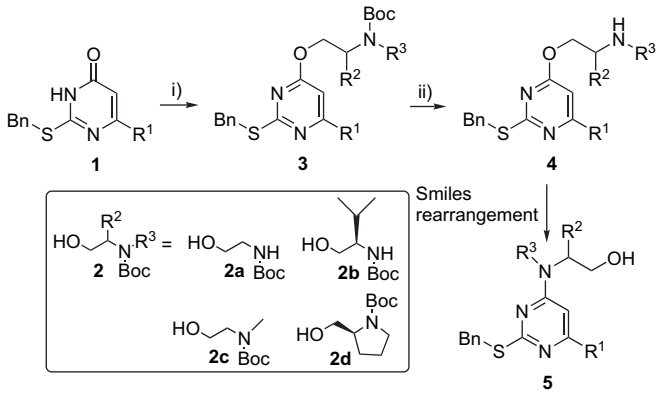
Within this context, we report here the extension of this methodology towards the synthesis of highly functionalized pyrimidines substituted at position 4 with an arylglycine residue. The results of this investigation are disclosed herein.

2. Results and discussion

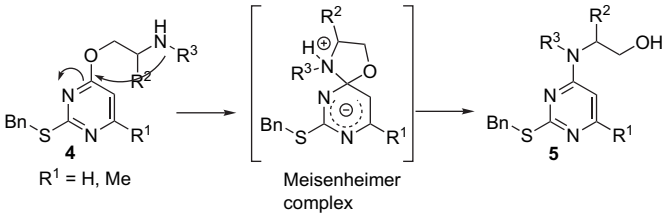
Consistent with this goal, we reasoned that the incorporation of an arylglycine residue at position 4 of a pyrimidine ring could be achieved via selective O-alkylation of 2-(alkylsulfanyl)-4(3*H*)-pyrimidinones **1** with *N*-Boc β-aminoalcohols under Mitsunobu conditions, followed by subsequent acidic removal of the *N*-Boc protecting group and Petasis reaction with glyoxylic acid and an arylboronic acid. Thus, when the easily available 2-(benzylsulfanyl)-4(3*H*)-pyrimidinones[10b] **1** were treated with different primary and secondary *N*-Boc aminoalcohols **2**, PPh_3 and DIAD in anhydrous THF at room temperature for 1–5 h, 4-alkoxypyrimidines **3** were obtained in good yields (Scheme 2, Table 1). Removal of the *N*-Boc group was carried out by treatment of compounds **3** with TFA/CH_2Cl_2 (1:1) at room temperature giving the corresponding amines **4** in good yields (Scheme 2, Table 1).



Scheme 2. *Reagents and conditions*: (i) **2**, DIAD, PPh_3, THF, rt, 1–5 h; (ii) TFA/CH_2Cl_2 (1:1), 0 °C to rt, 30 min to 1 h.

In several cases (Table 1, entries 3, 4, 6 and 8), the isolated amines **4** were not stable and slowly underwent a spontaneous Smiles rearrangement[11] to produce the alcohol derivatives **5** at room temperature or even when stocked inside the refrigerator. It should be noted that the amines **4** were the sole products observed by TLC during the acidic removal of the *N*-Boc group and that the formation of compounds **5** were detected after the neutralization step performed during the work-up. As evidenced in Table 1, this rearrangement is favoured by the nucleophilicity of the amine group. Secondary and sterically hindered primary amines (Table 1, entries 3, 4, 6 and 8) easy underwent Smiles rearrangement whereas the primary amines **4a** and **4b** (Table 1, entries 1 and 2) are stable and did not undergo Smiles rearrangement. On the other hand, when the pyrimidine ring is substituted at position 6 with a phenyl group, the pyrimidines **4** kept stable even those bearing the most nucleophilic amines (Table 1, entries 5, 7 and 10).

Probably, the steric effect of the phenyl group prevents the spontaneous Smiles rearrangement. In agreement with the addition–elimination mechanism proposed for this reaction, the rearrangement of compounds **4** involves the formation of a spiro Meisenheimer complex intermediate by nucleophilic attack of the amine group and the subsequent elimination of alcohol group (Scheme 3).

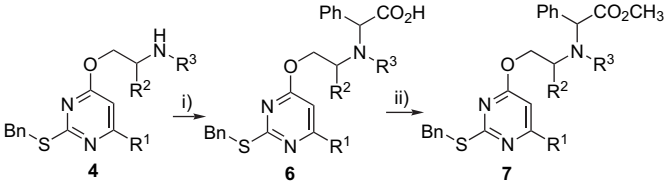


Scheme 3. Proposed mechanism for alcohols **5**.

Recently, several examples of the Smiles rearrangement reaction were reported as a synthetic tool in the preparation of pyrimidinic scaffolds.[12] This rearrangement normally requires basic or acid conditions and/or high temperature. However, to the best our knowledge the spontaneous N–O-type Smiles rearrangement of compounds **4** constitutes the first example involving a pyrimidine ring that occurs at room or low temperature.

The Petasis reaction was then studied with the stable amines **4** (Table 1, entries 1, 2, 5, 7, 9 and 10), which did not undergo the Smiles rearrangement. Thus, treatment of the amines **4a**, **4b**, **4e**, **4g**, **4i** and **4j** with glyoxylic acid and phenylboronic acid in CH_2Cl_2 at room temperature afforded arylglycines **6** (Scheme 4, Table 2).

Since the isolation of compounds **6** proved to be problematic, we decided to treat the crude product with $CsCO_3$ and CH_3I in order to obtain the corresponding methyl esters **7** (Scheme 4, Table 2). The Petasis reaction proceeded well with the secondary amines and



Scheme 4. *Reagents and conditions*: (i) OHC–CO_2H, $PhB(OH)_2$, (ii) MeI, Cs_2CO_3, DMF, rt, 1 h.

Table 1
Yields for the sequence depicted in Scheme 2

Entry	R^1	**2**	R^2	R^3	**3** (yield)[a]	**4** (yield)[a]	**5** (yield)[a]
1	H	**2a**	H	H	**3a** (75)	**4a** (92)	
2	Ph	**2a**	H	H	**3b** (82)	**4b** (89)	
3	H	**2b**	$CH(CH_3)_2$	H	**3c** (84)	**4c** (74)[b]	**5c** (21)
4	Me	**2b**	$CH(CH_3)_2$	H	**3d** (96)	**4d** (60)[b]	**5d** (15)
5	Ph	**2b**	$CH(CH_3)_2$	H	**3e** (84)	**4e** (97)	
6	Me	**2c**	H	Me	**3f** (84)	**4f** (67)[b]	**5f** (30)
7	Ph	**2c**	H	Me	**3g** (74)	**4g** (90)	
8	H	**2d**	$-(CH_2)_3-$		**3h** (88)	**4h** (60)[b]	**5h** (28)
9	Me	**2d**	$-(CH_2)_3-$		**3i** (93)	**4i** (83)	
10	Ph	**2d**	$-(CH_2)_3-$		**3j** (89)	**4j** (89)	

[a] Isolated % yield after purification by flash chromatography.
[b] Yield calculated after flash chromatography. Amine **4** was slowly turning up into alcohol **5** at room and low temperature.

Table 2
Yields for the sequence depicted in Scheme 4

Entry	R^1	R^2	R^3	**6** (yield)[a]	**7** (yield)[a]	dr[c] (%)
1	H	H	H	—		
2	Ph	H	H	—		
3	Ph	$CH(CH_3)_2$	H		**7e** (55)[b]	40
4	Ph	H	Me		**7g** (50)	
5	Me	$-(CH_2)_3-$			**7i** (68)	70
6	Ph	$-(CH_2)_3-$		**6j** (86)	**7j** (94)	73

[a] Isolated % yield after purification by flash chromatography.
[b] Compound **7e** was obtained as an inseparable diastereomeric mixture.
[c] Diastereomeric ratio was calculated by HPLC of the Petasis reaction crude product.

sterically hindered primary amines (Table 2, entries 3, 4, 5 and 6). These results are in agreement with precedent literature.[9]

When the Petasis reaction was carried out with the chiral amines **4e**, **4i** and **4j**, the arylglycine **6j** and arylglycinates **7e**, **7i** and **7j** were obtained as a diastereomeric mixture (Table 2). In agreement with previous reports,[9b] the chiral secondary amines **4i** and **4j** (Table 2, entries 5 and 6) underwent the Petasis reaction in much greater stereoselectivity than the chiral primary amine **4e** (Table 2, entry 3). The two diastereomers could easily be separated by flash chromatography except in the case of **7e** (Table 2, entry 3). In the case of **6j** the unambiguous assignment of the major diastereomer **6ja** was achieved by X-ray analysis (Fig. 1).

In order to increase the molecular diversity of arylglycinates **7** at position 2 of the pyrimidine ring, we focused our attention on the nucleophilic displacement of the benzylsulfanyl group through the methodology described previously.[10] Thus, arylglycinates **7** were treated with 2.5 equiv of *m*-CPBA at 0 °C to afford the corresponding sulfones. Unfortunately, this reaction also produced the oxidation of tertiary and secondary amines to *N*-oxides and nitrones, respectively.

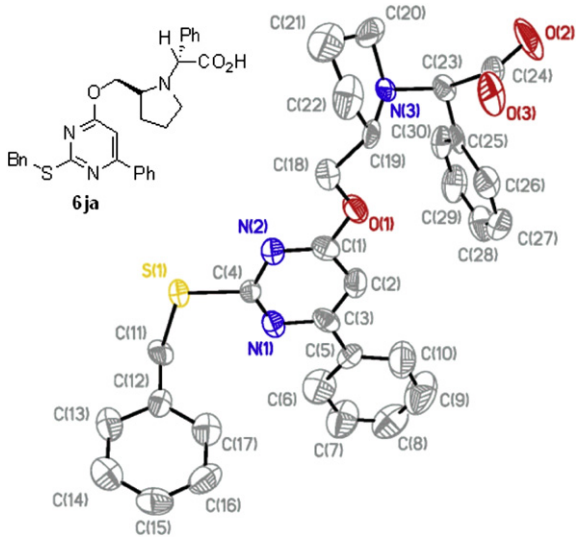


Figure 1. ORTEP diagram of pyrimidinyl arylglycine **6ja**.

Table 3
Yields for the sequence depicted in Scheme 5

Entry	Compound	R^1	R^2	R^3	Yield[a] (%)
1	**8e**	Ph	$CH(CH_3)_2$	H	62
2	**8g**	Ph	H	Me	75
3	**8i**	Me	$-(CH_2)_3-$		65
4	**8j**	Ph	$-(CH_2)_3-$		73

[a] Isolated % yield after purification by flash chromatography.

To circumvent this problem, the amino group was protected as its hydrochloric salt and the amount of *m*-CPBA was reduced to 1.2 equiv. The subsequent nucleophilic *ipso*-substitution displacement with morpholine afforded the pyrimidinyl arylglycines **8** in good yields (Scheme 5, Table 3).

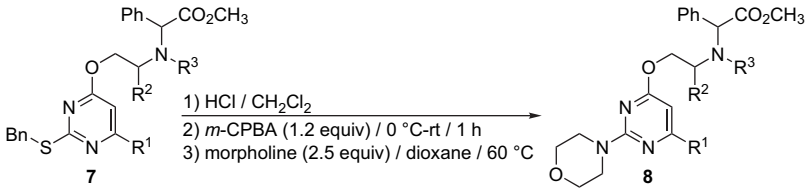
3. Conclusion

In summary, an efficient synthetic strategy to prepare highly functionalized pyrimidinyl arylglycines via a subsequent Mitsunobu and Petasis reaction has been described. Best results were obtained with secondary and sterically hindered primary amines. The nucleophilic *ipso*-substitution of the activated sulfur with nucleophiles allows the introduction of additional molecular diversity over the pyrimidine ring. Several pyrimidinyl amines **4** underwent an unexpected spontaneous Smiles rearrangement even at low temperature. Future efforts will focus on the application of this method to the preparation of new pyrimidinyl arylglycines through combinatorial chemistry.

4. Experimental

4.1. General

All commercially available chemicals were used as purchased without further purification. DMF was dried over activated molecular sieves (4 Å). THF was dried over Na/benzophenone prior to use. Melting points (capillary tube) were measured with an Electrothermal digital melting point apparatus IA 91000 and are uncorrected. IR spectra were recorded on a Mattson-Galaxy Satellite FT-IR using a single reflection ATR system as a sampling accessory. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). NMR spectra were recorded on a Brucker DPX200 Advance spectrometer. ^{1}H NMR spectra were recorded at 200 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 50 MHz. Spectra recorded in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C. Spectra recorded in DMSO-d_6 were referenced to residual DMSO at 2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C. Coupling constants (J) are given in hertz (Hz). The following abbreviations were used for spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, sept=septet, m=multiplet, dd=double doublet, br=broad. EI mass spectra were recorded on a Thermo Quest 2000 series apparatus for the EI (70 eV). ESI mass spectra were recorded using a Navigator quadrupole instrument. FAD mass spectra were recorded on a VG Quattro instrument, using 3-NBA or 1-thioglycerol as the matrix. High resolution mass spectra (HRMS) were determined under conditions of ESI on a Bucker



Scheme 5. Synthesis of arylglycinates **8**.

MicroTof-Q instrument using a lock-spray source. Optical rotations were measured on a Perkin–Elmer polarimeter 241, using the sodium D line. High performance liquid chromatography (HPLC) analyses were carried out using a Dionex P680 instrument. Separations were achieved on an analytical C_{18} Kromasil reversed phase column (4.6 mm×40 mm; 3.5 μm particle size). Analytical thin layer chromatography (TLC) was performed on precoated TLC plates, silica gel 60 F_{254} (Merck). The spots on the TLC plates were visualized with UV/visible light (254 nm) and/or stained with a solution of potassium permanganate (1.5 g/100 mL H_2O). Flash chromatography (FC) purifications were performed on silica gel 60 (230–400 mesh, Merck).

4.2. General procedure for the Mitsunobu reaction. Synthesis of pyrimidines 3

The appropriate 2-(benzylsulfanyl)pyrimidin-4(3*H*)-one **1** (1.0 equiv) was dissolved in dry THF (3 mL/mmol pyrimidinone) under a nitrogen atmosphere, and the solution was cooled in an ice bath. Triphenylphosphine (1.0–1.3 equiv) and the corresponding *N*-Boc protected aminoalcohols **2** (1.0–1.3 equiv) were added. DIAD (1.0–1.3 equiv) was added dropwise as a THF solution (1 mL/mmol DIAD). The resulting mixture was warmed to room temperature and stirred under nitrogen. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (*n*-hexane/ethyl acetate 9:1) to afford pyrimidines **3**.

4.2.1. *tert*-Butyl 2-(2-(benzylsulfanyl)pyrimidin-4-yloxy)-ethylcarbamate (**3a**)

Synthesized according to general procedure (3 h) from 2-(benzylsulfanyl)pyrimidin-4(3*H*)-one (**1a**) (1.0 g, 4.58 mmol), PPh_3 (1.32 g, 5.04 mmol), *N*-Boc-ethanolamine **2a** (812 mg, 5.04 mmol) and DIAD (0.98 mL, 5.04 mmol), 1.24 g (75%) of compound **3a** was obtained as a colourless solid. Mp: 101–102 °C. TLC: R_f 0.55 (*n*-hexane/ethyl acetate 1:1). IR (KBr): 3373 (s), 3291 (w), 3260 (w), 3023 (w), 2978 (m), 2932 (m), 1687 (s), 1561 (s), 1532 (s), 1439 (s), 1321 (s), 1259 (s), 1236 (s), 1167 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.26 (d, J=5.6 Hz, 1H), 7.45–7.25 (m, 5H), 6.41 (d, J=5.6 Hz, 1H), 4.98 (br, 1H), 4.41 (s, 2H), 4.39 (t, J=5.4 Hz, 2H), 3.50 (q, J=5.4 Hz, 3H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 171.2 (s), 168.3 (s), 157.4 (d), 155.7 (s), 137.4 (s), 128.7 (d, 2C), 128.4 (d, 2C), 127.0 (d), 103.8 (d), 79.5 (s), 65.7 (t), 39.6 (t), 35.2 (t), 28.3 (q, 3C). MS (FAB) *m*/*z* (%): 363 ($[M+2]^+$, 12), 362 ($[M+1]^+$, 57), 306 (12), 220 (19), 219 (100), 218 (24), 154 (23), 137 (14), 136 (21). Anal. Calcd for $C_{18}H_{23}N_3O_3S$: C, 59.81; H, 6.41; N, 11.63; S, 8.87. Found: C, 59.63; H, 6.59; N, 11.41; S, 8.49.

4.2.2. *tert*-Butyl 2-(2-(benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)-ethylcarbamate (**3b**)

Synthesized according to general procedure (3 h) from 2-(benzylsulfanyl)-6-phenylpyrimidin-4(3*H*)-one (**1c**) (900 mg, 3.06 mmol), PPh_3 (963 mg, 3.67 mmol), *N*-Boc-ethanolamine **2a** (592 mg, 3.67 mmol) and DIAD (0.71 mL, 3.67 mmol), 1.10 g (82%) of compound **3b** was obtained as a colourless solid. Mp: 105–106 °C. TLC: R_f 0.59 (*n*-hexane/ethyl acetate 1:1). IR (KBr): 3391 (s), 2976 (m), 2924 (m), 2869 (w), 1692 (s), 1574 (s), 1529 (s), 1421 (m), 1380 (m), 1262 (s), 1221 (m), 1168 (s), 1046 (m), 901 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.10–8.00 (m, 2H), 7.50–7.48 (m, 5H), 7.40–7.27 (m, 3H), 6.84 (s, 1H), 4.91 (br, 1H), 4.53 (s, 2H), 4.47 (t, J=5.4 Hz, 2H), 3.55 (q, J=5.4 Hz, 3H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 171.0 (s), 169.6 (s), 164.9 (s), 155.7 (s), 137.8 (s), 136.5 (s), 130.7 (d), 128.78 (d, 2C), 128.72 (d, 2C), 128.5 (d), 127.07 (d, 2C), 127.04 (d, 2C), 99.0 (d), 79.5 (s), 65.8 (t), 39.8 (t), 35.4 (t), 28.3 (q, 3C). MS (FAB) *m*/*z* (%): 439 ($[M+2]^+$, 12), 438 ($[M+1]^+$, 40), 295 (27), 176 (21), 155 (33), 154 (100), 138 (39), 137 (71), 136 (89). Anal. Calcd for $C_{24}H_{27}N_3O_3S$: C, 65.88; H, 6.22; N, 9.60; S, 7.33. Found: C, 65.98; H, 6.41; N, 9.72; S, 7.70.

4.2.3. *tert*-Butyl (*S*)-1-(2-(benzylsulfanyl)pyrimidin-4-yloxy)-3-methylbutan-2-ylcarbamate (**3c**)

Synthesized according to general procedure (4 h) from pyrimidinone **1a** (546 mg, 2.50 mmol), PPh_3 (787 mg, 3.00 mmol), *N*-Boc-L-valinol **2b** (610 mg, 3.00 mmol) and DIAD (0.58 mL, 3.00 mmol), 847 mg (84%) of compound **3c** was obtained as a colourless solid. Mp: 113–114 °C. TLC: R_f 0.32 (*n*-hexane/ethyl acetate 4:1). IR (ATR): 3369 (m), 2987 (w), 2934 (w), 1690 (s), 1569 (s), 1546 (s), 1521 (s), 1461 (w), 1436 (s), 1399 (m), 1364 (m), 1321 (s), 1285 (s), 1228 (s), 1173 (s), 1157 (s), 1075 (m), 1042 (m), 996 (s), 979 (w), 937 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.26 (d, J=5.6 Hz, 1H), 7.49–7.24 (m, 5H), 6.43 (s, J=5.6 Hz, 1H), 4.67 (br, 1H), 4.43 (s, 2H), 4.38–4.30 (m, 2H), 3.88–3.69 (m, 1H), 1.91 (sept, J=6.8 Hz, 1H), 1.47 (s, 9H), 0.99 (d, J=6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 171.3 (s), 168.6 (s), 157.4 (d), 155.7 (s), 137.5 (s), 128.8 (d, 2C), 128.5 (d, 2C), 127.1 (d), 103.9 (d), 79.3 (s), 66.9 (t), 54.8 (d), 35.2 (t), 29.6 (d), 28.3 (q, 3C), 19.5 (q), 18.4 (q). MS (ESI) *m*/*z*: 462 $[M+CH_3CN+NH_4]^+$, 426 $[M+Na]^+$, 404 $[M+H]^+$. Anal. Calcd for $C_{21}H_{29}N_3O_3S$: C, 62.50; H, 7.24; N, 10.41; S, 7.95. Found: C, 62.38; H, 7.51; N, 10.69; S, 8.25.

4.2.4. *tert*-Butyl (*S*)-1-(2-(benzylsulfanyl)-6-methylpyrimidin-4-yloxy)-3-methylbutan-2-ylcarbamate (**3d**)

Synthesized according to general procedure (2 h) from 2-(benzylsulfanyl)-6-methylpyrimidin-4(3*H*)-one (**1b**) (696 mg, 3.00 mmol), PPh_3 (944 mg, 3.6 mmol), *N*-Boc-L-valinol **2b** (732 mg, 3.60 mmol) and DIAD (0.70 mL, 3.60 mmol), 1.20 g (96%) of compound **3d** was obtained as a colourless solid. Mp: 131–133 °C. TLC: R_f 0.35 (*n*-hexane/ethyl acetate 4:1). IR (ATR): 3372 (m), 3032 (w), 2978 (w), 2961 (w), 2869 (w), 1681 (s), 1577 (s), 1547 (s), 1522 (s), 1497 (w), 1459 (m), 1439 (m), 1410 (w), 1367 (m), 1350 (s), 1281 (s), 1244 (s), 1167 (s), 1048 (m), 1034 (m), 1007 (w), 943 (w), 921 (w), 897 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.48–7.25 (m, 5H), 6.27 (s, 1H), 4.63 (br, 1H), 4.42 (s, 2H), 4.34–4.28 (m, 2H), 3.82–3.69 (m, 1H), 2.40 (s, 3H), 1.88 (sept, J=6.8 Hz, 1H), 1.46 (s, 9H), 0.97 (d, J=6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.4 (s), 169.1 (s), 167.8 (s), 155.7 (s), 137.9 (s), 128.8 (d, 2C), 128.4 (d, 2C), 127.0 (d), 102.3 (d), 79.2 (s), 66.7 (t), 54.8 (d), 35.2 (t), 29.6 (d), 28.3 (q, 3C), 23.7 (q), 19.5 (q), 18.4 (q). MS (ESI) *m*/*z*: 418 $[M+H]^+$. Anal. Calcd for $C_{22}H_{31}N_3O_3S$: C, 63.28; H, 7.48; N, 10.06; S, 7.68. Found: C, 63.11; H, 7.70; N, 10.25; S, 7.97.

4.2.5. *tert*-Butyl (*S*)-1-(2-(benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)-3-methylbutan-2-ylcarbamate (**3e**)

Synthesized according to general procedure (3 h) from pyrimidinone **1c** (1.47 g, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), *N*-Boc-L-valinol **2b** (1.12 g, 5.50 mmol) and DIAD (1.10 mL, 5.50 mmol), 2.01 g (84%) of compound **3e** was obtained as a colourless solid. Mp: 130–131 °C. TLC: R_f 0.80 (*n*-hexane/ethyl acetate 1:1). IR (ATR): 3368 (w), 2967 (w), 1680 (s), 1565 (s), 1524 (s), 1406 (w), 1357 (m), 1270 (m), 1242 (m), 1174 (s), 1004 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.09–8.02 (m, 2H), 7.52–7.48 (m, 5H), 7.39–7.24 (m, 3H), 6.84 (s, 1H), 4.74 (d, J=9.2 Hz, 1H), 4.55 (s, 2H), 4.40 (dd, J=12.0 Hz, J'=5.2 Hz, 1H), 4.38 (dd, J=12.0 Hz, J'=4.2 Hz, 1H), 3.82–3.74 (m, 1H), 1.94 (sept, J=6.8 Hz, 1H), 1.48 (s, 9H), 1.02 (d, J=6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.9 (s), 169.8 (s), 164.8 (s), 155.7 (s), 137.9 (s), 136.5 (s), 130.6 (d), 128.79 (d, 2C), 128.70 (d, 2C), 128.5 (d, 2C), 128.4 (d), 127.0 (d, 2C), 99.0 (d), 79.3 (s), 67.0 (t), 54.9 (d), 35.4 (t), 29.6 (d), 28.3 (q, 3C), 19.5 (q), 18.4 (q). MS (ESI) *m*/*z*: 480 $[M+H]^+$. Anal. Calcd for $C_{27}H_{33}N_3O_3S$: C, 67.61; H, 6.93; N, 8.76; S, 6.69. Found: C, 67.44; H, 7.08; N, 8.94; S, 6.91.

4.2.6. *tert*-Butyl 2-(2-(benzylsulfanyl)-6-methylpyrimidin-4-yloxy)ethylmethylcarbamate (**3f**)

Synthesized according to general procedure (5 h) from pyrimidinone **1b** (697 mg, 3.00 mmol), PPh_3 (1.02 g, 3.90 mmol), *N*-Boc-2-(methylamino)ethanol **2c** (683 mg, 3.90 mmol) and DIAD (0.76 mL, 3.90 mmol), 981 mg (84%) of compound **3f** was obtained as a colourless oil. TLC: R_f 0.71 (*n*-hexane/ethyl acetate 1:1). IR (ATR): 2975 (m), 2929 (w), 1695 (s), 1581 (s), 1548 (w), 1454 (m), 1393 (m), 1341 (m), 1283 (s), 1158 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.45–7.20 (m, 5H), 6.24 (s, 1H), 4.43–4.40 (m, 4H), 3.55 (t, *J*=5.4 Hz, 2H), 2.92 (s, 3H), 2.38 (s, 3H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.2 (s), 168.8 (s), 164.6 (s), 155.4 (s), 137.7 (s), 128.6 (d, 2C), 128.2 (d, 2C), 126.8 (d), 102.2 (d), 79.4 (s), 64.0 (t), 47.6 (t), 35.0 (t), 28.2 (q, 4C), 23.53 (q). MS (EI) *m*/*z* (%): 289 ([M−100(Boc)]$^{\bullet+}$, 48), 258 (12), 256 (16), 234 (15), 233 (100), 199 (13), 167 (31), 136 (35). Anal. Calcd for $C_{20}H_{27}N_3O_3S$: C, 61.67; H, 6.99; N, 10.79; S, 8.23. Found: C, 61.43; H, 7.21; N, 10.62; S, 8.54.

4.2.7. *tert*-Butyl 2-(2-(benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)ethylmethylcarbamate (**3g**)

Synthesized according to general procedure (3 h) from pyrimidinone **1c** (1.82 g, 6.25 mmol), PPh_3 (1.84 g, 7.00 mmol), *N*-Boc-2-(methylamino)ethanol **2c** (1.22 g, 7.00 mmol) and DIAD (1.35 mL, 7.00 mmol), 2.25 g (80%) of compound **3g** was obtained as a colourless oil. TLC: R_f 0.64 (*n*-hexane/ethyl acetate 1:1). IR (ATR): 3062 (w), 3029 (w), 2974 (w), 2930 (w), 1690 (s), 1568 (s), 1535 (s), 1494 (m), 1480 (m), 1451 (m), 1411 (m), 1390 (m), 1366 (m), 1344 (m), 1307 (m), 1289 (m), 1267 (s), 1206 (s), 1150 (s), 1070 (w), 1038 (w), 1021 (m), 989 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.09–8.03 (m, 2H), 7.52–7.49 (m, 5H), 7.40–7.28 (m, 3H), 6.82 (s, 1H), 4.55–4.51 (m, 4H), 3.63 (t, *J*=5.4 Hz, 2H), 2.98 (s, 3H), 1.51 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.9 (s), 169.6 (s), 164.8 (s), 155.6 (s), 137.8 (s), 136.5 (s), 130.6 (d), 128.8 (d, 2C), 128.7 (d, 2C), 128.5 (d, 2C), 128.4 (d), 127.0 (d, 2C), 99.3 (d), 79.6 (s), 64.5 (t), 47.7 (t), 35.3 (t), 28.2 (q, 5C). MS (ESI) *m*/*z*: 452 $[M+H]^+$. Anal. Calcd for $C_{25}H_{29}N_3O_3S$: C, 66.49; H, 6.47; N, 9.31; S, 7.10. Found: C, 66.33; H, 6.67; N, 9.25; S, 7.25.

4.2.8. (*S*)-*tert*-Butyl 2-((2-(benzylsulfanyl)pyrimidin-4-yloxy)-methyl)pyrrolidine-1-carboxylate (**3h**)

Synthesized according to general procedure (1 h) from pyrimidinone **1a** (1.09 g, 5.00 mmol), PPh_3 (1.51 g, 5.75 mmol), *N*-Boc-L-prolinol **2d** (1.16 g, 5.75 mmol) and DIAD (1.16 mL, 5.75 mmol), 1.76 g (88%) of compound **3h** was obtained as a colourless oil. TLC: R_f 0.74 (*n*-hexane/ethyl acetate 1:2). IR (ATR): 2974 (m), 2934 (w), 2880 (w), 1690 (s), 1556 (s), 1435 (m), 1390 (s), 1316 (s), 1167 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.25 (d, *J*=5.6 Hz, 1H), 7.47–7.21 (m, 5H), 6.42 (d, *J*=5.6 Hz, 1H), 4.43 (s, 2H), 4.35–4.15 (m, 3H), 3.48–3.31 (m, 2H), 1.95–1.85 (m, 4H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 171.2 (s), 168.5 (s), 155.2 (d), 154.4 (s), 137.5 (s), 128.8 (d, 2C), 128.4 (d, 2C), 127.0 (d), 103.8 (d), 79.4 (s), 66.7 (t), 55.6 (d), 46.5 (t), 35.2 (t), 28.4 (q, 3C), 23.6 (t), 22.9 (t). MS (FAB) *m*/*z* (%): 402 ($[M+1]^+$, 18), 328 (12), 220 (14), 219 (100), 218 (11), 154 (12), 147 (17). Anal. Calcd for $C_{21}H_{27}N_3O_3S$: C, 62.82; H, 6.78; N, 10.47; S, 7.99. Found: C, 62.96; H, 6.95; N, 10.63; S, 8.28.

4.2.9. (*S*)-*tert*-Butyl 2-((2-(benzylsulfanyl)-6-methylpyrimidin-4-yloxy)methyl)pyrrolidine-1-carboxylate (**3i**)

Synthesized according to general procedure (4 h) from pyrimidinone **1b** (697 mg, 3.00 mmol), PPh_3 (1.02 g, 3.90 mmol), *N*-Boc-L-prolinol **2d** (784 mg, 3.90 mmol) and DIAD (0.75 mL, 3.90 mmol), 1.16 g (93%) of compound **3i** was obtained as a colourless oil. TLC: R_f 0.36 (*n*-hexane/ethyl acetate 4:1). IR (ATR): 2973 (w), 2930 (w), 2879 (w), 1689 (s), 1578 (s), 1545 (s), 1494 (w), 1443 (m), 1389 (s), 1361 (s), 1339 (m), 1281 (s), 1250 (m), 1161 (s), 1133 (w), 1107 (m), 1043 (m), 1002 (w), 910 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.48–7.25 (m, 5H), 6.27 (s, 1H), 4.43 (s, 2H), 4.32–4.08 (m, 3H), 3.47–3.32 (m, 2H), 2.40 (s, 3H), 1.95–1.83 (m, 4H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.3 (s), 169.1 (s), 167.7 (s), 154.4 (s), 137.8 (s), 128.8 (d, 2C), 128.3 (d, 2C), 126.9 (d), 102.2 (d), 79.5 (s), 66.5 (t), 55.7 (d), 46.6 (t), 35.1 (t), 28.4 (q, 3C), 26.7 (t), 23.6 (q), 22.9 (t). MS (ESI) *m*/*z*: 474 $[M+CH_3CN+NH_4]^+$, 438 $[M+Na]^+$, 416 $[M+H]^+$. Anal. Calcd for $C_{22}H_{29}N_3O_3S$: C, 63.59; H, 7.03; N, 10.11; S, 7.72. Found: C, 63.72; H, 7.20; N, 10.03; S, 7.48.

4.2.10. (*S*)-*tert*-Butyl 2-((2-(benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)methyl)pyrrolidine-1-carboxylate (**3j**)

Synthesized according to general procedure (3 h) from pyrimidinone **1b** (1.77 g, 6.00 mmol), PPh_3 (1.89 g, 7.20 mmol), *N*-Boc-L-prolinol **2d** (1.45 g, 7.20 mmol) and DIAD (1.40 mL, 7.20 mmol), 2.49 g (87%) of compound **3j** was obtained as a colourless oil. TLC: R_f 0.67 (*n*-hexane/ethyl acetate 1:1). IR (ATR): 2972 (m), 1689 (s), 1569 (s), 1535 (s), 1390 (s), 1263 (m), 1207 (m), 1167 (m), 1107 (m), 768 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.09–8.042 (m, 2H), 7.52–7.49 (m, 5H), 7.39–7.27 (m, 3H), 6.84 (s, 1H), 4.40 (s, 2H), 4.35–4.20 (m, 3H), 3.48–3.30 (m, 2H), 2.00–1.90 (m, 4H), 1.51 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.9 (s), 169.8 (s), 164.8 (s), 154.5 (s), 137.9 (s), 136.6 (s), 130.6 (d), 128.8 (d), 128.6 (d, 2C), 128.4 (d, 2C), 127.0 (d, 3C), 99.0 (d), 79.5 (s), 66.8 (t), 55.8 (d), 46.6 (t), 35.4 (t), 28.4 (q, 3C), 22.2 (q), 21.9 (t). MS (FAB) *m*/*z* (%): 478 ($[M+1]^+$, 38), 296 (25), 295 (100), 281 (19), 221 (17), 207 (36), 154 (23), 147 (60), 129 (63). Anal. Calcd for $C_{27}H_{31}N_3O_3S$: C, 67.90; H, 6.54; N, 8.80; S, 6.71. Found: C, 67.74; H, 6.67; N, 8.69; S, 6.98.

4.3. General procedure for the *N*-Boc removal. Synthesis of amines 4 and alcohols 5

The appropriate pyrimidine **3** (1.0 equiv) was dissolved in CH_2Cl_2 (1.5 mL/mmol pyrimidine) and the solution was cooled in an ice bath. TFA (1.5 mL/mmol pyrimidine) was added dropwise and the resulting mixture was stirred at 0 °C. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the residue was dissolved in AcOEt (30 mL), washed with a saturated $NaHCO_3$ solution (2×10 mL) and brine (1×10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The resulting crude material was purified by flash chromatography (*n*-hexane/ethyl acetate 1:4 to 0:1) to provide pure pyrimidines **4** or in some case together with the corresponding Smiles rearrangement compound **5**.

4.3.1. 2-(2-(Benzylsulfanyl)pyrimidin-4-yloxy)ethanamine (**4a**)

Synthesized according to general procedure (35 min) from pyrimidine **3a** (1.0 g, 2.77 mmol), 665 mg (92%) of compound **4a** was obtained as a colourless oil. TLC: R_f 0.47 (CH_2Cl_2/MeOH/NH_3 12:2:0.2). IR (film): 3370 (w), 3060 (w), 3030 (br), 2937 (m), 1684 (m), 1573 (s), 1539 (s), 1498 (m), 1412 (m), 1344 (w), 1272 (m), 1209 (s), 1016 (m), 841 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.24 (d, *J*=5.6 Hz, 1H), 7.45–7.23 (m, 5H), 6.42 (d, *J*=5.6 Hz, 1H), 4.41 (s, 2H), 4.35 (t, *J*=5.4 Hz, 2H), 3.03 (t, *J*=5.4 Hz, 2H), 1.45 (br, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 171.0 (s), 168.5 (s), 157.2 (d), 137.4 (s), 128.7 (d, 2C), 128.3 (d, 2C), 126.9 (d), 103.7 (d), 68.6 (t), 40.7 (t), 35.1 (t). MS (EI) *m*/*z* (%): 261 ([M]$^{\bullet+}$, 10), 228 (82), 184 (27), 152 (15), 139 (97). Anal. Calcd for $C_{13}H_{15}N_3OS$: C, 59.74; H, 5.79; N, 16.08; S, 12.27. Found: C, 59.57; H, 5.95; N, 16.17; S, 12.51.

4.3.2. *tert*-Butyl 2-(2-(benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)ethylcarbamate (**4b**)

Synthesized according to general procedure (45 min) from pyrimidine **3b** (950 mg, 2.17 mmol), 651 mg (89%) of compound **4b** was obtained as a colourless oil. TLC: R_f 0.20 (*n*-hexane/ethyl acetate 1:4). IR (film): 3057 (w), 3025 (w), 2962 (br), 2893 (m), 1578 (s), 1547 (s), 1498 (m), 1452 (m), 1405 (m), 1347 (m), 1299 (m), 1272

(m), 1217 (m), 1019 (m), 846 (w), 768 (m), 696 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.01–8.04 (m, 2H), 7.53–7.47 (m, 5H), 7.35–7.27 (m, 3H), 6.86 (s, 1H), 4.54 (s, 2H), 4.43 (t, J=5.4 Hz, 2H), 3.10 (t, J=5.4 Hz, 2H), 1.56 (br, 2H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ (ppm) 171.0 (s), 169.2 (s), 164.1 (s), 137.9 (s), 135.6 (s), 131.1 (d), 128.9 (d, 2C), 128.7 (d, 2C), 128.4 (d, 2C), 127.03 (d), 126.9 (d, 2C), 99.1 (d), 63.3 (t), 37.8 (t), 34.4 (t). MS (FAB) m/z (%): 338 ($[M+1]^+$, 42), 207 (29), 155 (57), 154 (100), 149 (21), 139 (25), 138 (64), 137 (90). Anal. Calcd for $C_{19}H_{19}N_3OS$: C, 67.63; H, 5.68; N, 12.45; S, 9.50. Found: C, 67.51; H, 5.91; N, 12.57; S, 9.78.

*4.3.3. N-Boc protecting group removal from pyrimidine **3c***

According to the general procedure (45 min) and starting from **3c** (710 mg, 1.76 mmol), 395 mg (74%)[13] of amine **4c** and 83 mg (21%) of alcohol **5c** were obtained.

*4.3.3.1. (S)-1-(2-(Benzylsulfanyl)pyrimidin-4-yloxy)-3-methylbutan-2-amine (**4c**).* Isolated as a colourless oil. TLC: R_f 0.59 (CH_2Cl_2/MeOH/NH_3 12:2:0.2). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) (10:1, amine **4c**/alcohol **5c**)[14] 8.26 (d, J=5.6 Hz, 1H), 7.49–7.23 (m, 5H), 6.46 (d, J=5.6 Hz, 1H), 4.44 (s, 2H), 4.41 (dd, J=10.6 Hz, J'=3.8 Hz, 1H), 4.16 (dd, J=10.6 Hz, J'=8.0 Hz, 1H), 3.00–2.91 (m, 1H), 1.78 (sept, J=6.8 Hz, 1H), 1.49 (s, 2H), 1.02 (d, J=6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 171.2 (s), 168.8 (s), 157.3 (d), 137.6 (s), 128.8 (d, 2C), 128.5 (d, 2C), 127.2 (d), 104.0 (d), 70.1 (t), 55.5 (d), 35.2 (t), 30.9 (d), 19.3 (q), 17.9 (q). MS (ESI) m/z: 607 $[2M+H]^+$, 304 $[M+H]^+$. Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85; S, 10.57. Found: C, 63.19; H, 7.14; N, 13.99; S, 10.32.

*4.3.3.2. (S)-2-(2-(Benzylsulfanyl)pyrimidin-4-ylamino)-3-methylbutan-1-ol (**5c**).* Isolated as a colourless solid. Mp: 89–91 °C. TLC: R_f 0.51 (CH_2Cl_2/MeOH/NH_3 12:2:0.2). IR (ATR): 3273 (w), 3149 (w), 3084 (w), 3053 (w), 2957 (w), 2869 (w), 1600 (s), 1580 (s), 1484 (s), 1451 (m), 1344 (s), 1325 (m), 1264 (w), 1187 (s), 1071 (m), 1025 (m), 996 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 200 MHz): δ (ppm) 7.94 (d, J=5.8 Hz, 1H), 7.51–7.31 (m, 5H), 6.36 (d, J=5.8 Hz, 1H), 4.73–4.67 (m, 1H), 4.40 (s, 2H), 4.06 (br, 1H), 3.58–3.55 (m, 2H), 1.99 (sept, J=6.8 Hz, 1H), 0.97 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6, 200 MHz): δ (ppm) 168.9 (s), 161.9 (s), 153.6 (d), 138.7 (s), 128.7 (d, 2C), 128.3 (d, 2C), 126.7 (d), 102.4 (d), 60.8 (t), 56.1 (d), 33.7 (t), 28.3 (d), 19.4 (q), 18.2 (q). MS (ESI) m/z: 607 $[2M+H]^+$, 304 $[M+H]^+$. Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85; S, 10.57. Found: C, 63.28; H, 7.11; N, 13.71; S, 10.74.

*4.3.4. N-Boc protecting group removal from pyrimidine **3d***

Synthesized according to the general procedure (1 h) and starting from **3d** (1.15 g, 2.75 mmol), 523 mg (60%)[13] of amine **4d** and 131 mg (15%) of alcohol **5d** were obtained.

*4.3.4.1. (S)-1-(2-(Benzylsulfanyl)-6-methylpyrimidin-4-yloxy)-3-methylbutan-2-amine (**4d**).* Isolated as a colourless oil. TLC: R_f 0.77 (CH_2Cl_2/MeOH/NH_3 12:2:0.2). IR (ATR): 3061 (w), 2957 (w), 2926 (w), 2871 (w), 1578 (s), 1543 (s), 1492 (m), 1440 (m), 1417 (m), 1350 (m), 1338 (m), 1280 (s), 1112 (w), 1041 (m), 971 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.49–7.25 (m, 5H), 6.29 (s, 1H), 4.43 (s, 2H), 4.39 (dd, J=10.6 Hz, J'=4.0 Hz, 1H), 4.13 (dd, J=10.6 Hz, J'=7.8 Hz, 1H), 2.97–2.88 (m, 1H), 2.28 (s, 3H), 1.75 (sept, J=6.8 Hz, 1H), 1.29 (s, 2H), 0.95 (d, J=6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.4 (s), 169.3 (s), 167.7 (s), 137.9 (s), 128.8 (d, 2C), 128.4 (d, 2C), 127.0 (d), 102.4 (d), 70.0 (t), 55.5 (d), 35.2 (t), 30.9 (d), 23.7 (q), 19.5 (q), 18.8 (q). MS (ESI) m/z: 635 $[2M+H]^+$, 318 $[M+H]^+$. Anal. Calcd for $C_{17}H_{23}N_3OS$: C, 64.32; H, 7.30; N, 13.24; S, 10.10. Found: C, 64.49; H, 7.48; N, 13.11; S, 10.42.

*4.3.4.2. (S)-2-(2-(Benzylsulfanyl)-6-methylpyrimidin-4-ylamino)-3-methylbutan-1-ol (**5d**).* Isolated as a colourless solid. Mp: 106–109 °C. TLC: R_f 0.63 (CH_2Cl_2/MeOH/NH_3 12:2:0.2). IR (ATR): 3273 (br), 3146 (br), 3062 (w), 3031 (w), 2957 (m), 2927 (m), 2871 (w), 1592, 1493, 1452 (m), 1426 (m), 1390 (m), 1364 (m), 1344 (w), 1284 (s), 1218 (m), 1187 (s), 1069 (m), 1030 (m), 968 (m), 912 (w), 832 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.49–7.25 (m, 5H), 5.95 (s, 1H), 4.81 (br, 1H), 4.39 (s, 2H), 3.81–3.65 (m, 3H), 2.30 (s, 3H), 1.93 (sept, J=6.8 Hz, 1H), 0.99 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.0 (s), 165.2 (s), 162.8 (s), 138.3 (s), 128.9 (d, 2C), 128.3 (d, 2C), 126.8 (d), 100.0 (d), 63.7 (t), 58.0 (d), 35.0 (t), 29.6 (d), 23.7 (q), 19.5 (q), 18.8 (q). MS (ESI) m/z: 635 $[2M+H]^+$, 318 $[M+H]^+$. Anal. Calcd for $C_{17}H_{23}N_3OS$: C, 64.32; H, 7.30; N, 13.24; S, 10.10. Found: C, 64.51; H, 7.52; N, 13.39; S, 10.45.

*4.3.5. (S)-1-(2-(Benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)-3-methylbutan-2-amine (**4e**)*

Synthesized according to general procedure (30 min) from pyrimidinone **3e** (1.92 g, 4.00 mmol), 1.36 g (90%) of compound **4e** was obtained as a colourless solid. Mp: 176–178 °C. TLC: R_f 0.55 (CH_2Cl_2/MeOH/NH_3 12:2:0.2). IR (ATR): 2969 (w), 2928 (w), 2895 (w), 1689 (m), 1569 (s), 1536 (s), 1493 (m), 1455 (w), 1415 (w), 1364 (m), 1315 (m), 1270 (m), 1201 (s), 1177 (s), 1136 (s), 1022 (m), 915 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.10–8.05 (m, 2H), 7.54–7.48 (m, 5H), 7.39–7.28 (m, 3H), 6.88 (s, 1H), 4.54 (s, 2H), 4.44 (dd, J=10.8 Hz, J'=4.0 Hz, 1H), 4.22 (dd, J=10.8 Hz, J'=8.0 Hz, 1H), 3.04–2.95 (m, 1H), 1.80 (sept, J=6.6 Hz, 1H), 1.41 (br, 2H), 1.03 (d, J=6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.8 (s), 169.9 (s), 164.7 (s), 137.9 (s), 136.6 (s), 130.6 (d), 128.77 (d, 2C), 128.67 (d, 2C), 128.4 (d, 2C), 127.0 (d, 3C), 99.1 (d), 70.2 (t), 55.5 (d), 35.3 (t), 30.9 (d), 19.3 (q), 17.9 (q). MS (ESI) m/z: 380 $[M+H]^+$. Anal. Calcd for $C_{22}H_{25}N_3OS$: C, 69.62; H, 6.64; N, 11.07; S, 8.45. Found: C, 69.83; H, 6.48; N, 11.19; S, 8.81.

*4.3.6. N-Boc protecting group removal from pyrimidine **3f***

Synthesized according to the general procedure (45 min) and starting from **3f** (800 mg, 2.05 mmol), 397 mg (67%)[13] of amine **4f** and 178 mg (30%) of alcohol **5f** were obtained.

*4.3.6.1. 2-(2-(Benzylsulfanyl)-6-methylpyrimidin-4-yloxy)-N-methylethanamine (**4f**).* Isolated as a colourless oil. TLC: R_f 0.21 (CH_2Cl_2/MeOH 10:1). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) (10:7, amine **4f**/alcohol **5f**)[14] 7.46–7.22 (m, 5H), 6.26 (s, 1H), 4.47–4.42 (m, 2H), 4.40 (s, 2H), 2.97 (t, J=5.2 Hz, 2H), 2.50 (s, 3H), 2.37 (s, 3H).

*4.3.6.2. 2-(N-(2-(Benzylsulfanyl)-6-methylpyrimidin-4-yl)-N-methylamino)ethanol (**5f**).* Isolated as a colourless solid. Mp: 95–96 °C. TLC: R_f 0.55 (CH_2Cl_2/MeOH 10:1). IR (ATR): 3196 (br), 2944 (w), 2910 (w), 2868 (w), 1581 (s), 1502 (s), 1406 (s), 1310 (m), 1195 (s), 1036 (m), 811 (w), 709 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.45–7.20 (m, 5H), 6.00 (s, 1H), 4.37 (s, 2H), 3.79–3.67 (m, 4H), 3.26 (br, 1H), 3.06 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 169.3 (s), 165.1 (s), 162.1 (s), 138.1 (s), 128.6 (d, 2C), 128.2 (d, 2C), 126.7 (d), 97.2 (d), 60.6 (t), 51.8 (d), 36.51 (q), 34.9 (t), 23.8 (q). MS (EI) m/z: 290 ($[M+1]^+$, 34), 289 ($[M]^+$, 100), 258 (52), 256 (68), 212 (37), 167 (81), 165 (33), 136 (86). Anal. Calcd for $C_{15}H_{19}N_3OS$: C, 62.25; H, 6.62; N, 14.52; S, 11.08. Found: C, 62.39; H, 6.85; N, 14.41; S, 11.39.

*4.3.7. 2-(2-(Benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)-N-methylethanamine (**4g**)*

Synthesized according to general procedure (1 h) from pyrimidinone **3g** (1.58 g, 3.5 mmol), 1.10 g (90%) of **4g** was obtained as a colourless oil. TLC: R_f 0.30 (CH_2Cl_2/MeOH 10:1). IR (ATR): 3212 (br), 3060 (w), 3028 (w), 2944 (w), 2846 (w), 2725 (w), 1569 (s), 1535 (s), 1495 (m), 1450 (m), 1412 (m), 1372 (m), 1340 (m), 1309 (m), 1267 (s), 1289 (m), 1228 (m), 1208 (s), 1147 (w), 1119 (w), 1019 (m),

920 (w), 980 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.09–8.03 (m, 2H), 7.52–7.48 (m, 5H), 7.40–7.28 (m, 3H), 6.86 (s, 1H), 4.54–4.50 (m, 4H), 3.00 (t, J=5.6 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 169.9 (s), 168.8 (s), 163.8 (s), 136.9 (s), 135.6 (s), 129.6 (d), 127.8 (d, 2C), 127.7 (d, 2C), 127.4 (d, 2C), 126.0 (d, 3C), 98.2 (d), 64.8 (t), 49.4 (t), 35.3 (q), 34.4 (t). MS (ESI) m/z: 352 $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}N_3OS$: C, 68.35; H, 6.02; N, 11.96; S, 9.12. Found: C, 68.49; H, 6.27; N, 12.11; S, 9.39.

*4.3.8. N-Boc protecting group removal from pyrimidine **3h***

Synthesized according to the general procedure (30 min) and starting from **3h** (1.5 g, 3.74 mmol), 680 mg (60%)[13] of amine **4h** and 310 mg (28%) of alcohol **5h** were obtained.

*4.3.8.1. 2-(Benzylsulfanyl)-4-[((S)-pyrrolidin-2-yl)methoxy]pyrimidine (**4h**).* Isolated as a colourless oil. TLC: R_f 0.36 (CH_2Cl_2/MeOH 10:1). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) (10:9, amine **4h**/alcohol **5h**)[14] 8.24 (d, J=5.6 Hz, 1H), 7.49–7.26 (m, 5H), 6.44 (d, J=5.6 Hz, 1H), 4.43 (s, 2H), 4.40–4.24 (m, 3H), 3.07–2.98 (m, 2H), 1.90–1.81 (m, 4H).

*4.3.8.2. [(S)-1-(2-(Benzylsulfanyl)pyrimidin-4-yl)pyrrolidin-2-yl]methanol (**5h**).* Isolated as a colourless oil. TLC: R_f 0.50 (CH_2Cl_2/MeOH 10:1). IR (ATR): 3257 (br), 3025 (w), 2968 (w), 2928 (w), 2871 (w), 1572 (s), 1536 (m), 1473 (s), 1362 (m), 1339 (m), 1275 (w), 1225 (w), 1174 (w), 1147 (m), 1044 (w), 1023 (w), 798 (w), 751 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.98 (d, J=6.0 Hz, 1H), 7.47–7.24 (m, 5H), 6.05 (d, J=6.0 Hz, 1H), 4.46–4.17 (m, 3H), 3.71 (dd, J=11.0 Hz, J'=4.6 Hz, 1H), 3.65 (dd, J=11.0 Hz, J'=6.8 Hz, 1H), 3.52–3.37 (m, 2H), 2.14–1.86 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.0 (s), 160.0 (s), 154.9 (d), 137.6 (s), 129.4 (d, 2C), 128.9 (d, 2C), 127.6 (d), 100.8 (d), 65.8 (t), 60.2 (d), 47.6 (t), 35.0 (t), 28.5 (t), 23.6 (t). MS (FAB) m/z (%): 303 ($[M+2]^+$, 21), 302 ($[M+1]^+$, 100), 301 (9), 270 (10). Anal. Calcd for $C_{16}H_{19}N_3OS$: C, 63.76; H, 6.35; N, 13.94; S, 10.64. Found: C, 63.58; H, 6.60; N, 13.72; S, 10.31.

*4.3.9. 2-(Benzylsulfanyl)-6-methyl-4-[((S)-pyrrolidin-2-yl)-methoxy]pyrimidine (**4i**)*

Synthesized according to general procedure (45 min) from pyrimidine **3i** (710 mg, 1.71 mmol), 447 mg (83%) of compound **4i** was obtained as a colourless solid. Mp: 101–104 °C. TLC: R_f 0.29 (CH_2Cl_2/MeOH 10:1). IR (ATR): 2962 (w), 2944 (w), 1666 (s), 1576 (s), 1547 (m), 1441 (m), 1349 (m), 1287 (m), 1202 (s), 1167 (s), 1129 (s), 1046 (s), 969 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.46–7.22 (m, 5H), 6.29 (s, 1H), 4.64 (dd, J=14.0 Hz, J'=4.0 Hz, 1H), 4.43 (dd, J=14.0 Hz, J'=8.0 Hz, 1H), 4.40 (s, 2H), 3.99–2.87 (m, 1H), 3.35–3.29 (m, 2H), 2.19–1.79 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.3 (s), 168.6 (s), 168.2 (s), 137.7 (s), 128.8 (d, 2C), 128.4 (d, 2C), 127.1 (d), 102.3 (d), 64.3 (t), 58.4 (d), 45.1 (t), 35.2 (t), 26.6 (t), 23.7 (t), 23.6 (q). MS (ESI) m/z: 631 $[2M+H]^+$, 316 $[M+H]^+$. Anal. Calcd for $C_{17}H_{21}N_3OS$: C, 64.73; H, 6.71; N, 13.32; S, 10.17. Found: C, 64.57; H, 6.90; N, 13.18; S, 10.39.

*4.3.10. 2-(Benzylsulfanyl)-6-phenyl-4-[((S)-pyrrolidin-2-yl)-methoxy]pyrimidine (**4j**)*

Synthesized according to general procedure (45 min) from pyrimidine **3j** (2.20 g, 4.61 mmol), 1.54 g (89%) of compound **4j** was obtained as a colourless oil. TLC: R_f 0.45 (CH_2Cl_2/MeOH/NH_3 12:2:0.2). IR (ATR): 2972 (w), 1538 (s), 1538 (m), 1513 (w), 1494 (m), 1452 (w), 1410 (w), 1266 (m), 1227 (w), 1200 (s), 1176 (m), 1130 (m), 1021 (w), 919 (w), 758 (m), 716 (m), 693 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.0–8.10 (m, 2H), 7.50–7.25 (m, 8H), 6.86 (s, 1H), 4.81 (br, 1H), 4.52 (s, 2H), 4.50 (dd, J=11.2 Hz, J'=4.4 Hz, 1H), 4.36 (dd, J=11.2 Hz, J'=7.4 Hz, 1H), 3.70–3.65 (m, 1H), 3.20–3.10 (m, 2H), 2.05–1.50 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 170.8 (s), 169.5 (s), 164.9 (s), 137.8 (s), 136.4 (s), 130.7 (d), 128.79 (d, 2C), 128.71 (d, 2C), 128.58 (d, 2C), 128.45 (d), 127.1 (d, 2C), 99.1 (d), 67.8 (t), 57.4 (d), 46.0 (t), 35.4 (t), 27.5 (t), 24.7 (t). MS (FAB) m/z (%): 379 ($[M+2]^+$, 28), 378 ($[M+1]^+$, 100), 377 (10), 295 (16), 154 (19), 136 (21). Anal. Calcd for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13; S, 8.49. Found: C, 69.83; H, 6.31; N, 11.28; S, 8.67.

4.4. General procedure for the Petasis reaction. Synthesis of arylglycines 6

To a suspension of glyoxylic acid monohydrate (1.05 equiv) in dichloromethane (6 mL/mmol pyrimidine) phenylboronic acid (1.05 equiv) and the appropriate pyrimidine **4** (1.0 equiv) were added. The resulting mixture was stirred at room temperature under nitrogen atmosphere. Upon completion of the reaction (TLC monitoring) solvent was removed under reduced pressure and the resulting crude product was purified by flash chromatography (ethyl acetate/methanol 10:1) or used in the next step without more purification.

*4.4.1. Petasis reaction of the pyrimidine **4j***

Synthesized according to the general procedure (20 h) and starting from **4j** (943 mg, 2.5 mmol), 1.09 g (86%) of arylglycine **6j** was obtained as a separable diastereomeric mixture (dr=73%) of **6ja** (1.06 g, 83%) and **6jb** (0.03 g, 3%).

*4.4.1.1. (R)-2-[(S)-2-((2-(Benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)-methyl)pyrrolidin-1-yl]-2-phenylacetic acid (**6ja**).* Isolated as a colourless solid. Mp: 148–149 °C. TLC: R_f 0.31 ($CHCl_3$/MeOH/NH_3 12:2:0.2). $[\alpha]_D^{25}$ −95.0 (c 0.4, DMF). IR (ATR): 3061 (w), 2953 (w), 1570 (s), 1536 (s), 1493 (m), 1307 (m), 1071 (m), 1028 (m), 919 (m), 839 (m), 755 (m), 731 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 200 MHz): δ (ppm) 8.27–8.24 (m, 2H), 7.60–7.40 (m, 13H), 7.24 (s, 1H), 4.70 (s, 1H), 4.60 (s, 2H), 4.26–4.14 (m, 2H), 3.53 (br, 1H), 3.0 (br, 1H), 2.60 (br, 1H), 2.00–1.80 (m, 4H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ (ppm) 172.5 (s), 170.0 (s), 169.6 (s), 164.0 (s), 138.1 (s), 136.8 (s), 135.7 (s), 131.0 (d), 128.9 (d, 2C), 128.80 (d, 2C), 128.76 (d, 3C), 128.39 (d, 2C), 128.24 (d), 126.99 (d, 2C), 126.96 (d, 2c), 98.9 (d), 69.5 (d), 68.7 (t), 59.1 (d), 51.4 (t), 34.4 (t), 27.9 (t), 22.9 (t). HRMS (ESI) m/z: calcd for $C_{30}H_{30}N_3O_3S_1$ $[M+H]^+$ 512.2002; found 512.2022.

*4.4.1.2. (S)-2-[(S)-2-((2-(Benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)-methyl)pyrrolidin-1-yl]-2-phenylacetic acid (**6jb**).* Isolated as a colourless solid. Mp: 131–132 °C. TLC: R_f 0.24 ($CHCl_3$/MeOH/NH_3 12:2:0.2). IR (ATR): 2958 (w), 2930 (m), 2858 (m), 1570 (s), 1538 (s), 1365 (m), 1270 (m), 1206 (m), 1018 (m), 696 (s) cm^{-1}. ^1H NMR (DMSO-d_6, 200 MHz): δ (ppm) 8.27–8.23 (m, 2H), 7.60–7.35 (m, 13H), 7.23 (s, 1H), 4.73 (s, 1H), 4.57 (s, 2H), 4.26–4.13 (m, 2H), 3.46 (br, 1H), 3.00 (br, 1H), 2.80 (br, 1H), 2.05–1.75 (m, 4H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ (ppm) 173.0 (s), 170.0 (s), 169.7 (s), 164.0 (s), 138.3 (s), 138.8 (s), 135.7 (s), 131.0 (d), 128.8 (d, 2C), 128.70 (d, 2C), 128.6 (d, 2C), 128.4 (d, 2C), 128.1 (d, 2C), 127.5 (d), 127.0 (d, 2C), 126.7 (d, 2C), 98.9 (d), 68.8 (d), 68.3 (t), 59.3 (d), 49.5 (t), 34.3 (t), 28.3 (t), 23.1 (t). MS (FAB) m/z (%): 512 ($[M+1]^+$, 21), 466 (10), 281 (21), 221 (18), 218 (100), 207 (27), 174 (22), 172 (27).

4.5. General procedure for the esterification reaction. Synthesis of arylglycinates 7

To a suspension of Cs_2CO_3 (1.15 equiv) in dry DMF (5 mL/mmol amino acid) the appropriate arylglycine **6** (1.0 equiv) was added. The resulting mixture was stirred for 15 min at room temperature and then methyl iodide (1.2 equiv) was added. Upon completion of the reaction (TLC monitoring) solvent was removed under reduced pressure and the residue was partitioned between AcOEt (20 mL/mmol) and H_2O (20 mL/mmol). The organic layer was separated and the aqueous layer was extracted with AcOEt (3×20 mL/mmol).

Then the organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The resulting crude material was purified by flash chromatography (*n*-hexane/ethyl acetate 14:1 to 9:1) to provide pure arylglycinates **7**.

*4.5.1. Methyl 2-[(S)-1-(2-(benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)-3-methylbutan-2-ylamino]-2-phenylacetate (**7e**)*

Synthesized according to the general procedures and starting from **4e** (1.326 g, 3.5 mmol), 1.01 g (55%) of arylglycinate **7e** was obtained as an inseparable diastereomeric mixture (dr=40%). TLC: R_f 0.78 (*n*-hexane/ethyl acetate 1:1). IR (ATR): 3061 (w), 3028 (w), 2956 (w), 1735 (s), 1567 (s), 1534 (s), 1493 (m), 1450 (m), 1412 (m), 1265 (s), 1204 (m), 1170 (w), 1011 (m), 694 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) major diastereomer: δ (ppm) 8.10–8.03 (m, 2H), 7.52–7.29 (m, 13H), 6.78 (s, 1H), 4.67 (s, 1H), 4.51 (s, 2H), 4.38–4.25 (m, 2H), 3.73 (s, 3H), 2.84–2.76 (m, 1H), 2.08–1.87 (m, 1H), 1.06 (d, J=6.8 Hz, 3H), 1.04 (d, J=6.8 Hz, 3H); minor diastereomer: δ (ppm) 8.10–8.03 (m, 2H), 7.52–7.29 (m, 13H), 6.86 (s, 1H), 4.67 (s, 1H), 4.55 (s, 2H), 4.45–4.34 (m, 2H), 3.66 (s, 3H), 2.69–2.61 (m, 1H), 2.36–1.97 (m, 1H), 1.01 (d, J=6.8 Hz, 3H), 0.94 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) major diastereomer: δ (ppm) 173.7 (s), 170.5 (s), 169.7 (s), 164.6 (s), 138.7 (s), 137.9 (s), 136.6 (s), 130.6 (d), 128.8 (d, 2C), 128.7 (d, 2C), 128.57 (d, 2C), 128.51 (d), 127.9 (d, 2C), 127, 7 (d), 127.4 (d, 2C), 127.0 (d, 2C), 99.27 (d), 67.3 (t), 63.6 (d), 59.6 (d), 52.1 (q), 35.3 (t), 29.7 (d), 18.6 (q), 18.5 (q); minor diastereomer: δ (ppm) 173.7 (s), 170.5 (s), 169.7 (s), 164.6 (s), 138.7 (s), 137.9 (s), 136.6 (s), 130.6 (d), 128.8 (d, 2C), 128.7 (d, 2C), 128.57 (d, 2C), 128.45 (d), 127.9 (d, 2C), 127.7 (d), 127.4 (d, 2C), 127.0 (d, 2C), 99.22 (d), 67.3 (t), 63.4 (d), 58.6 (d), 52.1 (q), 35.3 (t), 29.6 (d), 18.9 (q), 18.8 (q). HRMS (ESI) m/z: calcd for $C_{31}H_{34}N_3O_3S_1$ $[M+H]^+$ 528.2315; found 528.2293.

*4.5.2. Methyl 2-(N-(2-(2-(benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)ethyl)-N-methylamino)-2-phenylacetate (**7g**)*

Synthesized according to general procedure from pyrimidine **4g** (1.053 g, 3.00 mmol), 1.49 g (50%) of compound **7g** was obtained as a colourless oil. TLC: R_f 0.42 (*n*-hexane/ethyl acetate 4:1). IR (ATR): 3060 (w), 3029 (w), 2950 (w), 1735 (m), 1568 (s), 1535 (s), 1494 (m), 1451 (m), 1413 (m), 1375 (m), 1345 (s), 1309 (m), 1289 (m), 1266 (s), 1242 (m), 1207 (s), 1158 (m), 1021 (s), 998 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.07–8.02 (m, 2H), 7.52–7.29 (m, 12H), 6.78 (s, 1H), 4.5 (s, 2H), 4.47 (s, 1H), 4.44–4.42 (m, 2H), 3.75 (s, 3H), 3.06–3.82 (m, 2H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 171.3 (s), 169.8 (s), 168.6 (s), 163.6 (s), 136.9 (s), 135.6 (s), 135.2 (s), 129.6 (d), 127.9 (d, 2C), 127.8 (d, 2C), 127.77 (d, 2C), 127.71 (d, 2C), 127.4 (d, 2C), 127.2 (d, 2C), 126.9 (d), 126.0 (d), 98.3 (d), 71.5 (d), 63.4 (t), 51.2 (t), 50.8 (q), 39.2 (q), 34.4 (t). HRMS (ESI) m/z: calcd for $C_{29}H_{30}N_3O_3S_1$ $[M+H]^+$ 500.2002; found 500.2015.

*4.5.3. Petasis reaction and esterification of pyrimidine **4i***

According to the general procedure and starting from **4i** (475 mg, 1.5 mmol), 314 mg (68%) of arylglycinate **7i** was obtained as a separable diastereomeric mixture (dr=70%) of **7ia** (250 mg, 54%) and **7ib** (64 mg, 14%).

*4.5.3.1. (R)-Methyl 2-((S)-2-((2-(benzylsulfanyl)-6-methylpyrimidin-4-yloxy)methyl)pyrrolidin-1-yl)-2-phenylacetate (**7ia**).* Isolated as a colourless oil. TLC: R_f 0.23 (*n*-hexane/ethyl acetate 4:1). $[\alpha]_D^{27}$ −133.24 (*c* 0.352, CH_3OH). IR (ATR): 3026 (w), 2949 (w), 2924 (w), 2871 (w), 1739 (m), 1578 (s), 1542 (s), 1493 (w), 1448 (m), 1410 (m), 1350 (m), 1279 (s), 1239 (m), 1197 (m), 1162 (s), 1039 (m), 1001 (w), 911 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.45–7.22 (m, 10H), 6.18 (s, 1H), 4.63 (s, 1H), 4.37 (s, 2H), 4.13–3.96 (m, 2H), 3.65 (s, 3H), 3.34–3.31 (m, 1H), 3.03–3.00 (m, 1H), 2.49–2.34 (m, 1H), 2.33 (s, 3H), 1.92–1.64 (m, 4H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ (ppm) 172.7 (s), 170.41 (s), 169.1 (s), 167.6 (s), 138.0 (s), 136.2 (s), 129.1 (d, 2C), 128.98 (d, 2C), 128.45 (d, 2C), 128.4 (d, 2C), 128.2 (d), 127.0 (d), 102.3 (d), 69.5 (d), 68.8 (t), 59.1 (d), 51.83 (q), 51.82 (t), 35.2 (t), 28.4 (t), 23.7 (q), 23.2 (t). HRMS (ESI) m/z: calcd for $C_{26}H_{30}N_3O_3S_1$ $[M+H]^+$ 464.2002; found 464.2011.

*4.5.3.2. (S)-Methyl 2-((S)-2-((2-(benzylsulfanyl)-6-methylpyrimidin-4-yloxy)methyl)pyrrolidin-1-yl)-2-phenylacetate (**7ib**).* Isolated as a colourless oil. TLC: R_f 0.31 (*n*-hexane/ethyl acetate 4:1). $[\alpha]_D^{25}$ −11.11 (*c* 0.05, CH_3OH). IR (ATR): 3026 (w), 2949 (w), 2923 (w), 2853 (w), 1736 (m), 1544 (s), 1494 (w), 1451 (m), 1448 (m), 1412 (w), 1350 (m), 1281 (s), 1240 (w), 1202 (w), 1164 (s), 1042 (w), 700 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.48–7.26 (m, 10H), 6.23 (s, 1H), 4.78 (s, 1H), 4.41 (s, 2H), 4.18–4.15 (m, 2H), 3.74 (s, 3H), 3.38–3.35 (m, 1H), 2.99–2.92 (m, 1H), 2.83–2.81 (m, 1H), 2.39 (s, 3H), 2.09–1.79 (m, 4H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ (ppm) 172.6 (s), 170.4 (s), 169.2 (s), 167.7 (s), 138.0 (s), 137.4 (s), 128.9 (d, 2C), 128.7 (d, 2C), 128.46 (d, 2C), 128.42 (d, 2C), 128.0 (d), 127.0 (d), 102.3 (d), 69.2 (d), 68.5 (t), 59.6 (d), 51.6 (q), 49.8 (t), 35.2 (t), 28.8 (t), 23.7 (q), 23.5 (t). HRMS (ESI) m/z: calcd for $C_{26}H_{30}N_3O_3S_1$ $[M+H]^+$ 464.2002; found 464.2011.

*4.5.4. (R)-Methyl 2-((S)-2-((2-(benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)methyl)pyrrolidin-1-yl)-2-phenylacetate (**7ja**)*

Synthesized according to general procedure from amino acid **6ja** (767 mg, 1.50 mmol), 740 mg (94%) of compound **7ja** was obtained as a colourless solid. Mp: 148–149 °C. TLC: R_f 0.92 (*n*-hexane/ethyl acetate 1:1). $[\alpha]_D^{25}$ −99.65 (*c* 0.273, CH_3OH). IR (ATR): 3029 (w), 2950 (w), 1740 (m), 1570 (s), 1567 (s), 1534 (s), 1494 (m), 1450 (m), 1412 (m), 1356 (w), 1307 (m), 1288 (m), 1266 (s), 1230 (m), 1204 (s), 1164 (m), 1140 (m), 1015 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.08–8.03 (m, 2H), 7.53–7.27 (m, 13H), 6.78 (s, 1H), 4.24 (s, 1H), 4.52 (s, 2H), 4.24 (dd, J=10.8 Hz, J'=5.2 Hz, 1H), 4.12 (s, 2H), 4.24 (dd, J=10.8 Hz, J'=6.8 Hz, 1H), 3.71 (s, 3H), 3.48–3.41 (m, 1H), 3.10–3.07 (m, 1H), 2.60–2.48 (m, 1H), 2.08–1.80 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 173.4 (s), 171.6 (s), 170.4 (s), 165.3 (s), 138.6 (s), 137.3 (s), 136.9 (s), 131.2 (d), 129.8 (d, 2C), 129.6 (d, 2C), 129.4 (d, 2C), 129.1 (d, 4C), 128.9 (d), 127.7 (d, 3C), 99.8 (d), 70.2 (d), 69.7 (t), 59.8 (d), 52.6 (q), 52.5 (t), 36.1 (t), 29.1 (t), 23.9 (t). HRMS (ESI) m/z: calcd for $C_{31}H_{32}N_3O_3S_1$ $[M+H]^+$ 526.2159; found 526.2151.

4.6. General procedure for the synthesis of 2-morpholino-pyrimidines 8

The appropriate arylglycinates **7** (1.0 equiv) was dissolved in diethyl ether (3 mL/mmol) and the solution was cooled in an ice bath. This solution was bubbled for 15 min with gaseous HCl, generated in situ by a reaction of NaCl with concentrated sulfuric acid. The resulting white solid precipitate was collected by filtration and washed sequentially with small portion of diethyl ether and *n*-pentane. Then, the hydrochloride compound was dissolved in CH_2Cl_2 (5 mL/mmol) and *m*-CPBA (1.2 equiv) was added in small portions. The resulting mixture was warmed to room temperature and stirred for 1 h. After this time, the solvent was removed under reduced pressure and the residue was dissolved in AcOEt (20 mL), washed with saturated $NaHCO_3$ solution (2×10 mL) and brine (1×10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. Next, the crude material was dissolved in dry 1,4-dioxane and morpholine (2.5 equiv) was added. The reaction mixture was the stirred under a nitrogen atmosphere at 60 °C. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (*n*-hexane/ethyl acetate 14:1 to 9:1) to afford compounds **8**.

*4.6.1. Methyl 2-((S)-1-(2-morpholino-6-phenylpyrimidin-4-yloxy)-3-methylbutan-2-ylamino)-2-phenylacetate (**8e**)*

Synthesized according to general procedure from arylglycinate **7e** (0.90 g, 1.7 mmol), 516 mg (62%) of an inseparable diastereomeric mixture of compound **8e** was obtained as a colourless oil. TLC: R_f 0.39 (*n*-hexane/ethyl acetate 4:1). IR (ATR): 2956 (w), 2924 (w), 2852 (w), 1737 (m), 1558 (s), 1493 (m), 1448 (m), 1396 (m), 1340 (m), 1301 (w), 1266 (s), 1249 (w), 1206 (s), 1170 (w), 1115 (m), 1023 (m), 988 (w), 770 (m), 695 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) major diastereomer: δ (ppm) 8.08–8.02 (m, 2H), 7.50–7.31 (m, 13H), 6.45 (s, 1H), 4.65 (s, 1H), 4.35–4.15 (m, 2H), 3.85–3.77 (m, 8H), 3.72 (s, 3H), 2.86–2.77 (m, 1H), 2.09–1.85 (m, 1H), 1.08 (d, J=6.8 Hz, 3H), 1.04 (d, J=6.8 Hz, 3H); minor diastereomer: δ (ppm) 8.08–8.02 (m, 2H), 7.50–7.31 (m, 13H), 6.51 (s, 1H), 4.65 (s, 1H), 4.55–4.38 (m, 2H), 3.95–3.85 (m, 8H), 3.67 (s, 3H), 2.77–2.51 (m, 1H), 2.09–1.85 (m, 1H), 1.02 (d, J=6.8 Hz, 3H), 0.93 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) major diastereomer: δ (ppm) 174.4 (s), 171.5 (s), 165.94 (s), 162.4 (s), 139.36 (s), 138.6 (s), 130.7 (d), 129.3 (d, 2C), 129.2 (d, 2C), 128.64 (d), 128.12 (d, 2C), 127.6 (d, 2C), 93.5 (d), 67.6 (t, 2C), 66.96 (t), 64.30 (d), 60.14 (d), 52.91 (q), 45.12 (t, 2C), 30.2 (d), 19.27 (q), 19.15 (q); minor diastereomer: δ (ppm) 174.4 (s), 171.4 (s), 165.90 (s), 162.3 (s), 139.45 (s), 138.6 (s), 130.7 (d), 129.3 (d, 2C), 129.2 (d, 2C), 128.64 (d), 128.12 (d, 2C), 127.6 (d, 2C), 93.5 (d), 67.6 (t, 2C), 67.03 (t), 64.36 (d), 59.97 (d), 52.86 (q), 45.08 (t, 2C), 30.4 (d), 19.56 (q), 19.27 (q). HRMS (ESI) m/z: calcd for $C_{28}H_{34}N_4NaO_4$ $[M+Na+H]^+$ 513.2472; found 513.2463.

*4.6.2. Methyl 2-(N-(2-(2-morpholino-6-phenylpyrimidin-4-yloxy)ethyl)-N-methylamino)-2-phenylacetate (**8g**)*

Synthesized according to general procedure from arylglycinate **7g** (1.248 g, 2.5 mmol), 866 mg (75%) of compound **8g** was obtained as a colourless oil. TLC: R_f 0.62 (*n*-hexane/ethyl acetate 1:1). IR (ATR): 3062 (w), 2953 (w), 1736 (m), 1558 (s), 1493 (m), 1448 (m), 1397 (m), 1363 (m), 1341 (m), 1301 (m), 1266 (s), 1207 (s), 1156 (m), 1115 (s), 1069 (w), 1023 (s), 995 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.05–8.00 (m, 2H), 7.49–7.3 (m, 8H), 6.46 (s, 1H), 4.48–4.42 (m, 3H), 3.87–3.80 (m, 8H), 3.75 (s, 3H), 3.07–3.85 (m, 2H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 172.2 (s), 170.5 (s), 165.2 (s), 161.6 (s), 137.9 (s), 136.3 (s), 130.0 (d), 128.7 (d, 2C), 128.5 (d, 4C), 128.2 (d), 126.85 (d, 2C), 92.7 (d), 72.6 (d), 66.9 (t, 2C), 63.6 (t), 52.4 (t), 51.8 (q), 44.3 (t, 2C), 40.3 (q). HRMS (ESI) m/z: calcd for $C_{26}H_{31}N_4O_4$ $[M+H]^+$ 463.2340; found 463.2307.

*4.6.3. (R)-Methyl 2-((S)-2-((6-methyl-2-morpholinopyrimidin-4-yloxy)methyl)pyrrolidin-1-yl)-2-phenylacetate (**8ia**)*

Synthesized according to general procedure from arylglycinate **7ia** (510 mg, 1.10 mmol), 304 mg (65%) of compound **8ia** was obtained as a colourless oil. TLC: R_f 0.46 (*n*-hexane/ethyl acetate 1:1). $[\alpha]_D^{27}$ −110.07 (*c* 0.21, CH_3OH). IR (ATR): 2955 (w), 2920 (w), 2851 (w), 1739 (m), 1568 (s), 1494 (m), 1444 (m), 1397 (m), 1301 (w), 1273 (m), 1244 (m), 1199 (m), 1161 (s), 1114 (m), 1041 (m), 1014 (m), 999 (m), 911 (w), 700 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.46–7.3 (m, 5H), 5.87 (s, 1H), 4.68 (s, 1H), 4.08–4.03 (m, 2H), 3.78–3.74 (m, 8H), 3.69 (s, 3H), 3.40–3.32 (m, 1H), 3.10–3.03 (m, 1H), 2.52–2.37 (m, 1H), 2.28 (s, 3H), 1.93–1.75 (m, 4H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ (ppm) 172.7 (s), 169.9 (s), 167.9 (s), 161.5 (s), 136.2 (s), 129.0 (d, 2C), 128.4 (d, 2C), 128.1 (d), 95.5 (d), 69.6 (d), 67.9 (t), 66.8 (t, 2C), 59.5 (d), 51.83 (q), 51.82 (t), 44.3 (t, 2C), 28.4 (t), 24.0 (q), 23.0 (t). HRMS (ESI) m/z: calcd for $C_{23}H_{31}N_4O_4$ $[M+H]^+$ 427.2340; found 427.2316.

*4.6.4. (R)-Methyl 2-((S)-2-((2-morpholino-6-phenylpyrimidin-4-yloxy)methyl)pyrrolidin-1-yl)-2-phenylacetate (**8ja**)*

Synthesized according to general procedure from arylglycinate **7ja** (652 mg, 1.25 mmol), 445 mg (73%) of compound **8ja** was obtained as a colourless oil. TLC: R_f 0.66 (*n*-hexane/ethyl acetate 1:1). $[\alpha]_D^{25}$ −100.29 (*c* 0.168, CH_3OH). IR (ATR): 2955 (w), 2895 (w), 2850 (w), 1738 (m), 1558 (s), 1493 (m), 1445 (m), 1393 (m), 1352 (m), 1299 (w), 1264 (m), 1204 (m), 1142 (m), 1112 (m), 1075 (w), 1022 (m), 990 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.06–8.01 (m, 2H), 7.48–7.34 (m, 8H), 6.46 (s, 1H), 4.7 (s, 1H), 4.19–4.11 (m, 2H), 3.93–3.79 (m, 8H), 3.71 (s, 3H), 3.49–3.42 (m, 1H), 3.12–3.06 (m, 1H), 2.60–2.48 (m, 1H), 1.94–1.77 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 172.8 (s), 170.7 (s), 165.2 (s), 161.7 (s), 137.9 (s), 136.4 (s), 130.0 (d), 129.1 (d, 2C), 128.5 (d, 4C), 128.2 (d), 126.9 (d, 2C), 92.5 (d), 69.7 (d), 68.3 (t), 66.9 (t, 2C), 59.6 (d), 51.9 (q), 51.8 (t), 44.4 (t, 2C), 28.5 (t), 23.1 (t). HRMS (ESI) m/z: calcd for $C_{28}H_{33}N_4O_4$ $[M+H]^+$ 489.2496; found 489.2497.

4.7. X-ray crystallographic details of compound 6ja

$C_{30}H_{29}N_3O_3S\cdot DMF$ M_r=511.62, orthorhombic, space group $P22121$, a=5.4908(6) Å, b=14.5712(17) Å, c=38.386(5) Å, V=3071.2(6) $Å^3$, Z=4, D_x=1.265 g cm^{-3}, T=100(2) K, crystal dimensions: 0.2×0.1×0.08 mm. The measurements were carried out on a BRUCKER SMART APEX CCD diffractometer using graphite-monochromated Mo Kα radiation (λ=0.71073 Å) from an X-ray Tube. The measurements were made in the range 2.12–27.00° for θ. Full-sphere data collection was carried out with ω and φ scans. A total of 42,657 reflections were collected of which 6675 [R(int)=0.1082] were unique. The programs that were used follow: data collection Smart version 5.631 (Bruker AXS 1997–02); data reduction Saint+version 6.36A (Bruker AXS 2001); absorption correction SADABS version 2.10 (Bruker AXS 2001). Crystal structure solution was achieved using SHELXTL Version 6.14 (Bruker AXS 2000–2003). A considerable amount of electron density attributable to partially disordered DMF solvent molecule was removed with the SQUEEZE option of PLATON.[15] The DMF molecule is, however, included in the reported chemical formula and derived values (e.g., formula weight, F_000, etc.). Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in geometrically optimized positions and refined without constrains. The chosen enantiomer was based on the assumption that the chiral centre in the pyrrolidine ring has the *S*-configuration as a result of the known configuration of the reagents used in the reaction.

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Supplementary data

CCDC-664273 contains the supplementary crystallographic data for compounds **6ja**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.035.

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