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A simple approach for the synthesis of new pyrimidinyl α-amino acids

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ABSTRACT

A simple synthetic method for the preparation of optically active pyrimidinyl α-amino acids is presented. A nucleophilic *ipso*-substitution reaction between 2-(benzylsulfonyl)-4-isopropoxypyrimidines and a nucleophilic side chain of several protected natural α-amino acids is investigated to obtain new pyrimidin-2-yl α-amino acids. A detailed optimisation study of this reaction is discussed. Moreover, the selective *O*-alkylation of 2-(benzylsulfanyl)-4(3*H*)pyrimidinones with a hydroxylic side chain of some natural α-amino acids under Mitsunobu conditions is studied as a method to prepare new pyrimidin-4-yl α-aminoesters.

1. Introduction

In drug discovery, interest in non-proteinogenic amino acids is increasing as a result of their intrinsic biological properties—antibiotic, antiviral and antitumour[1]—and their utility as building blocks and molecular scaffolds in the synthesis of combinatorial libraries of non-peptidic compounds.[2] Many of these non-proteinogenic amino acids are also critical components in pharmaceuticals and developmental drugs.[3] Furthermore, their incorporation into biologically active peptides has been used to improve the activity, stability, bioavailability and selectivity of peptides in their use as a therapeutic agents.[4] For these reasons, research into methods that will allow the efficient synthesis of novel non-proteinogenic amino acids is crucial.[5] From among the various non-proteinogenic amino acids, such as α,α-disubstituted α-amino acids,[6] arylglycines,[7] β and γ-amino acids,[8] proline derivatives[9] and conformationally restricted amino acids[10] we have focused our attention on the heterocyclic amino acids type I (Fig. 1), a class of non-proteinogenic α-amino acids, substituted on the side chain by an heterocyclic ring.[11] Many of these compounds are natural and have been discovered and isolated from natural sources.[12] Examples include willardiine,[13] discadenine,[14] L-azatyrosine[15], L-lathyrine[16] and ibotenic acid[17] (Fig. 1), which all displayed a wide range of biological properties such as antibacterial or antitumour activities. Moreover, in recent years a number of stereoselective methods for rendering new synthetic enantiopure heterocyclic α-amino acids have been reported.[18] These methods are mainly based on the enantioselective transformation of prochiral starting materials or on chiral pool synthesis by transformation of natural α-amino acids.

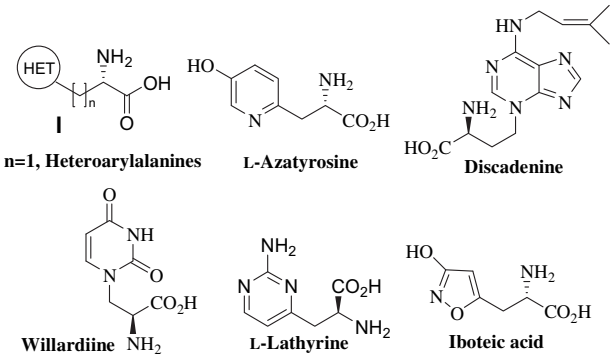

Figure 1. Examples of heterocyclic α-amino acids.

Pyrimidine rings are present in some important natural biologically active compounds[19] and synthetic pyrimidine derivatives have important pharmaceutical and agrochemical properties.[20] Apart from willardiine[13] and lathyrine analogues[16,21] only a small number of synthetic methods for obtaining new unnatural pyrimidinyl α-amino acids are reported in the literature.[22]

One of our research interest lies in the development of efficient methods for the preparation of pyrimidinyl compound libraries with a high degree of molecular diversity through solution or solid-

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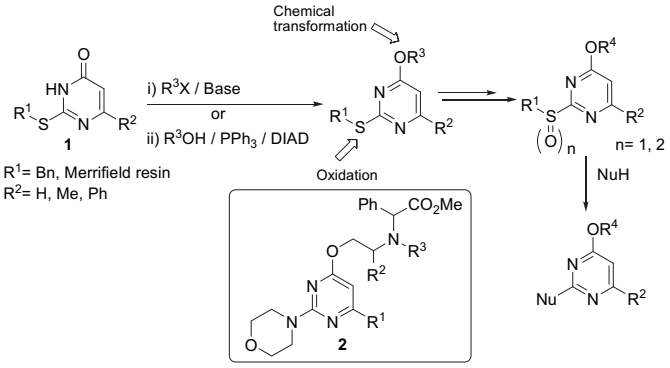
phase synthesis.[23] The highlight in our synthetic sequences include selective O-alkylation of 2-(alkylsulfanyl)-4(3*H*)pyrimidinones **1** with alkyl halides under basic conditions or with alcohols under Mitsunobu conditions, followed by chemical transformations at position 4 of the pyrimidine ring and a final nucleophilic *ipso*-substitution step of the oxidised sulfur with a variety of nucleophiles (Scheme 1). This last step is used not only for introducing molecular diversity but also as cleavage reaction in solid-phase synthesis. Both nucleophilic *ipso*-substitution reaction of alkylsulfonyl groups and Mitsunobu reaction are versatile and useful methods currently employed in the development of synthetic strategies for the construction of highly functionalised pyrimidines.[24] In this connection, we have recently described the synthesis of novel *N*-pyrimidinyl arylglycines type **2** through subsequent Mitsunobu, Petasis and *ipso*-substitution reactions[25] (Scheme 1).



Scheme 1. Synthesis of highly functionalised pyrimidines.

As a part of our research aimed at synthesising novel, modified antimicrobial peptides by incorporation of unnatural α-amino acids, we centred our attention on the synthesis of novel, unnatural pyrimidinyl α-amino acids. Specifically, we prepared a series of pyrimidines substituted at position 2 and/or 4 with an α-amino acid residue, following the method described by our research group. The results of this investigation are disclosed herein.

2. Results and discussion

Consistent with our goal, we reasoned that the incorporation of an α-amino acid residue at position 2 of a pyrimidine ring could be achieved by nucleophilic *ipso*-substitution of the sulfones **3** with a nucleophilic side chain of several protected natural α-amino acid. For this purpose, the easily available 2-(benzylsulfonyl)-4-isopropoxypyrimidines[23c] **3** were treated under basic conditions, with N^{α}-Boc-aminoesters **4** with an amine (lysine), an heteroaryl (histidine and tryptophan), an alcohol (serine) or a phenol (tyrosine) functions in the side chain in order to obtain the corresponding pyrimidinyl α-aminoesters type **5** (Table 1, entries 1–32).

When a ring nitrogen of the imidazole of the N^{α}-Boc-histidine methyl ester **4a** was employed as a nucleophile the best results were obtained using DBU as a base and heating at 50 °C (Table 1, entries 2–5). Under these conditions all compounds **5a–c** were isolated in good yields and without appreciable racemisation except for compound **5c**, which contained a phenyl group at position 6 of pyrimidine ring that showed a substantial degree of racemisation (Table 1, entry 4). It proved possible to avoid racemisation of **5c** carrying out the reaction at room temperature (Table 1, entry 5). The two nitrogen atoms of the imidazole ring of histidine are not equivalent. The nucleophilic attack could, in principle, take place by

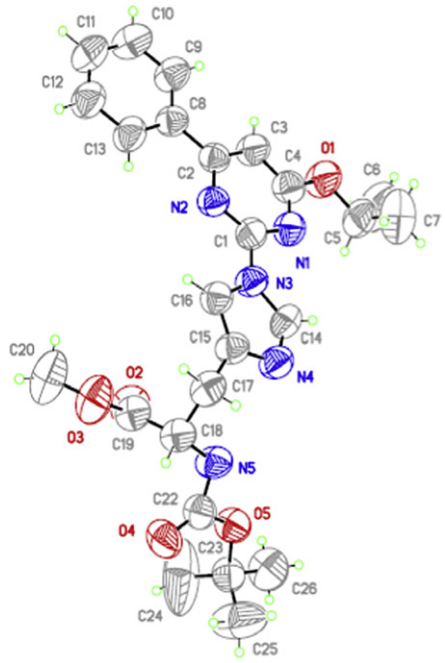


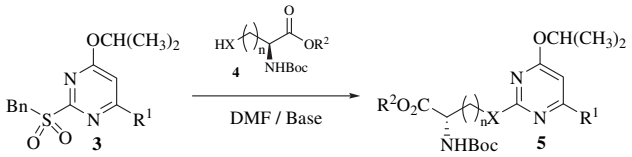
Figure 2. X-ray crystal structure of compound **5c**.

N(π) or N(τ) atoms and consequently two regioisomers would be isolated. Although the N(τ) derivative is often the major product resulting from steric factors, it is rarely exclusive. However, in all cases (Table 1, entries 1–5) the reaction was completely regioselective in favour of the N(τ) derivative. The unambiguous assignment of the structures **5a–c** was achieved by X-ray analysis of compound **5c**. As evidenced in Figure 2, the histidine residue is attached to position 2 of the pyrimidine ring by the N(τ) of the imidazole ring.

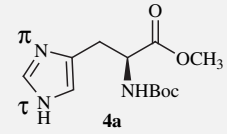
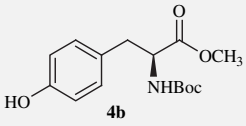
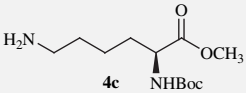
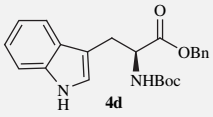
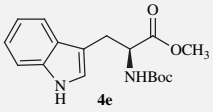
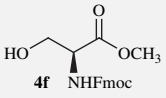
In our initial experiments with N^{α}-Boc-tyrosine methyl ester **4b**, we first studied the nucleophilic *ipso*-substitution reaction by employing several bases and starting from 2-benzylsufonylpyrimidine **3a**. No reaction took place when potassium *tert*-butoxide was used as a base (Table 1, entry 6). Better results were obtained using both NaH and potassium carbonate affording pyrimidinyl amino ester **5d** without appreciable racemisation (Table 1, entries 7 and 8). In the case of potassium carbonate, reaction required heating at 50 °C for completion. These reaction conditions were then extended to 2-benzylsufonylpyrimidines **3b** and **3c**, which afforded the corresponding pyrimidinyl aminoesters **5e** and **5f** in good yields (Table 2, entries 9 and 10). Unfortunately compound **5f** was obtained with a high degree of racemisation (60:40 enantiomeric ratio). In order to avoid racemisation the temperature reaction was decreased. When this reaction was carried out at 40 °C a substantial reduction in racemisation was observed (87:13 enantiomeric ratio) whereas at room temperature pyrimidinyl amino ester **5f** was obtained without appreciable racemisation but with a lower yield (Table 1 entries 11 and 12). It was possible to obtain an X-ray analysis of structure **5f** (Fig. 3) in which the tyrosine residue links to position 2 of the pyrimidine ring by the phenoxy group could be seen.

In the case of N^{α}-Boc-lysine methyl ester (Table 1, entries 9–12) we used the commercially available N^{α}-Boc-lysine methyl ester acetate salt **4c**. For this reason the *ipso*-substitution reaction between 2-benzylsulfonylpyrimidines **3** and amino ester **4c** also needed basic conditions. The reaction was not complete even after several days heating at 50 °C when Et_3N and DIEA were employed as a base and the corresponding pyrimidinyl amino ester **5g** was isolated in poor yield (Table 1, entries 13 and 14). It

Table 1
Synthesis of pyrimidinyl aminoesters **5**



R^1= H, Me, Ph

Entry	Amino acid **4**	R^1	Base (equiv)	Time (h)	Temp (°C)	Product **5**	Yield[a] (%)	Enantiomeric ratio[f]
1	 **4a**	H	KO^{t}Bu (1.1)	15	50	**5a**	37	
2		H	DBU (1.2)	8	50	**5a**	80	
3		Me	DBU (1.2)	8	50	**5b**	79	
4		Ph	DBU (1.2)	24	50	**5c**	79[b]	(70:30)
5		Ph	DBU (1.2)	24	rt	**5c**	58	
6	 **4b**	H	KO^{t}Bu (1.1)	24	80	**5d**	—	
7		H	NaH (1.2)	18	rt	**5d**	60	
8		H	K_2CO_3 (2.4)	24	50	**5d**	79	
9		Me	K_2CO_3 (2.4)	24	50	**5e**	60	
10		Ph	K_2CO_3 (2.4)	24	50	**5f**	90[b]	(60:40)
11		Ph	K_2CO_3 (2.4)	24	40	**5f**	58[b]	(87:13)
12		Ph	K_2CO_3 (2.4)	24	rt	**5f**	40	
13	 **4c**	H	Et_3N (2.0)	96	50	**5g**	14	
14		H	DIEA (2.0)	48	50	**5g**	16	
15		H	DBU (1.2)	28	50	**5g**	60[b]	(89:11)
16		H	K_2CO_3 (4.0)	24	40	**5g**	88	
17		Me	DBU (1.2)	24	50	**5h**	43	
18		Ph	DBU (1.2)	24	50	**5i**	42	
19	 **4d**	H	KO^{t}Bu (1.2)	1	50	**5j**	5[c]	
20		H	DBU (1.2)	24	50	**5j**	50[e]	(50:50)
21		H	DBU (1.2)	24	rt	**5j**	50[e]	(50:50)
22		H	NaH (1.2)	24	rt	**5j**	34[e]	(50:50)
23		H	K_2CO_3 (2.4)	24	50	**5j**	37[b,d]	(75:25)
24		H	K_2CO_3 (2.4)	24	rt	**5j**	19[d]	
25		Me	DBU (1.2)	24	50	**5k**	40[e]	(50:50)
26		Ph	DBU (1.2)	24	50	**5l**	57[e]	(50:50)
27	 **4e**	H	K_2CO_3 (4.0)	24	40	**5m**	40[d]	
28		H	K_2CO_3 (4.0)	48	40	**5m**	40[d]	
29		H	K_2CO_3 (4.0)	7 days	rt	**5m**	35[d]	
30	 **4f**	H	KO^{t}Bu (1.2)	24	rt	**5n**	—	
31		H	KO^{t}Bu (1.2)	48	80	**5n**	—	
32		H	NaH (1.2)	24	rt	**5n**	—	

[a] Isolated yields.
[b] Partial racemisation observed.
[c] N^{α}-Boc-tryptophan ^{t}Bu ester isolated as a major product reaction.
[d] About 50% of starting sulfone **3a** recovered.
[e] Complete racemisation observed.
[f] Determined by HPLC of dipeptide derivatives **8.**

was possible to improve yield and reduce reaction time using DBU and heating at 50 °C. Under these conditions compounds **5h** and **5i** were obtained in moderate yields and without appreciable racemisation (Table 1, entries 15, 17 and 18). However compound **5g** was isolated with a noticeable degree of racemisation (89:11 enantiomeric ratio). The racemisation of compound **5g** was completely avoided by employing K_2CO_3 as a base. In addition, this reaction afforded N^{α}-Boc-aminoester **5g** in good yield (Table 1, entry 16).

The nucleophilic *ipso*-substitution reaction between sulfones **3** and N^{α}-Boc-tryptophan was first studied using the commercially available benzyl ester **4d**. When this reaction was carried out with sulfone **3a** in the presence of potassium *tert*-butoxide at 50 °C, the desired amino ester **5j** was obtained in only 5% yield. The major compound isolated was the transesterification product N^{α}-Boc-tryptophan *tert*-butyl ester (Table 1, entry 19). By employing DBU or NaH as a base the corresponding aminoesters **5j–l** were obtained in moderate yields. However, DBU and NaH caused the complete racemisation of compounds **5j–l** even at room temperature (Table 1, entries 20–22, 25 and 26). The degree of racemisation was substantially reduced when sulfone **3a** and tryptophan **4d** were treated with K_2CO_3 at 50 °C (75:25 enantiomeric ratio), while at room temperature pyrimidinyl amino ester **5j** was obtained without appreciable racemisation but in low yield (Table 1 entries 23 and 24). We continued our studies using N^{α}-Boc-tryptophan methyl ester **4e** instead of benzyl ester derivative **4d**. Treatment of sulfone **3a** with **4e** in the presence of an excess of K_2CO_3 (4 equiv) at 40 °C afforded amino ester **5m** in a moderate yield without appreciable racemisation (Table 1, entry 27). These results clearly indicate that using K_2CO_3 racemisation can be completely avoided by performing the *ipso*-substitution reaction below 40 °C. The main cause of low yields of compounds **5j** and **5m** employing K_2CO_3 could be

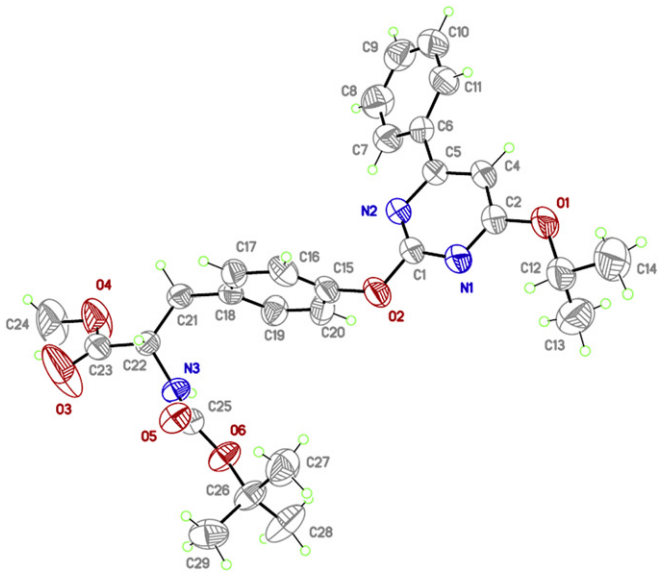
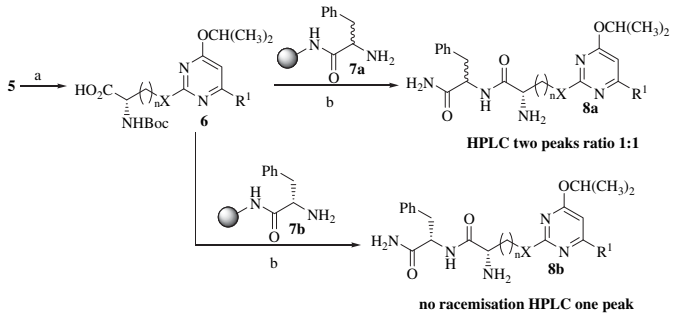
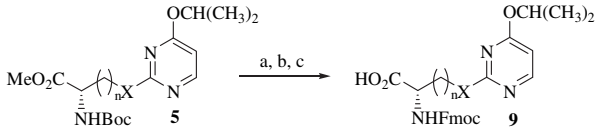


Figure 3. X-ray crystal structure of compound **5f**.



Scheme 2. Solid-phase synthesis of dipeptides **8**. Reagents and conditions: (a) LiOH, THF/MeOH/H_2O (1:2:2), rt, 3–4 h. (b) (i) HBTU, DIEA, DMF, rt, 3 h; (ii) TFA/H_2O/TIS (95:2.5:2.5), rt, 2 h.



Scheme 3. Synthesis of N^{α}-Fmoc-pyrimidinyl amino acids **9**. Reagents and conditions: (a) LiOH, THF/MeOH/H_2O (1:2:2), rt, 3–4 h. (b) TFA, CH_2Cl_2, 0 °C, 1-2 h. (c) Fmoc-Osu, Na_2CO_3 (pH 7), 1,4-dioxane, rt, 8–12 h.

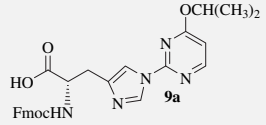
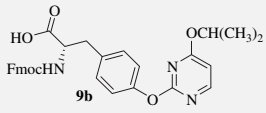
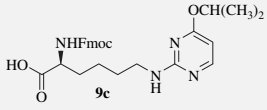
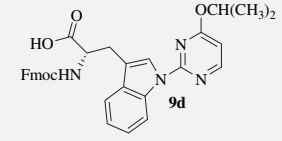
attributed to incomplete reactions. In general, the conversion of starting sulfone **3a** was about 50%. However, an increase in reaction time did not improve reaction conversion (Table 1, entries 28 and 29).

Disappointingly, no reaction took place when N^{α}-Boc-serine methyl ester **4f** was employed as nucleophile in any of the experimental conditions tested (Table 1, entries 30–32). In all cases, starting sulfone **3a** was totally recovered whereas basic conditions and high temperature caused dehydratation of N^{α}-Boc-serine methyl ester **4f** (Table 1, entry 31).

The optical purity of compounds **5** was verified by coupling the new pyrimidinyl α-amino acids **6** with both racemic phenylalanine and L-phenylalanine in order to measure the degree of racemisation by HPLC. Thus, samples of N^{α}-Boc-aminoesters **5** were deprotected using lithium hydroxide to give free N^{α}-Boc-amino acids **6** in quantitative yield. These compounds were first coupled to resin bound racemic phenylalanine **7a** using standard protocols for solid-phase peptide synthesis following Fmoc/*tert*-butyl strategy. After cleavage from the resin, the HPLC analyses of the resulting dipeptides **8a** showed the formation of two diastereoisomers. Dipeptides **8b** were then synthesised analogously by coupling N^{α}-Boc-amino acids **6** to L-phenylalanine resin bound **7b**. When no reasonable racemisation occurred during the synthesis of **5**, HPLC analyses of **8b** showed the formation of one single diastereoisomer (Scheme 2). However, N^{α}-Boc-amino acids **6** are not useful tools for solid-phase peptide synthesis following Fmoc/*tert*-butyl strategy. To circumvent this problem we explored the synthesis of the N^{α}-Fmoc-protected derivatives **9**. For this purpose, we selected amino ester **5a**, **5d**, **5g** and **5m**, each with a different α-amino acid residue at position 2 of the pyrimidine ring. First, methyl ester of compounds **5** was deprotected using lithium hydroxide. After cleavage of N^{α}-Boc protecting group by treatment with TFA, the free amino group was reprotected with Fmoc-Osu leading the expected N^{α}-Fmoc-amino acids **9** in high yields (Scheme 3, Table 2).

On the other hand, we expected that an amino acid residue with an hydroxyl function in the side chain could be easily incorporated at position 4 of a pyrimidine ring by selective O-alkylation of 2-(benzylsulfanyl)-4(3*H*)pyrimidinones **1** under a Mitsunobu reaction. We have shown previously that Mitsunobu reactions between pyrimidinones **1** and bulky alcohols are completely regioselective in favour of *O*-alkylated derivative.[23] Initially, N^{α}-Boc methyl serinate **4f** and 4(3*H*)-pyrimidinone **1a** were

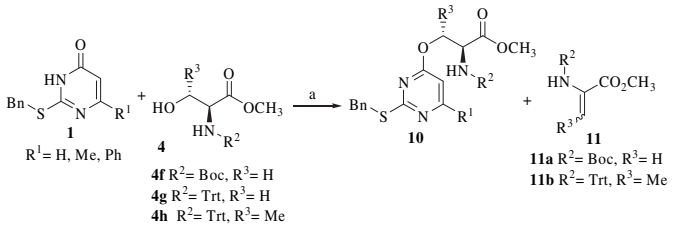
Table 2
Yields of N^{α}-Fmoc-pyrimidinyl amino acids **9**

Entry	N^{α}-Boc-amino ester **5**	Product **9**	Yield[a] (%)
1	**5a**	 **9a**	96
2	**5b**	 **9b**	57
3	**5c**	 **9c**	77
4	**5d**	 **9d**	77

[a] Isolated yields.

treated with PPh_3 and diisopropyl azodicarboxylate (DIAD) in anhydrous THF (Scheme 4, Table 3). Under these conditions only 14% yield of the substitution product **10a** was obtained (Table 3, entry 1).

The major compound isolated was the dehydroalanine derivative **11a**, produced from serine by β-elimination through the action of DIAD and PPh_3 (Scheme 4). To circumvent this side reaction a literature search of serine-based Mitsunobu reaction was carried out. We found that Cherney et al. had demonstrated that a Mitsunobu reaction performed with both N^{α}-phenylfluorenyl and N^{α}-trityl-serine completely prevents β-elimination reaction, whereas a Mitsunobu reaction using N^{α}-Boc-serine methyl ester afford a large amount of dehydroalanine **11a**.[26] In good agreement with this study, when N^{α}-trityl-serine methyl ester[27] **4g** was used



Scheme 4. Synthesis of pyrimidines **10** substituted at position 4 with an amino acid residue. Reagents and conditions: (a) Ph_3P, DIAD, THF, 0 °C to rt, 4–6 h.

Table 3
Yields of pyrimidinyl amino ester **10**

Entry	Amino ester **4**	R^1	Product **10**	Yield[a] (%)
1	**4e**	H	**10a**	14
2	**4f**	H	**10b**	97
3	**4f**	Me	**10c**	64
5	**4f**	Ph	**10d**	93
5	**4g**	H	**10e**	17

[a] Isolated yields.

instead of the N^{α}-Boc derivative **4f**, the desired compounds **10b–d** were isolated in high yields (Table 3, entries 2–4) as the sole reaction products. We then examined the same Mitsunobu reaction using N^{α}-trityl threonine methyl ester **4h**. In this case, the substitution product **10e** was obtained in only a 17% yield along with a large amount of the elimination derivative **11b** (Table 3, entry 5).

In order to increase the molecular diversity of aminoesters **10** at position 2 of the pyrimidine ring, we examined the nucleophilic displacement of the activated benzylsulfanyl group using the methodology described previously. Accordingly, compounds **10b–d** were treated with 2.5 equiv of *m*-CPBA at 0 °C to afford the corresponding sulfones **12a–c** (Scheme 5). Compound **12b** was crystallised giving crystals suitable for X-ray analysis (Fig. 4). This was not only unambiguous proof of the constitution and configuration of sulfone derivatives **12** but also their aminoesters **10** precursors. As expected the N^{α}-trityl methyl serinate residue was attached to position 4 of the pyrimidine ring by the alcohol

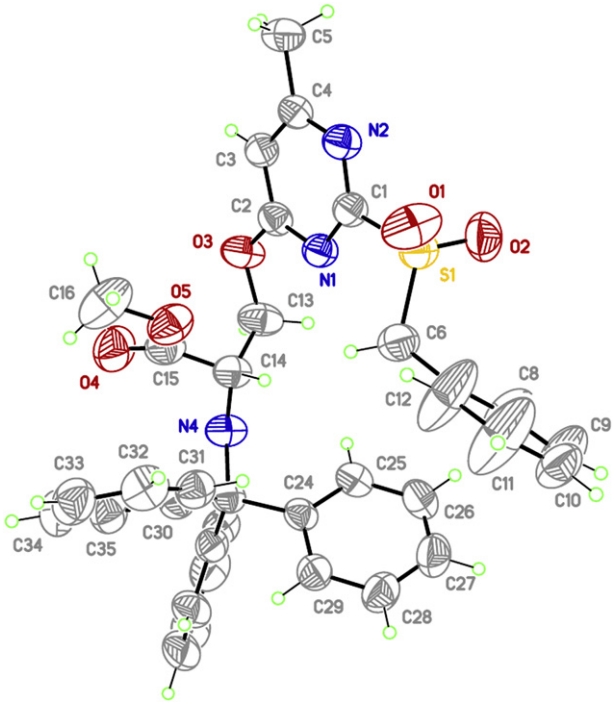
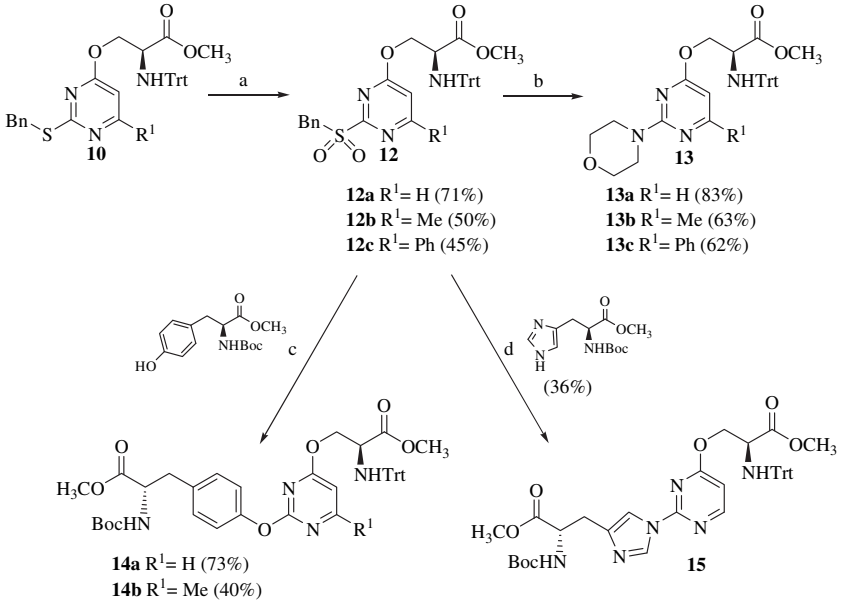


Figure 4. X-ray crystal structure of compound **12b**.

function. This clearly confirmed that Mitsunobu reaction was completely regioselective in favour of O-regioisomer.

The subsequent nucleophilic *ipso*-substitution displacement of sulfones **12** with morpholine afforded the pyrimidinyl aminoesters **13** in good yields. In addition, compounds **12** were treated with N^{α}-Boc methyl tyrosinate **4b** and N^{α}-Boc methyl histidinate **4a** under previously optimised reaction conditions, leading the desired pyrimidines **14** and **15**, with an amino acid residue at position 2 and 4 of the pyrimidine ring, in moderate yields (Scheme 5). Compounds **14** and **15** were obtained as a sole diastereoisomer. No other diastereoisomer could be detected by ^1H NMR. This result proved



Scheme 5. Functionalisation of pyrimidines **10** at position 2. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 2–4 h. (b) morpholine, 1,4-dioxane, 60 °C, 12–15 h. (c) NaH, DMF, rt, 12–15 h; d) DBU, DMF, 50 °C, 15 h.

that both Mitsunobu reaction and nucleophilic *ipso*-substitution displacement proceeded without racemisation.

3. Conclusion

A simple synthetic strategy to prepare new N^{α}-Boc-pyrimidin-2-yl aminoesters **5** via an *ipso*-substitution reaction between sulfones **3** and a nucleophilic side chain of several N^{α}-Boc-aminoesters **4** has been described. The results of this investigation show that the base and reaction temperature play a crucial role in obtaining the target compounds **5** in good yield and without racemisation. In the case of histidine derivatives **5a**–**c**, the described reaction proved to be totally regioselective in favour of N(τ) regioisomer. N^{α}-Boc-pyrimidin-2-yl aminoesters **5** were easily converted into N^{α}-Fmoc-pyrimidin-2-yl amino acids **9** using standard deprotecting and protecting group procedures. The N^{α}-Fmoc-protected derivatives **9a**–**d** are useful building blocks for the solid-phase peptide synthesis following Fmoc/*tert*-butyl strategy. The effect of its incorporation into bioactive peptides is currently underway. We have also described the synthesis of highly functionalised N^{α}-trityl-pyrimidin-4-yl aminoesters **13** via a subsequent Mitsunobu and *ipso*-substitution reaction. Best results were obtained when Mitsunobu reaction was carried out employing N^{α}-trityl-serine methyl ester **4g**. Finally, the synthesis of new pyrimidines substituted at position 2 and 4 by an amino ester residue **14** and **15** has been achieved applying the synthetic strategies optimised in this work.

4. Experimental section

4.1. General information

All commercially available chemicals were used as purchased without further purification. DMF and dioxane were dried over activated molecular sieves (4 Å). THF was dried over Na/benzophenone prior 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 DPX Advance spectrometer. ^{1}H NMR spectra were recorded at 400 or 200 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 100 or 50 MHz. Spectra recorded in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm for ^{1}H or 77.0 ppm for ^{13}C. Spectra recorded in DMSO-d_6 were referenced to residual DMSO-d_6 at 2.49 ppm for ^{1}H or 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=quarter, sept=septet, m=multiplet, dd=double doublet, br=broad. ESI mass spectra were recorded using a Navigator quadrupole instrument. High resolution mass spectra (HRMS) were determined under conditions of ESI on a Brucker MicroTof-Q instrument using a lock-spray source. Elemental analyses were performed on an apparatus from Thermo Instruments, model EA1110-CHNS. Optical rotations were measured on a Perkin–Elmer polarimeter 241. Specific rotation $[\alpha]_D$ are given in 10^{-1} cm^2 g^{-1}, and the concentration (*c*) are expressed in g per 100 mL. Analytical thin layer chromatography (TLC) analyses were carried out on 0.25 mm thick precoated plates (Merk Fertigplatten Kieselgel 60F_{254}) and spots were visualized with UV light (254 nm) and/or stained with a solution of potassium permanganate (1.5 g/100 mL H_2O). High performance liquid chromatography (HPLC) was performed on a Summit Dionex instruments composed of P680 binary pump, UVD 170U 4-Channel UV–vis Detector, ASI-100 Autosampler and the Chromaleon 6.60 software from Dionex, on a C_{18} Kromasil reverse-phase column (4.6×40 mm; 3.5 μm particle size). Flash chromatography purifications were performed on silica gel 60 (230–400 mesh, Merck).

4.2. Synthesis of pyrimidin-4(3*H*)-ones 1a–c and pyrimidines 3a–c

The synthesis of these compounds were described in Ref. 23c.

4.3. Representative procedure for the synthesis of N^{α}-Boc-pyrimidin-2-yl aminoesters 5a–m

The appropriate N^{α}-Boc-aminoester **4a**–**f** (1.1–1.2 equiv) was dissolved in dry DMF (2.5 mL/mmol) under a nitrogen atmosphere. The corresponding base (1.2–4.0 equiv) was added and the resulting mixture was stirred at room temperature for 15 min. Then, pyrimidinyl sulfone **3a**–**c** (1 equiv) was added as a DMF solution (1 mL/mmol **3a**–**c**). The resulting mixture was stirred under nitrogen at the temperature specified in Table 1. Upon completion of the reaction (TLC monitoring; reaction time specified in Table 1), the solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (*n*-hexane/ethyl acetate 10:1–1:1) to afford N^{α}-Boc-pyrimidinyl aminoesters **5**.

*4.3.1. tert-Butyl (S)-1-(methoxycarbonyl)-2-(1-(4-isopropoxypyrimidin-2-yl)-1H-imidazol-4-yl)ethylcarbamate (**5a**).* Synthesised according to general procedure from pyrimidinyl sulfone **3a** (292.4 mg, 1.0 mmol), N^{α}-Boc-(*S*)-histidine methyl ester **4a** (296.2 mg, 1.1 mmol) and DBU (1.52 mL, 1.2 mmol), 324 mg (80%) of compound **5a** was obtained as a colourless solid. Mp 100–101 °C. TLC: R_f=0.19 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +8.19 (*c*=0.5, MeOH). IR (ATR): 3264 (w), 2980 (w), 1744 (m), 1700 (s), 1586 (m), 1562 (s), 1473 (m), 1437 (s), 1366 (s), 1349 (m), 1315 (w), 1275 (m), 1248 (m), 1215 (w), 1174 (s), 1092 (m), 1056 (m), 1022 (s), 971 (w), 948 (m), 823 (m) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.43 (d, *J*=6.2 Hz, 6H, CH(CH_3)$_2$), 1.46 (s, 9H, C(CH_3)$_3$), 3.11–3.14 (m, 2H, CH_2-β), 3.74 (s, 3H, OCH_3), 4.60–4.64 (m, 1H, C*H*-α), 5.42 (sept, *J*=6.2 Hz, 1H, C*H*(CH$_3$)$_2$), 5.86 (d, *J*=8.0 Hz, 1H, N*H*), 6.54 (d, *J*=5.8 Hz, 1H, *H*(5)$_{pym}$), 7.61 (d, 1H, ^{4}*J*=1.2 Hz, *H*(5)$_{imid}$), 8.32 (d, *J*=5.8 Hz, 1H, *H*(6)$_{pym}$), 8.46 (d, 1H, ^{4}*J*=1.2 Hz, *H*(2)$_{imid}$). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.4 (q, 2C), 28.0 (q, 3C), 29.6 (t), 51.8 (q), 53.4 (d), 70.2 (d), 78.3 (s), 106.2 (d), 113.9 (d), 135.3 (d), 139.1 (s), 153.4 (s), 155.3 (s), 159.1 (d), 169.5 (s), 172.4 (s). MS (ESI) *m*/*z*: 405.9 [M+H]$^{+}$. Calcd for $C_{19}H_{27}N_5O_5$: C, 56.28; H, 6.71; N, 17.27. Found: C, 56.35; H, 6.58; N, 17.42.

*4.3.2. tert-Butyl (S)-1-(methoxycarbonyl)-2-(1-(4-isopropoxy-6-methylpyrimidin-2-yl)-1H-imidazol-4-yl)ethylcarbamate (**5b**).* Synthesised according to general procedure from pyrimidinyl sulfone **3b** (306.0 mg, 1.0 mmol), N^{α}-Boc-(*S*)-histidine methyl ester **4a** (296.2 mg, 1.1 mmol) and DBU (1.52 mL, 1.2 mmol), 330 mg (79%) of compound **5b** was obtained as a colourless solid. Mp 110–111 °C. TLC: R_f=0.29 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +10.23 (*c*=0.17, MeOH). IR (ATR): 3344 (w), 2978 (w), 1711 (m), 1600 (s), 1554 (m), 1481 (s), 1450 (m), 1401 (s), 1366 (m), 1311 (s), 1164 (s), 1102 (m), 1042 (m), 1014 (s), 866 (m) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.41 (d, *J*=6.2 Hz, 6H, CH(CH_3)$_2$), 1.46 (s, 9H, C(CH_3)$_3$), 2.43 (s, 3H, CH_3), 3.11–3.13 (m, 2H, CH_2-β), 3.75 (s, 3H, OCH_3), 4.59–4.63 (m, 1H, C*H*-α), 5.39 (sept, *J*=6.2 Hz, 1H, C*H*(CH$_3$)$_2$), 5.86 (br, 1H, N*H*), 6.38 (s, 1H, *H*(5)$_{pym}$), 7.63 (s, 1H, *H*(5)$_{imid}$), 8.48 (s, 1H, *H*(2)$_{imid}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.4 (q, 2C), 24.4 (q), 29.0 (q, 3C), 31.0 (t), 52.9 (q), 54.1 (d), 70.7 (d), 80.3 (s), 105.3 (d), 114.8 (d), 136.6 (d), 139.1 (s), 154.2 (s), 156.2 (s), 169.7 (s), 171.0 (s), 173.2

(s). MS (ESI) *m*/*z*: 419.9 $[M+H]^+$. Calcd for $C_{20}H_{29}N_5O_5$: C, 57.17; H, 6.97; N, 16.70. Found: C, 57.35; H, 7.09; N, 16.82.

*4.3.3. tert-Butyl (S)-1-(methoxycarbonyl)-2-(1-(4-isopropoxy-6-phenylpyrimidin-2-yl)-1H-imidazol-4-yl)ethylcarbamate (**5c**).* Synthesised according to general procedure from pyrimidinyl sulfone **3c** (368.4 mg, 1.0 mmol), N^{α}-Boc-(*S*)-histidine methyl ester **4a** (296.2 mg, 1.1 mmol) and DBU (1.52 mL, 1.2 mmol), 278 mg (58%) of compound **5c** was obtained as a colourless solid. Mp 133–134 °C. TLC: R_f=0.35 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{24}$ +23.28 (*c*=0.35, MeOH). IR (ATR): 3344 (w), 2978 (w), 1711 (m), 1600 (s), 1554 (m), 1481 (s), 1450 (m), 1401 (s), 1366 (m), 1311 (s), 1164 (s), 1102 (m), 1042 (m), 1014 (s), 866 (m) cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ=1.45 (s, 9H, C(CH_3)$_3$), 1.49 (d, *J*=6.2 Hz, 6H, CH(CH_3)$_2$), 3.02–3.05 (m, 2H, CH_2-β), 3.74 (s, 3H, OCH_3), 4.42–4.45 (m, 1H, C*H*-α), 5.59 (sept, *J*=6.2 Hz, 1H, C*H*(CH$_3$)$_2$), 7.01 (br, 1H, N*H*), 7.32 (s, 1H, *H*(5)$_{pym}$), 7.45–7.66 (m, 3H, CH_{Aryl}), 7.91 (s, 1H, *H*(5)$_{imid}$), 8.36–8.38 (m, 2H, CH_{Aryl}), 8.77 (s, 1H, *H*(2)$_{imid}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.5 (q, 2C), 29.0 (q, 3C), 31.1 (t), 52.9 (q), 54.2 (d), 71.2 (d), 80.3 (s), 101.9 (d), 114.9 (d), 127.6 (d, 2C), 129.5 (d, 2C), 131.7 (d), 136.7 (d), 139.3 (s), 154.5 (s), 156.0 (s), 166.6 (s), 171.7 (s), 173.2 (s). MS (ESI) *m*/*z*: 480.9 $[M+H]^+$. Calcd for $C_{25}H_{31}N_5O_5$: C, 62.36; H, 6.49; N, 14.54. Found: C, 62.45; H, 6.61; N, 14.72.

*4.3.4. tert-Butyl (S)-1-(methoxycarbonyl)-2-(4-(4-isopropoxypyrimidin-2-yloxy)phenyl)ethylcarbamate (**5d**).* Synthesised according to general procedure from pyrimidinyl sulfone **3a** (292.4 mg, 1.1 mmol), N^{α}-Boc-(*S*)-tyrosine methyl ester **4b** (354.4 mg, 1.2 mmol) and K_2CO_3 (136.7 mg, 1.2 mmol), 340 mg (79%) of compound **5d** was obtained as a colourless solid. Mp 114–115 °C. TLC: R_f=0.27 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ −2.80 (*c*=0.14, MeOH). IR (ATR): 3360 (w), 2978 (w), 1739 (s), 1699 (s), 1517 (s), 1508 (s), 1450 (m), 1383 (s), 1366 (s), 1321 (w), 1272 (s), 1252 (w), 1223 (s), 1202 (s), 1171 (s), 1150 (s), 1110 (m), 1041 (s), 1017 (m), 978 (w), 839 (m), 817 (w), 786 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=1.34 (d, *J*=6.2 Hz, 6H, CH(CH_3)$_2$), 1.45 (s, 9H, C(CH_3)$_3$), 3.12–3.16 (m, 2H, CH_2-β), 3.74 (s, 3H, OCH_3), 4.60–4.63 (m, 1H, C*H*-α), 5.01 (br, 1H, N*H*), 5.27 (sept, *J*=6.2 Hz, 1H, C*H*(CH$_3$)$_2$), 6.38 (d, *J*=5.6 Hz, 1H, *H*(5)$_{pym}$), 7.16–7.29 (m, 4H, CH_{Aryl}), 8.18 (d, *J*=5.6 Hz, 1H, *H*(6)$_{pym}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.4 (q, 2C), 28.9 (q, 3C), 38.5 (t), 52.9 (q), 55.1 (d), 70.6 (d), 104.5 (d), 122.5 (d, 2C), 130.9 (d, 2C), 133.6 (s), 152.7 (s), 161.7 (s), 165.7 (s), 171.6 (s), 172.9 (s). MS (ESI) *m*/*z*: 431.9 $[M+H]^+$. Calcd for $C_{22}H_{29}N_3O_6$: C, 61.24; H, 6.77; N, 9.74. Found: C, 61.39; H, 6.88; N, 9.90.

*4.3.5. tert-Butyl (S)-1-(methoxycarbonyl)-2-(4-(4-isopropoxy-6-methylpyrimidin-2-yloxy)phenyl)ethylcarbamate (**5e**).* Synthesised according to general procedure from pyrimidinyl sulfone **3b** (306.4 mg, 1.1 mmol), N^{α}-Boc-(*S*)-tyrosine methyl ester **4b** (354.4 mg, 1.2 mmol) and K_2CO_3 (136.7 mg, 1.2 mmol), 266 mg (60%) of compound **5e** was obtained as a colourless oil. TLC: R_f=0.49 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{27}$ −28.6 (*c*=0.3, MeOH). IR (ATR): 3355 (w), 2979 (w), 1744 (m), 1712 (s), 1596 (s), 1561 (m), 1533 (w), 1505 (s), 1452 (w), 1354 (s), 1321 (s), 1247 (m), 1211 (s), 1165 (s), 1101 (s), 1075 (m), 1017 (s), 731 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=1.24 (d, *J*=6.2 Hz, 6H, CH(CH_3)$_2$), 1.43 (s, 9H, C(CH_3)$_3$), 2.34 (s, 3H, CH_3), 3.09–3.12 (m, 2H, CH_2-β), 3.71 (s, 3H, OCH_3), 4.61 (br, 1H, N*H*), 5.01–5.08 (m, 1H, C*H*-α), 5.10 (sept, *J*=6.2 Hz, 1H, C*H*(CH$_3$)$_2$), 6.22 (s, 1H, *H*(5)$_{pym}$), 7.13 (s, 4H, CH_{Aryl}). ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.0 (q, 2C), 23.7 (q), 28.2 (q, 3C), 37.7 (t), 52.7 (q), 54.4 (d), 70.1 (d), 79.9 (s), 101.8 (d), 121.7 (d, 2C), 130.3 (d, 2C), 132.4 (s), 152.2 (s), 155.0 (s), 164.4 (s), 169.6 (s), 171.1 (s), 172.2 (s). MS (ESI) *m*/*z*: 446 $[M+H]^+$. Calcd for $C_{23}H_{31}N_3O_6$: C, 62.01; H, 7.01; N, 9.43. Found: C, 62.19; H, 7.19; N, 9.57.

*4.3.6. tert-Butyl (S)-1-(methoxycarbonyl)-2-(4-(4-isopropoxy-6-phenylpyrimidin-2-yloxy)phenyl)ethylcarbamate (**5f**).* Synthesised according to general procedure from pyrimidinyl sulfone **3c** (368.4 mg, 1.1 mmol), N^{α}-Boc-(*S*)-tyrosine methyl ester **4b** (354.4 mg, 1.2 mmol) and K_2CO_3 (136.7 mg, 1.2 mmol), 202 mg (40%) of compound **5f** was obtained as a colourless oil. TLC: R_f=0.52 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ −6.23 (*c*=0.26, MeOH). IR (ATR): 3442 (w), 2978 (w), 2928 (w), 1744 (w), 1713 (s), 1580 (s), 1549 (s), 1503 (s), 1453 (w), 1431 (w), 1356 (s), 1324 (s), 1250 (w), 1212 (s), 1164 (s), 1095 (w), 1065 (s), 1018 (w), 939 (m), 770 (m), 731 (w) 693 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=1.35 (d, *J*=6.2 Hz, 6H, CH(CH_3)$_2$), 1.47 (s, 9H, C(CH_3)$_3$), 3.16 (d, *J*=5.4 Hz, 2H, CH_2-β), 3.73 (s, 3H, OCH_3), 4.63–4.67 (m, 1H, C*H*-α), 4.61 (d, *J*=8.2 Hz, 1H, N*H*), 5.27 (sept, *J*=6.2 Hz, 1H, C*H*(CH$_3$)$_2$), 6.81 (s, 1H, *H*(5)$_{pym}$), 7.21–7.26 (m, 4H, CH_{Aryl}), 7.43–7.50 (m, 3H, CH_{Aryl}), 7.94–8.01 (m, 2H, CH_{Aryl}). ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.5 (q, 2C), 29.0 (q, 3C), 38.6 (t), 52.8 (q), 55.2 (d), 70.7 (d), 82.1 (s), 99.3 (d), 122.7 (d, 2C), 127.7 (d, 2C), 129.4 (d, 2C), 130.6 (d, 2C), 131.4 (d), 133.2 (s), 137.1 (s), 153.0 (s), 155.8 (s), 165.7 (s), 167.1 (s), 172.7 (s), 172.9 (s). MS (ESI) *m*/*z*: 508 $[M+H]^+$. Calcd for $C_{28}H_{33}N_3O_6$: C, 66.26; H, 6.55; N, 8.28. Found: C, 66.17; H, 6.41; N, 8.37.

*4.3.7. tert-Butyl (S)-1-(methoxycarbonyl)-5-(4-isopropoxy-6-methylpyrimidin-2-ylamino)pentylcarbamate (**5g**).* Synthesised according to general procedure from pyrimidinyl sulfone **3a** (292.4 mg, 1.0 mmol), N^{α}-Boc-(*S*)-lysine methyl ester **4c** (384.4 mg, 1.2 mmol) and K_2CO_3 (275.8 mg, 2.0 mmol), 262 mg (66%) of compound **5g** was obtained as a colourless oil. TLC: R_f=0.27 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ −5.6 (*c*=0.19, MeOH). IR (ATR): 3387 (w), 3316 (w), 2978 (w), 2930 (w), 1739 (m), 1708 (s), 1667 (m), 1579 (s), 1525 (s), 1458 (m), 1422 (m), 1390 (w), 1365 (s), 1302 (m), 1232 (m), 1163 (s), 800 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=1.34 (d, *J*=6.2 Hz, 6H, CH(CH_3)$_2$), 1.46 (s, 9H, C(CH_3)$_3$), 1.53–1.88 (m, 6H, (-CH_2)$_3$), 3.38 (q-apparent, *J*=6.4 Hz, 2H, NCH_2), 3.75 (s, 3H, OCH_3), 4.29–4.32 (m, 1H, C*H*-α), 5.14 (br, 1H, N*H*), 5.28 (sept, *J*=6.2 Hz, 1H, C*H*(CH$_3$)$_2$), 5.83 (d, 1H, *J*=5.6 Hz, *H*(5)$_{pym}$), 6.36 (br, 1H, N*H*), 7.98 (d, 1H, *J*=5.6 Hz, *H*(6)$_{pym}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.5 (q, 2C), 23.4 (t), 29.6 (q, 3C), 30.3 (t), 33.2 (t), 41.7 (t), 52.8 (q), 53.9 (d), 68.9 (d), 80.5 (s), 98.3 (d), 158.6 (d), 163.1 (s), 170.1 (s), 173.9 (s), 176.3 (s). MS (ESI) *m*/*z*: 396.9 $[M+H]^+$. Calcd for $C_{19}H_{32}N_4O_5$: C, 57.56; H, 8.14; N, 14.13. Found: C, 57.64; H, 8.23; N, 14.17.

*4.3.8. tert-Butyl (S)-1-(methoxycarbonyl)-5-(4-isopropoxy-6-methylpyrimidin-2-ylamino)pentylcarbamate (**5h**).* Synthesised according to general procedure from pyrimidinyl sulfone **3b** (306.4 mg, 1.0 mmol), N^{α}-Boc-(*S*)-lysine methyl ester **4c** (384.4 mg, 1.2 mmol) and DBU (1.52 mL, 1.2 mmol), 176 mg (43%) of compound **5h** was obtained as a colourless oil. TLC: R_f=0.46 (*n*-hexane/ethyl acetate, 2:1). $[\alpha]_D^{25}$ −12.38 (*c*=0.1, MeOH). IR (ATR): 3397 (w), 3317 (w), 2964 (w), 2930 (w), 1717 (m), 1687 (s), 1657 (s), 1477 (m), 1435 (w), 1364 (m), 1335 (w), 1259 (m), 1221 (w), 1164 (s), 1098 (m), 1075 (m), 1051 (s), 1018 (s), 798 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=1.34 (d, *J*=6.2 Hz, 6H, CH(CH_3)$_2$), 1.47 (s, 9H, C(CH_3)$_3$), 1.63–2.07 (m, 6H, (-CH_2)$_3$), 2.29 (s, 3H, CH_3), 3.38 (q-apparent, *J*=6.4 Hz, 2H, NCH_2), 3.76 (s, 3H, OCH_3), 4.30–4.34 (m, 1H, C*H*-α), 4.97 (br, 2H, N*H*), 5.26 (sept, *J*=6.2 Hz, 1H, C*H*(CH$_3$)$_2$), 5.83 (s, 1H, *H*(5)$_{pym}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.9 (q, 2C), 22.7 (t), 23.7 (q), 28.1 (q, 3C), 29.4 (t), 32.5 (t), 41.0 (t), 52.2 (q), 53.3 (d), 68.1 (d), 79.8 (s), 96.1 (d), 155.3 (s), 162.3 (s), 167.8 (s), 170.0 (s), 173.3 (s). MS (ESI) *m*/*z*: 411 $[M+H]^+$. Calcd for $C_{20}H_{34}N_4O_5$: C, 58.52; H, 8.35; N, 13.65. Found: C, 58.65; H, 8.51; N, 13.71.

*4.3.9. tert-Butyl (S)-1-(methoxycarbonyl)-5-(4-isopropoxy-6-phenylpyrimidin-2-ylamino)pentylcarbamate (**5i**).* Synthesised according to general procedure from pyrimidinyl sulfone **3c** (368.4 mg, 1.0 mmol), N^{α}-Boc-(*S*)-lysine methyl ester **4c** (384.4 mg, 1.2 mmol) and DBU (1.52 mL, 1.2 mmol), 198 mg (42%) of compound **5i** was obtained as a colourless oil. TLC: R_f=0.50 (*n*-hexane/ethyl acetate, 2:1). $[\alpha]_D^{25}$ −18.55 (*c*=0.15, MeOH). IR (ATR): 3367 (w), 3315 (w),

2977 (w), 2930 (w), 1739 (m), 1709 (s), 1578 (s), 1559 (m), 1497 (m), 1459 (w), 1391 (m), 1366 (m), 1319 (w), 1210 (s), 1164 (s), 909 (w), 771 (w), 733 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=1.39 (d, J=6.2 Hz, 6H, CH(CH_3)$_2$), 1.47 (s, 9H, C(CH_3)$_3$), 1.66–2.07 (m, 6H, (–CH_2)$_3$), 3.49 (q-apparent, J=6.4 Hz, 2H, NCH_2), 3.76 (s, 3H, OCH_3), 4.27–4.33 (m, 1H, CH-α), 5.15 (br, 2H, NH), 5.37 (sept, J=6.2 Hz, 1H, CH(CH_3)$_2$), 6.41 (s, 1H, $H(5)_{pym}$), 7.38–7.47 (m, 3H, CH_{Aryl}), 7.95–8.00 (m, 2H, CH_{Aryl}). ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.1 (q, 2C), 23.1 (t), 29.0 (q, 3C), 30.5 (t), 32.7 (t), 41.3 (t), 52.3 (q), 53.4 (d), 68.4 (d), 80.0 (s), 93.6 (d), 126.9 (d, 2C), 128.9 (d, 2C), 131.0 (d), 138.1 (s), 155.4 (s), 162.7 (s), 165.6 (s), 170.9 (s), 173.4 (s). MS (ESI) m/z: 473 $[M+H]^+$. Calcd for $C_{25}H_{36}N_4O_5$: C, 63.54; H, 7.68; N, 11.86. Found: C, 63.67; H, 7.71; N, 11.81.

*4.3.10. tert-Butyl (S)-1-((benzyloxy)carbonyl)-2-(1-(4-isopropoxypyrimidin-2-yl)-1H-indol-3-yl)ethylcarbamate (**5j**).* Synthesised according to general procedure from pyrimidinyl sulfone **3a** (292.4 mg, 1.0 mmol), N^{α}-Boc-(*S*)-tryptophan benzyl ester **4d** (433.8 mg, 1.1 mmol) and DBU (1.52 mL, 1.2 mmol), 265 mg (50%) of compound **5j** was obtained as a colourless solid. Mp 103–104 °C. TLC: R_f=0.71 (*n*-hexane/ethyl acetate, 2:1). $[\alpha]_D^{25}$ racemic. IR (ATR): 3365 (w), 2973 (w), 1735 (m), 1695 (s), 1565 (s), 1506 (m), 1470 (m), 1447 (s), 1434 (s), 1372 (m), 1254 (m), 1293 (m), 1166 (s), 1140 (s), 1106 (m), 1017 (m), 940 (w), 816 (m), 743 (s), 703 (m) cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ=1.41 (s, 9H, C(CH_3)$_3$), 1.51 (d, J=6 Hz, 6H, CH(CH_3)$_2$), 3.21–3.26 (m, 2H, CH_2-β), 4.45–4.48 (m, 1H, CH-α), 5.20 (s, 2H, OCH_2Ph), 5.52 (sept, J=6 Hz, 1H, CH(CH_3)$_2$), 6.75 (d, J=5.6 Hz, 1H, $H(5)_{pym}$), 7.30–7.55 (m, 8H, 5CH_{aryl}, NH, $H(5)_{ind}$, $H(6)_{ind}$), 7.70 (d, 1H, J=7.6 Hz, $H(7)_{ind}$), 8.24 (s, 1H, $H(2)_{ind}$), 8.61 (d, J=5.6 Hz, 1H, $H(6)_{pym}$), 8.77 (d, 1H, J=8.0 Hz, $H(4)_{ind}$). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.5 (q, 2C), 26.4 (t), 28.0 (q, 3C), 54.0 (d), 65.8 (t), 69.8 (d), 78.3 (s), 103.6 (d), 115.3 (s), 118.6 (d), 121.8 (d), 123.7 (d), 124.2 (d), 127.6 (d, 2C), 127.9 (d), 128.2 (d, 2C), 130.4 (s), 134.8 (s), 135.8 (s), 155.4 (s), 156.3 (s), 158.8 (d), 169.0 (s), 172 (s). MS (ESI) m/z: 531.0 $[M+H]^+$. Calcd for $C_{30}H_{34}N_4O_5$: C, 67.91; H, 6.46; N, 10.56. Found: C, 67.84; H, 6.58; N, 10.62.

*4.3.11. tert-Butyl (S)-1-((benzyloxy)carbonyl)-2-(1-(4-isopropoxy-6-methylpyrimidin-2-yl)-1H-indol-3-yl)ethylcarbamate (**5k**).* Synthesised according to general procedure from pyrimidinyl sulfone **3b** (306.4 mg, 1.1 mmol), N^{α}-Boc-(*S*)-tryptophan benzyl ester **4d** (433.8 mg, 1.1 mmol) and DBU (1.52 mL, 1.2 mmol), 217 mg (40%) of compound **5k** was obtained as a colourless oil. TLC: R_f=0.59 (*n*-hexane/ethyl acetate, 2:1). $[\alpha]_D^{25}$ racemic. IR (ATR): 3438 (w), 2976 (w), 1709 (m), 1588 (s), 1558 (m), 1458 (s), 1390 (s), 1323 (s), 1162 (s), 1102 (m), 1014 (w), 977 (w), 884 (w), 741 (s), 703 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=1.47 (s, 9H, C(CH_3)$_3$), 1.49 (d, J=6 Hz, 6H, CH(CH_3)$_2$), 2.52 (s, 3H, CH_3), 3.34–3.36 (m, 2H, CH_2-β), 4.73–4.77 (m, 1H, CH-α), 5.22 (s, 2H, OCH_2Ph), 5.32 (br, 1H, NH), 5.51 (sept, J=6 Hz, 1H, CH(CH_3)$_2$), 6.32 (s, 1H, $H(5)_{pym}$), 7.30–7.55 (m, 7H, 5CH_{aryl}, $H(5)_{ind}$, $H(6)_{ind}$), 7.59 (d, 1H, J=7.8 Hz, $H(7)_{ind}$), 8.11 (s, 1H, $H(2)_{ind}$), 8.80 (d, 1H, J=8.4 Hz, $H(4)_{ind}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.5 (q, 2C), 24.6 (q), 28.8 (t), 28.9 (q, 3C), 55.0 (d), 67.7 (t), 70.1 (d), 80.1 (s), 102.6 (d), 114.3 (s), 116.8 (d), 119.3 (d), 122.3 (d), 124.3 (d), 125.2 (d), 128.80 (d), 128.85 (d), 129.1 (d, 2C), 131.4 (s), 135.8 (s), 136.2 (s), 156.4 (s), 157.8 (s), 168.9 (s), 170.6 (s), 172.6 (s). MS (ESI) m/z: 545.0 $[M+H]^+$. Calcd for $C_{31}H_{36}N_4O_5$: C, 68.36; H, 6.66; N, 10.29. Found: C, 68.18; H, 6.90; N, 10.23.

*4.3.12. tert-Butyl (S)-1-((benzyloxy)carbonyl)-2-(1-(4-isopropoxy-6-phenylpyrimidin-2-yl)-1H-indol-3-yl)ethylcarbamate (**5l**).* Synthesised according to general procedure from pyrimidinyl sulfone **3c** (368.4 mg, 1.0 mmol), N^{α}-Boc-(*S*)-tryptophan benzyl ester **4d** (433.8 mg, 0.55 mmol) and DBU (1.52 mL, 1.2 mmol), 310 mg (57%) of compound **5j** was obtained as a colourless solid. Mp 140–141 °C. TLC: R_f=0.53 (*n*-hexane/ethyl acetate, 2:1). $[\alpha]_D^{25}$ racemic. IR (ATR): 3378 (w), 2977 (w), 1731 (m), 1682 (s), 1582 (s), 1552 (s), 1518 (s), 1465 (s), 1389 (s), 1369 (s), 1321 (w), 1286 (m), 1245 (s), 1210 (m), 1158 (m), 1101 (m), 1014 (w), 958 (w), 766 (m), 738 (s), 691 (m) cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ=1.41 (s, 9H, C(CH_3)$_3$), 1.55 (d, J=6 Hz, 6H, CH(CH_3)$_2$), 3.25–3.30 (m, 2H, CH_2-β), 4.49–4.53 (m, 1H, CH-α), 5.21 (s, 2H, OCH_2Ph), 5.61 (sept, J=6 Hz, 1H, CH(CH_3)$_2$), 7.30–7.55 (m, 13H, 8CH_{Aryl}, $H(5)_{pym}$, NH, $H(2)_{ind}$, $H(5)_{ind}$, $H(6)_{ind}$), 8.23–8.39 (m, 3H, 3CH_{Aryl}, $H(7)_{ind}$), 8.85 (d, 1H, J=8.2 Hz, $H(4)_{ind}$). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.6 (q, 2C), 26.4 (t), 28.0 (q, 3C), 54.0 (d), 65.9 (t), 69.9 (d), 78.3 (s), 98.5 (d), 115.3 (s), 115.7 (d), 118.7 (d), 121.8 (d), 123.7 (d), 124.4 (d), 127.60 (d, 2C), 127.8 (d, 2C), 128.2 (d), 128.5 (d, 2C), 128.9 (d, 2C), 130.5 (s), 131.1 (d), 134.9 (s), 135.8 (s), 136.1 (s), 155.4 (s), 156.3 (s), 165.1 (s), 170.4 (s), 172.0 (s). MS (ESI) m/z: 545.0 $[M+H]^+$. Calcd for $C_{36}H_{38}N_4O_5$: C, 71.27; H, 6.31; N, 9.23. Found: C, 70.99; H, 6.56; N, 9.31.

*4.3.13. tert-Butyl (S)-1-(methoxycarbonyl)-2-(1-(4-isopropoxypyrimidin-2-yl)-1H-indol-3-yl)ethylcarbamate (**5m**).* Synthesised according to general procedure from pyrimidinyl sulfone **3a** (292.4 mg, 1.0 mmol), *N*-Boc-(*S*)-tryptophan methyl ester **4e** (350 mg, 1.1 mmol) and K_2CO_3 (276 mg, 2.0 mmol), 182 mg (40%) of compound **5m** was obtained as a colourless solid. Mp 88–89 °C. TLC: R_f=0.61 (*n*-hexane/ethyl acetate, 2:1). $[\alpha]_D^{24}$ +9.90 (*c*=0.11, MeOH). IR (ATR): 3645 (w), 3371 (m), 2978 (w), 1735 (w), 1690 (s), 1572 (m), 1518 (w), 1465 (m), 1425 (s), 1360 (m), 1304 (m), 1271 (w), 1247 (s), 1159 (s), 1136 (w), 1107 (w), 1091 (m), 1076 (w), 1006 (s), 986 (w), 816 (w), 738 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ=1.44 (d, J=6.20 Hz, 6H, CH(CH_3)$_2$), 1.47 (s, 9H, C(CH_3)$_3$), 3.31 (m, 2H, CH_2-β), 3.70 (s, 3H, OCH_3), 4.70 (m, CH-α), 5.15 (d, J=7.81 Hz, 1H, NH), 5.51 (sept, J=6.20 Hz, 1H, CH(CH_3)$_2$), 6.32 (d, J=5.70 Hz, 1H, $H(5)_{pym}$), 7.14–7.18 (m, 1H, $H(5)_{ind}$), 7.23–7.27 (m, 1H, $H(6)_{ind}$), 7.55 (d, 1H, J=7.73 Hz, $H(7)_{ind}$), 8.05 (s, 1H, $H(2)_{ind}$), 8.36 (d, J=5.70 Hz, 1H, $H(6)_{pym}$), 8.73 (d, 1H, J=7.63 Hz, $H(4)_{ind}$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=20.8 (q, 3C), 27.0 (t), 28.0 (q, 2C), 51.2 (q), 52.9 (d), 68.8 (d), 78.8 (s), 102.7 (d), 113.3 (s), 115.1 (d), 117.8 (d), 120.8 (d), 122.8 (d), 123.3 (d), 130.1 (s), 134.6 (s), 154.2 (s), 156.0 (s), 156.9 (d), 168.5 (s), 171.5 (s). HRMS (ESI): m/z calcd for $C_{24}H_{30}N_4NaO_4$ $[M+Na]^+$ 477.2108, found 477.2121; calcd for $C_{24}H_{31}N_4O5_4$ $[M+H]^+$ 455.2289, found 455.2292.

4.4. Representative procedure for the synthesis of dipeptides 8

Dipeptides **8** were prepared manually by solid-phase method using Fmoc-Rink-MBHA resin (0.64 mmol/g) as solid support following standard Fmoc-strategy. Coupling of amino acids were mediated by HBTU (3 equiv) and DIEA (3 equiv) in DMF at room temperature for 3 h. Monitoring was carried out by ninhydrin test.[28] Washings were performed with DMF (6×1 min). Fmoc group was removed by treating the resin with 30% piperidine in DMF (v/v) and washed with DMF (6–1 min). The Fmoc-Rink-MBHA resin (10 mg) was placed into a plastic syringe fitted with a polypropylene frit to remove the Fmoc group and subsequently couple Fmoc-Phe-OH **7**. After Fmoc group removal resin was treated with pyrimidinyl amino acid **6** under coupling conditions. The resulting dipeptides were deprotected and cleaved from resin by treatment with TFA/H_2O/TIS (95:2.5:2.5) for 2 h. Then the solvents were evaporated to dryness and the crude dipeptides **8** were dissolved in H_2O, lyophilized and tested for purity on HPLC. Electrospray ionisation mass spectrometry was used to confirm peptide identity.

4.5. Representative procedure for the synthesis of N^{α}-Fmoc-pyrimidin-2-yl amino acids 9a–d

LiOH monohydrate (2.5 equiv) was added to a solution of appropriate N^{α}-Boc-amino methyl ester **5** (1 equiv) in THF/MeOH/water (1:2:2) (8 mL/mmol), and the reaction mixture was stirred at room temperature for 3–4 h. Upon completion of the reaction (TLC

monitoring), the organic solvents were removed under reduced pressure. The pH of the resulting aqueous solution was then adjusted to 4 with glacial acetic acid, and the solution was extracted with CH_2Cl_2 (3×5 mL). The combined organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Then, the free N^{α}-Boc-amino acid **6** was dissolved in CH_2Cl_2 (1.5 mL/mmol) and the solution was cooled in an ice bath. TFA (1.5 mL/mmol) was added dropwise and the resulting mixture was stirred at 0 °C for 1–2 h. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure. Next, the crude material was dissolved in 1,4-dioxane (3 mL/mmol). The resulting solution was adjusted to pH 7 with aqueous Na_2CO_3 (5%). Fmoc-Osu (1.05 equiv) was added slowly. During Fmoc-Osu addition, pH was readjusted to 7 with aqueous Na_2CO_3 (5%). The resulting mixture was stirred at room temperature for 8–12 h. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure. The resulting residue was dissolved in water (10 mL) and extracted with ethyl acetate (3×5 mL). The combined organic layer was back extracted with saturated $NaHCO_3$ solution (3×5 mL). Then the aqueous layer was acidified to pH 1–2 with aqueous HCl (1%), and extracted with ethyl acetate (3×5 mL). The combined organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (*n*-hexane/ethyl acetate/acetic acid 4:1:0–0:20:1) to afford N^{α}-Fmoc-amino acids **9**.

*4.5.1. (S)-N^{α}-Fmoc-2-amino-3-(1-(4-isopropoxypyrimidin-2-yl)-1H-imidazol-4-yl)propanoic acid (**9a**).* Synthesised according to general procedure from N^{α}-Boc-amino methyl ester **5a** (162 mg, 0.40 mmol), 197 mg (96%) of compound **9a** was obtained as a colourless solid. Mp 80–83 °C. TLC: R_f=0.50 (ethyl acetate/methanol/acetic acid, 5:3:0.2). $[\alpha]_D^{25}$ +5.50 (*c*=0.23, MeOH). IR (ATR): 3363 (w), 3337 (w), 1710 (m), 1592 (m), 1562 (m), 1486 (w), 1444 (s), 1380 (m), 1310 (m), 1248 (w), 1214 (m), 1188 (w), 1097 (m), 1046 (w), 1026 (m), 986 (w), 947 (m), 823 (w), 757 (m), 738 (s), 539 (w) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=1.28 (d, *J*=6.2 Hz, 3H, CH(CH_3)$_2$), 1.31 (d, *J*=6.2 Hz, 3H, CH(CH_3)$_2$), 2.90 (dd, 1H, *J*=14.5 Hz, *J′*=9.3 Hz, 1H, CH_2-β), 3.04 (dd, 1H, *J*=14.5 Hz, *J′*=3.7 Hz, 1H, CH_2-β), 4.17–4.29 (m, 4H, CH_{Fmoc}, OCH_2, CH-α), 5.34 (sept, *J*=6.2 Hz, 1H, $CH(CH_3)_2$), 6.76 (d, *J*=5.8 Hz, 1H, $H(5)_{pym}$), 7.18–7.38 (m, 4H, CH_{aryl}), 7.60–7.64 (m, 3H, NH, CH_{aryl}), 7.68 (s, 1H, $H(5)_{imid}$), 7.85 (d, *J*=7.5 Hz, 2H, CH_{aryl}), 8.43 (d, *J*=5.8 Hz, 1H, $H(6)_{pym}$), 8.46 (s, 1H, $H(2)_{imid}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ=21.5 (q, 2C), 29.6 (t), 46 (d), 53.4 (d), 65.4 (t), 70.0 (d), 105.9 (d), 113.5 (d), 119.7 (d, 2C), 124.9 (d, 2C), 126.7 (d, 2C), 127.2 (d, 2C), 135.0 (d), 139.3 (s), 140.3 (s, 2C), 143.4 (s, 2C), 153.2 (s), 155.6 (s), 158.8 (d), 169.2 (s), 173.1 (s). HRMS (ESI): *m*/*z* calcd for $C_{28}H_{28}N_5O_5$ $[M+H]^+$ 514.2085, found 514.2071.

*4.5.2. (S)-N^{α}-Fmoc-3-(4-(4-isopropoxypyrimidin-2-yloxy)phenyl)-2-amino propanoic acid (**9b**).* Synthesised according to general procedure from N^{α}-Boc-amino methyl ester **5d** (172 mg, 0.40 mmol), 123 mg (57%) of compound **9b** was obtained as a colourless solid. Mp 72–74 °C. TLC: R_f=0.71 (ethyl acetate/methanol/acetic acid, 10:3:0.2). $[\alpha]_D^{25}$ +5.92 (*c*=0.32, MeOH). IR (ATR) 3745 (w), 3709 (w), 3474 (w), 3414 (w), 3355 (w), 3327 (w), 2977 (w), 1711 (m), 1586 (m), 1563 (m), 1506 (m), 1451 (m), 1384 (s), 1324 (m), 1275 (s), 1245 (w), 1200 (s), 1143 (w), 1105 (m), 1046 (s), 893 (w), 759 (m), 739 (s), 539 (w), 515 (m) cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ=1.33 (d, *J*=6.0 Hz, 6H, CH(CH_3)$_2$), 3.20–3.22 (m, 2H, CH_2-β), 4.21–4.28 (m. 1H, CH_{Fmoc}), 4.42–4.55 (m, 2H, OCH_2), 4.74–4.76 (m, 1H, CH-α), 5.20 (sept, *J*=6.0 Hz, 1H, $CH(CH_3)_2$), 5.54 (br, 1H, NH), 6.41 (d, *J*=5.6 Hz, 1H, $H(5)_{pym}$), 7.30–7.46 (m, 4H, CH_{aryl}), 7.69–7.78 (m, 4H, CH_{aryl}), 7.59–7.62 (m, 2H, CH_{aryl}), 7.76–7.80 (m, 2H, CH_{aryl}), 7.16–7.29 (m, 4H, CH_{Aryl}), 8.20(d, *J*=5.6 Hz, 1H, $H(6)_{pym}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.0 (q, 2C), 37.7 (t), 47.6 (d), 55.1 (d), 67.4 (t), 70.9 (d), 104.3 (d), 120.4 (d, 2C), 122.2 (d, 2C), 125.5 (d, 2C), 127.5 (d, 2C), 128.2 (d, 2C), 131.0 (d, 2C), 133.5 (s), 141.7 (s, 2C), 144.1 (s), 144.3 (s), 152.2 (s), 156.3 (s), 158.0 (d), 165.0 (s), 171.6 (s), 174.6 (s). HRMS (ESI): *m*/*z* calcd for $C_{31}H_{30}N_3O_6$ $[M+H]^+$ 540.2129, found 540.2131.

*4.5.3. (S)-N^{α}-Fmoc-6-(4-isopropoxypyrimidin-2-ylamino)-2-amino-hexanoic acid (**9c**).* Synthesised according to general procedure from N^{α}-Boc-amino methyl ester **5g** (158 mg, 0.40 mmol), 155 mg (77%) of compound **9c** was obtained as a colourless solid. Mp 54–57 °C. TLC: R_f=0.57 (ethyl acetate/methanol/acetic acid, 10:3:0.2). $[\alpha]_D^{25}$ −5.91 (*c*=0.10, MeOH). IR (ATR) 3385 (w), 3343 (w), 3316 (w), 2358 (w), 2325 (w), 1674 (s), 1640 (s), 1474 (m), 1461 (m), 1400 (w), 1323 (w), 1201 (s), 1180 (s), 1130 (s), 841 (w), 799 (m), 750 (w), 721 (m), 694 (w), 643 (w), 615 (w), 561 (w). ^1H NMR (400 MHz, DMSO-d_6): δ=1.30 (d, *J*=6.0 Hz, 6H, CH(CH_3)$_2$), 1.66–1.68 (m, 2H, CH_2), 1.69–1.70 (m, 2H, CH_2), 1.73–1.75 (m, 2H, CH_2-β), 3.25–3.29 (m, 2H, NCH_2), 4.25–4.33 (m, 3H, OCH_2, CH_{Fmoc}), 5.27 (sept, *J*=6.0 Hz, 1H, $CH(CH_3)_2$), 5.94 (d, *J*=5.6 Hz, 1H, $H(5)_{pym}$), 7.37 (t, *J*=7.6 Hz, 2H, CH_{aryl}), 7.46 (t, *J*=7.2 Hz, 2H, CH_{aryl}), 7.67 (d, *J*=8.0 Hz, 1H, NH), 7.77 (d, *J*=7.2 Hz, 2H, CH_{aryl}), 7.93 (t, *J*=7.6 Hz, 2H, CH_{aryl}), 7.99 (d, *J*=5.6 Hz, 1H, $H(6)_{pym}$), 12.63 (br, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=21.8 (q, 2C), 23.5 (t), 29,1 (t), 32.0 (t), 41.8 (t), 48.0 (d), 55.8 (d), 68.5(t), 73.3 (d), 99.4 (d), 120.9 (d), 126.2 (d), 128.0 (d, 2C), 128.4 (d, 2C), 142.1 (s, 2C), 145.1 (s, 2C), 147.4 (s), 157.2 (s), 157.7 (d), 162.5 (s), 172.3 (s). HRMS (ESI): *m*/*z* calcd for $C_{28}H_{32}N_4NaO_5$ $[M+Na]^+$ 527.2265, found 527.2244; calcd for $C_{28}H_{33}N_4O_5$ $[M+H]^+$ 505.2445, found 505.2435.

*4.5.4. (S)-N^{α}-Fmoc-2-amino-3-(1-(4-isopropoxypyrimidin-2-yl)-1H-indol-3-yl) propanoic acid (**9d**).* Synthesised according to general procedure from N^{α}-Boc-amino methyl ester **5m** (182 mg, 0.40 mmol), 173 mg (77%) of compound **9d** was obtained as a colourless solid. Mp 174–176 °C. TLC: R_f=0.77 (ethyl acetate/methanol/acetic acid, 10:3:0.2). $[\alpha]_D^{25}$ +4.38 (*c*=0.14, MeOH). IR (ATR): 3342 (m), 1731 (m), 1686 (m), 1577 (m), 1559 (m), 1537 (m), 1469 (m), 1430 (s), 1361 (s), 1305 (m), 1235 (s), 1223 (s), 1140 (w), 1103 (w), 1087 (m), 1032 (m), 1000 (w), 945 (w), 756 (m), 733 (s) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=1.40 (d, *J*=6.0 Hz, 3H, CH(CH_3)$_2$), 1.42 (d, *J*=6.0 Hz, 3H, CH(CH_3)$_2$), 3.11 (dd, *J*=14.8 Hz, *J′*=10.4.0 Hz, 1H, CH_2-β), 3.26 (dd, *J*=14.8 Hz, *J′*=4.4.0 Hz, 1H, CH_2-β), 4.12–4.20 (m, 3H, OCH_2, CH_{Fmoc}), 5.40 (sept, *J*=6.0 Hz, 1H, $CH(CH_3)_2$), 6.61 (d, *J*=5.6 Hz, 1H, $H(5)_{pym}$), 7.14 (t, 1H, *J*=7.6 Hz, $H(5)_{ind}$), 7.23–7.30 (m, 2H, CH_{aryl}), 7.35–7.42 (m, 3H, CH_{aryl}, $H(6)_{ind}$), 7.56 (d, *J*=7.6 Hz, 1H, $H(7)_{ind}$), 7.61 (d, *J*=7.6 Hz, 1H, NH), 7.67 (d, *J*=7.6 Hz, 1H, CH_{aryl}), 7.82–7.87 (m, 3H, CH_{aryl}), 8.18 (s, 1H, $H(2)_{ind}$), 8.46 (d, *J*=5.60 Hz, 1H, $H(6)_{pym}$), 8.66 (d, 1H, *J*=8.4 Hz, $H(4)_{ind}$), 12.84 (br, 1H, OH). ^{13}C NMR (75 MHz, [DMSO-d_6): δ=21.49 (q), 21.52 (q), 26.5 (t), 46.5 (d), 53.9 (d), 65.7 (t), 69.7 (d), 103.5 (d), 115.7 (d), 118.8 (d), 119.9 (d, 2C), 121.8 (d), 123.6 (d), 124.1 (d), 125.11 (d), 125.16 (d), 126.8 (d), 126.9 (d), 127.4 (d), 127.5 (d), 130.5 (s), 134.8 (s), 140.6 (s), 143.6 (s), 143.7 (s), 156.0 (s), 156.3 (s), 158.7 (d), 169.0 (s), 173.4 (s). HRMS (ESI): *m*/*z* calcd for $C_{33}H_{30}N_4NaO_5$ $[M+Na]^+$ 477.2108, found 477.2121; calcd for $C_{33}H_{31}N_4O_5$ $[M+H]^+$ 585.2108, found 585.2107.

4.6. Synthesis of (*S*)-N^{α}-triphenylmethylserine methyl ester 4g

The synthesis of this compound was described in Ref. 27.

4.7. Representative procedure for the synthesis of N^{α}-trityl-pyrimidin-4-yl aminoesters 10b–d

The appropriate 2-(benzylsulfanyl)pyrimidin-4(3*H*)-ones **1a–c** (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 (1.1 equiv) and (*S*)-N^{α}-triphenylmethylserine methyl ester **4g** (1.1 equiv) were added. DIAD

(1.1 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 10:1–1:1) to afford pyrimidin-4-yl aminoesters **10**.

*4.7.1. (S)-Methyl 3-(2-(benzylsulfanyl)pyrimidin-4-yloxy)-2-(tritylamino)propanoate (**10b**).* Synthesised according to general procedure from pyrimidin-4(3*H*)-one **1a** (218 mg, 1.0 mmol), (*S*)-N^{α}-triphenylmethylserine methyl ester **4g** (400 mg, 1.1 mmol), PPh_3 (289 mg, 1.1 mmol) and DIAD (0.21 mL, 1.1 mmol), 545 mg (97%) of compound **10b** was obtained as a colourless solid. Mp 62–63 °C. TLC: R_f=0.43 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +79.91 (*c*=0.38, MeOH). IR (ATR): 3432 (w), 3058 (w), 3030 (w), 2949 (w), 1736 (m), 1554 (m), 1492 (m), 1433 (s), 1313 (s), 1227 (m), 1206 (s), 1173 (m), 1027 (m), 981 (w), 775 (m), 695 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=2.90 (d, *J*=10.4 Hz, 1H, N*H*), 3.21 (s, 3H, OCH_3), 3.72–3.83 (m, 1H, C*H*-α), 4.42 (s, 2H, SCH_2), 4.49 (dd, *J*=10.6 Hz, *J*′=6.4 Hz, 1H, OCH_2), 4.71 (dd, *J*=10.6 Hz, *J*′=5.4 Hz, 1H, OCH_2), 6.43 (d, *J*=5.6 Hz, 1H, $H(5)_{pym}$), 7.21–7.57 (m, 20H, CH_{Aryl}), 8.27 (d, *J*=5.6 Hz, 1H, $H(6)_{pym}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=35.9 (t), 52.6 (q), 56.3 (d), 68.7 (t), 71.6 (s), 104.6 (d), 127.2, 127.8, 128.6, 129.2, 129.4, 129.6 (d, 20C), 138.4 (s), 146.2 (s, 3C), 158.2 (d), 168.9 (s), 171.9 (s), 173.8 (s). MS (ESI) *m*/*z*: 562 $[M+H]^+$. Calcd for $C_{34}H_{31}N_3O_3S$: C, 72.70; H, 5.56; N, 7.48; S, 5.71. Found: C, 72.63; H, 5.43; N, 7.33; S, 6.06.

*4.7.2. (S)-Methyl 3-(2-(benzylsulfanyl)-6-methylpyrimidin-4-yloxy)-2-(tritylamino)propanoate (**10c**).* Synthesised according to general procedure from pyrimidin-4(3*H*)-one **1b** (232 mg, 1.0 mmol), (*S*)-N^{α}-triphenylmethylserine methyl ester **4g** (400 mg, 1.1 mmol), PPh_3 (289 mg, 1.1 mmol) and DIAD (0.21 mL, 1.1 mmol), 368 mg (64%) of compound **10c** was obtained as a colourless solid. Mp 62–63 °C. TLC: R_f=0.43 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +58.05 (*c*=0.42, MeOH). IR (ATR): 3422 (w), 3038 (w), 3027 (w), 2951 (w), 1736 (m), 1578 (m), 1547 (s), 1492 (w), 1445 (m), 1406 (m), 1346 (s), 1282 (s), 1206 (s), 1197 (m), 1161 (s), 1041 (m), 774 (m), 745 (m), 704 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=2.39 (s, 3H, CH_3), 2.80 (br, 1H, N*H*), 3.19 (s, 3H, OCH_3), 3.72–3.78 (m, 1H, C*H*-α), 4.40 (s, 2H, SCH_2), 4.46 (dd, *J*=10.6 Hz, *J*′=6.4 Hz, 1H, OCH_2), 4.66 (dd, *J*=10.6 Hz, *J*′=5.2 Hz, 1H, OCH_2), 6.27 (s, $H(5)_{pym}$), 7.19–7.55 (m, 20H, CH_{Aryl}). ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.6(q), 35.2 (t), 51.7 (q), 55.7 (d), 67.9 (t), 70.9 (s), 102.6 (d), 126.4, 127.5, 128.5, 128.8, 128.9, 129.2 (d, 20C), 137.8 (s), 145.6 (s, 3C), 167.8 (s), 168.7 (s), 170.4 (s), 173.0 (s). MS (ESI) *m*/*z*: 576 $[M+H]^+$. Calcd for $C_{35}H_{33}N_3O_3S$: C, 73.02; H, 5.78; N, 7.30; S, 5.57. Found: C, 73.14; H, 5.91; N, 7.41; S, 5.80.

*4.7.3. (S)-Methyl 3-(2-(benzylsulfanyl)-6-phenylpyrimidin-4-yloxy)-2-(tritylamino)propanoate (**10d**).* Synthesised according to general procedure from pyrimidin-4(3*H*)-one **1c** (294 mg, 1.0 mmol), (*S*)-N^{α}-triphenylmethylserine methyl ester **4g** (400 mg, 1.1 mmol), PPh_3 (289 mg, 1.1 mmol) and DIAD (0.21 mL, 1.1 mmol), 592 mg (93%) of compound **10d** was obtained as a colourless solid. Mp 77–78 °C. TLC: R_f=0.55 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +87.17 (*c*=0.11, MeOH). IR (ATR): 3431 (w), 3053 (w), 3029 (w), 2948 (w), 1737 (m), 1567 (s), 1536 (s), 1492 (m), 1448 (w), 1407 (w), 1351 (m), 1267 (w), 1204 (s), 1022 (m), 776 (m), 749 (m), 693 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=2.92 (d, *J*=10.4 Hz, 1H, N*H*), 3.22 (s, 3H, OCH_3), 3.73–3.84 (m, 1H, C*H*-α), 4.52 (s, 2H, SCH_2), 4.55 (dd, *J*=10.6 Hz, *J*′=6.4 Hz, 1H, OCH_2), 4.75 (dd, *J*=10.6 Hz, *J*′=5.2 Hz, 1H, OCH_2), 6.83 (s, $H(5)_{pym}$), 7.20–7.57 (m, 23H, CH_{Aryl}), 8.03–8.08 (m, 2H, CH_{Aryl}). ^{13}C NMR (50 MHz, $CDCl_3$): δ=36.1 (t), 52.6 (q), 56.4 (d), 69.0 (t), 71.7 (s), 99.8 (d), 127.2, 127.7, 128.6, 128.8, 129.2, 129.4, 129.6, 130.0, 131.4 (d, 25C), 137.2 (s), 138.6 (s), 145.3 (s, 3C), 165.6 (s), 170.2 (s), 171.6 (s), 173.8 (s). MS (ESI) *m*/*z*: 696 $[M+CH_3CN+NH_4]^+$, 638 $[M+H]^+$. Calcd for $C_{40}H_{35}N_3O_3S$: C, 75.33; H, 5.53; N, 6.59; S, 5.03. Found: C, 75.17; H, 5.64; N, 6.48; S, 5.41.

4.8. Representative procedure for the synthesis of sulfone derivatives 12a–c

The appropriate pyrimidinyl aminoesters **10b–d** (1.0 equiv) was dissolved in CH_2Cl_2 (5 mL/mmol). The solution was cooled in an ice bath and *m*-CPBA (2.2 equiv) was added in small portions. The resulting mixture was warmed to room temperature and stirred during 2–3 h. Upon completion of the reaction (TLC monitoring), 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 under reduced pressure. The resulting residue was purified by flash chromatography (*n*-hexane/ethyl acetate 10:1–1.1) to afford sulfones **12**.

*4.8.1. (S)-Methyl 3-(2-(benzylsulfonyl)pyrimidin-4-yloxy)-2-(tritylamino)propanoate (**12a**).* Synthesised according to general procedure from pyrimidinyl amino ester **10b** (337 mg, 0.6 mmol), 252 mg (71%) of compound **12a** was obtained as a colourless solid. Mp 71–72 °C. TLC: R_f=0.45 (*n*-hexane/ethyl acetate, 1:1). IR (ATR): 3029 (w), 2950 (w), 2923 (w), 1736 (m), 1578 (s), 1541 (w), 1491 (w), 1466 (s), 1446 (s), 1323 (s), 1203 (m), 1123 (s), 1026 (w), 985 (w), 776 (w), 747 (w), 696 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=3.23 (s, 3H, OCH_3), 3.82 (dd, *J*=6.6 Hz, *J*′=5.0 Hz, 1H, C*H*-α), 4.49 (dd, *J*=10.8 Hz, *J*′=6.6 Hz, 1H, OCH_2), 4.69 (s, 2H, $S(O)_2CH_2$), 4.83 (dd, *J*=10.8 Hz, *J*′=5.0 Hz, 1H, OCH_2), 6.90 (d, *J*=5.8 Hz, 1H, $H(5)_{pym}$), 7.22–7.55 (m, 20H, CH_{Aryl}), 8.61 (d, *J*=5.8 Hz, 1H, $H(6)_{pym}$). ^{13}C NMR (50 MHz, DMSO-d_6): δ=51.7 (q), 55.1 (d), 56.2 (t), 68.2 (t), 70.3 (s), 111.5 (d), 126.4, 127.4, 128.3, 128.4, 128.5, 131.3 (d, 20C), 127.9 (s), 145.4 (s, 3C), 159.0 (d), 164.0 (s), 169.2 (s), 172.1 (s). MS (ESI) *m*/*z*: 594 $[M+H]^+$. Calcd for $C_{34}H_{31}N_3O_5S$: C, 68.78; H, 5.26; N, 7.08; S, 5.40. Found: C, 68.92; H, 5.48; N, 7.17; S, 5.78.

*4.8.2. (S)-Methyl 3-(2-(benzylsulfonyl)-6-methylpyrimidin-4-yloxy)-2-(tritylamino)propanoate (**12b**).* Synthesised according to general procedure from pyrimidinyl amino ester **10c** (345 mg, 0.6 mmol), 182 mg (50%) of compound **12b** was obtained as a colourless solid. Mp 78–79 °C. TLC: R_f=0.42 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +66.01 (*c*=0.32, MeOH). IR (ATR): 3421 (w), 3058 (w), 3031 (w), 2951 (w), 1733 (s), 1591 (s), 1491 (w), 1445 (m), 1409 (m), 1351 (s), 1325 (s), 1205 (w), 1173 (m), 1138 (s), 1025 (s), 1042 (m), 776 (s), 747 (m), 696 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=2.56 (s, 3H, CH_3), 3.23 (s, 3H, OCH_3), 3.60 (br, 1H, N*H*), 3.81 (dd, *J*=6.6 Hz, *J*′=5.0 Hz, 1H, C*H*-α), 4.56 (dd, *J*=10.8 Hz, *J*′=6.6 Hz, 1H, OCH_2), 4.70 (s, 2H, $S(O)_2CH_2$), 4.81 (dd, *J*=10.8 Hz, *J*′=5.0 Hz, 1H, OCH_2), 6.72 (s, $H(5)_{pym}$), 7.21–7.99 (m, 20H, CH_{Aryl}). ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.7 (q), 51.9 (q), 55.4 (d), 57.2 (t), 69.2 (t), 70.9 (s), 109.5 (d), 126.6, 128.6, 129.0, 131.2 (d, 20C), 126.9 (s), 145.4 (s, 3C), 163.9 (s), 169.3 (s), 170.1 (s), 172.6 (s). MS (ESI) *m*/*z*: 608 $[M+H]^+$. Calcd for $C_{35}H_{33}N_3O_5S$: C, 69.17; H, 5.47; N, 6.91; S, 5.28. Found: C, 69.25; H, 6.70; N, 7.02; S, 5.79.

*4.8.3. (S)-Methyl 3-(2-(benzylsulfonyl)-6-phenylpyrimidin-4-yloxy)-2-(tritylamino)propanoate (**12c**).* Synthesised according to general procedure from pyrimidinyl amino ester **10d** (382 mg, 0.6 mmol), 180 mg (45%) of compound **7c** was obtained as a colourless solid. Mp 77–78 °C. TLC: R_f=0.53 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +38.17 (*c*=0.042, MeOH). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ=2.41 (br, 1H, N*H*), 3.25 (s, 3H, OCH_3), 3.38 (apparent t, *J*=5.2 Hz, 1H, C*H*-α), 4.66 (dd, *J*=10.6 Hz, *J*′=6.4 Hz, 1H, OCH_2), 4.82 (s, 2H, $S(O)_2CH_2$), 4.87 (dd, *J*=10.6 Hz, *J*′=4.8 Hz, 1H, OCH_2), 7.18–7.57 (m, 24H, $H(5)_{pym}$, CH_{Aryl}), 8.09–8.14 (m, 2H, CH_{Aryl}). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ=52.0 (q), 55.5 (d), 57.3 (t), 69.6 (t), 71.0 (s), 105.5 (d), 126.6, 127.3, 128.0, 128.7, 128.8, 129.1, 131.3, 131.8 (d, 25C), 127.0 (s), 134.7 (s),

145.5 (s, 3C), 164.7 (s), 165.9 (s), 171.0 (s), 172.6 (s). MS (ESI) *m/z*: 728 $[M+CH_3CN+NH_4]^+$, 670 $[M+H]^+$. Calcd for $C_{40}H_{35}N_3O_5S$: C, 71.73; H, 5.27; N, 6.27; S, 4.79. Found: C, 71.86; H, 5.53; N, 6.38; S, 5.10.

4.9. Representative procedure for synthesis of pyrimidinyl aminoesters 13a–c

The appropriate sulfone derivatives **12a–c** (1.0 equiv) was dissolved in dry 1,4-dioxane (5 mL/mmol sulfone) under a nitrogen atmosphere. Morpholine (2.5 equiv) was added and the reaction mixture was 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 10:1–1:1) to afford compounds **13**.

*4.9.1. (S)-Methyl 3-(2-morpholinopyrimidin-4-yloxy)-2-(tritylamino)-propanoate (**13a**).* Synthesised according to general procedure from sulfone derivative **12a** (178 mg, 0.3 mmol), 131 mg (83%) of compound **13a** was obtained as a colourless solid. Mp 68–69 °C. TLC: R_f=0.39 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +93.48 (*c*=0.352, MeOH). IR (ATR): 3027 (w), 2955 (w), 2923 (w), 1591 (m), 1564 (s), 1514 (w), 1466 (w), 1432 (s), 1339 (s), 1319 (m), 1309 (m), 1272 (w), 1257 (m), 1235 (m), 1210 (m), 1118 (s), 1029 (s), 991 (m), 799 (s), 776 (m), 704 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=2.89 (d, *J*=10.4 Hz, 1H, N*H*), 3.14 (s, 3H, OCH_3), 3.74–3.80 (m, 8H, 2×OCH_2CH_2N), 3.80–3.85 (m, 1H, C*H*-α), 4.41 (dd, *J*=10.6 Hz, *J*′=7.4 Hz, 1H, OCH_2), 4.73 (dd, *J*=10.6 Hz, *J*′=5.8 Hz, 1H, OCH_2), 6.02 (d, *J*=5.6 Hz, 1H, $H(5)_{pym}$), 7.34–7.57 (m, 15H, CH_{Aryl}), 8.08 (d, *J*=5.6 Hz, 1H, $H(6)_{pym}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=44.9 (t, 2C), 52.4 (q), 56.2 (d), 67.4 (t, 2C), 67.7 (t), 71.5 (s), 97.7 (d), 127.2, 128.5, 129.4 (d, 15C), 146.3 (s, 3C), 158.7 (d), 162.0 (s), 170.0 (s), 174.2 (s). MS (ESI) *m/z*: 525 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{31}H_{32}N_4NaO_4$ $[M+Na]^+$ 547.2316, found 547.2290.

*4.9.2. (S)-Methyl 3-(6-methyl-2-morpholinopyrimidin-4-yloxy)-2-(tritylamino)propanoate (**13b**).* Synthesised according to general procedure from sulfone derivative **12b** (151 mg, 0.25 mmol), 85 mg (63%) of compound **13b** was obtained as a colourless oil. TLC: R_f=0.41 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{27}$ +88.46 (*c*=0.25, MeOH). IR (ATR): 3046 (w), 2953 (w), 1735 (m), 1570 (s), 1491 (m), 1445 (m), 1394 (m), 1343 (s), 1275 (m), 1243 (w), 1207 (w), 1158 (s), 1115 (m), 906 (s), 728 (s), 705 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=2.09 (s, 3H, CH_3), 2.87 (d, *J*=10.4 Hz, 1H, N*H*), 3.17 (s, 3H, OCH_3), 3.64–3.79 (m, 8H, 2×OCH_2CH_2N), 3.82–3.87 (m, 1H, C*H*-α), 4.40 (dd, *J*=10.8 Hz, *J*′=7.4 Hz, 1H, OCH_2), 4.72 (dd, *J*=10.6 Hz, *J*′=5.8 Hz, 1H, OCH_2), 5.89 (s, 1H, $H(5)_{pym}$), 7.21–7.37 (m, 9H, CH_{Aryl}), 7.53–7.57 (m, 6H, CH_{Aryl}). ^{13}C NMR (50 MHz, $CDCl_3$): δ=24.0 (q), 44.3 (t, 2C), 51.7 (q), 55.6 (d), 66.8 (t, 2C), 67.0 (t), 70.8 (s), 95.6 (d), 126.5, 127.8, 128.7 (d, 15C), 146.7 (s, 3C), 161.4 (s), 168.2 (s), 169.5 (s), 173.7 (s). MS (ESI) *m/z*: 539 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{32}H_{34}N_4NaO_4$ $[M+Na]^+$ 561.2472, found 561.2462.

*4.9.3. (S)-Methyl 3-(2-morpholino-6-phenylpyrimidin-4-yloxy)-2-(tritylamino)propanoate (**13c**).* Synthesised according to general procedure from sulfone derivative **12c** (167 mg, 0.25 mmol), 93 mg (62%) of compound **13c** was obtained as a colourless oil. TLC: R_f=0.58 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +72.01 (*c*=0.05, MeOH). IR (ATR): 3042 (w), 2955 (w), 2921 (w), 1735 (w), 1571 (s), 1557 (s), 1491 (m), 1446 (m), 1392 (m), 1348 (m), 1264 (m), 1207 (s), 1114 (m), 1024 (s), 993 (w), 769 (s), 744 (m), 696 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=2.87 (d, *J*=10.6 Hz, 1H, N*H*), 3.18 (s, 3H, OCH_3), 3.79–3.84 (m, 9H, 2×OCH_2CH_2N, C*H*-α), 4.45 (dd, *J*=10.8 Hz, *J*′=7.4 Hz, 1H, OCH_2), 4.76 (dd, *J*=10.6 Hz, *J*′=5.6 Hz, 1H, OCH_2), 6.46 (s, 1H, $H(5)_{pym}$), 7.21–7.33 (m, 10H, CH_{Aryl}), 7.45–7.58 (m, 8H, CH_{Aryl}), 7.99–8.04 (m, 2H, CH_{Aryl}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=44.3 (t, 2C), 51.8 (q), 55.6 (d), 66.9 (t, 2C), 67.3 (t), 70.8 (s), 95.5 (d), 126.5, 126.9, 127.9, 128.5, 128.7, 130.1 (d, 20C), 137.7 (s), 145.7 (s, 3C), 161.5 (s), 165.4 (s), 170.3 (s), 173.7 (s). MS (ESI) *m/z*: 601 $[M+H]^+$. HRMS (ESI): *m/z* calcd. For $C_{37}H_{36}N_4NaO_4$ $[M+Na]^+$ 623.2629, found 623.2596.

4.10. Synthesis of (*S*)-methyl 3-(2-(4-(2-(*S*)-*tert*-butoxycarbonylamino-2-methoxycarbonylethyl)imidazol-1-yl)pyrimidinin-4-yloxy)-2-(tritylamino)propanoate (15)

N^{α}-Boc-(*S*)-histidine methyl ester **4a** (64.6 mg, 0.24 mmol) was dissolved in dry DMF (2.5 mL/mmol) under a nitrogen atmosphere. DBU (0.39 mL, 0.26 mmol) was added and the resulting mixture was stirred at room temperature for 15 min. Then, sulfone derivative **12a** (119 mg, 0.2 mmol) was added as a DMF solution (1 mL/mmol) and the resulting reaction was heated to 50 °C until total consumption of the starting material (TLC monitoring). The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (*n*-hexane/ethyl acetate 10:1–1:1) to give compound **15** (51 mg, 36%) as a colourless solid. Mp 81–83 °C. TLC: R_f=0.11 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +65.98 (*c*=0.47, MeOH). IR (ATR): 3350 (w), 3041 (w), 2974 (w) 1736 (m), 1711 (s), 1588 (s), 1569 (s), 1486 (s), 1424 (s), 1361 (m), 1316 (m), 1251 (m), 1204 (m), 1160 (s), 1028 (m), 705 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=1.37 (s, 9H, C(CH_3)$_3$), 2.83 (d, *J*=9.8 Hz, 1H, N*H*), 3.02 (dd, *J*=14.9 Hz, *J*′=5.0 Hz, 1H, CH_2-$\beta_{histidine}$), 3.10 (s, 3H, OCH_3), 3.07–3.12 (m, 1H, CH_2-$\beta_{histidine}$), 3.67 (s, 3H, OCH_3), 3.72–3.73 (m, 1H, C*H*-α_{serine}), 4.42 (dd, *J*=10.7 Hz, *J*′=6.8 Hz, 1H, CH_2-β_{serine}), 4.52–4.56 (m, 1H, C*H*-$\alpha_{histidine}$), 4.67 (dd, *J*=10.7 Hz, *J*′=5.4 Hz, 1H, CH_2-β_{serine}), 5.87 (d, *J*=8.2 Hz, 1H, N*H*), 6.53 (d, *J*=5.7 Hz, 1H, $H(5)_{pym}$), 7.10–7.22 (m, 9H, CH_{Aryl}), 7.42–7.46 (m, 6H, CH_{Aryl}), 7.50 (s, 1H, $H(5)_{imid}$), 8.27 (d, *J*=5.7 Hz, 1H, $H(6)_{pym}$), 8.38 (s, 1H, $H(2)_{imid}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=28.4 (q), 30.1 (t), 52.1 (q), 52.3 (q), 53.4 (d), 55.4 (d), 68.5 (t), 71.0 (s), 79.7 (s), 106.2 (d), 114.3 (d), 126.7 (d, 3C), 128.0 (d, 6C), 128.7 (d, 6C), 135.9 (d), 145.5 (s, 3C), 153.7 (s), 155.6 (s), 158.6 (d), 170.0 (s), 172.4 (s), 173.0 (s). MS (ESI) *m/z*: 707 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{39}H_{43}N_6O_7$ $[M+H]^+$ 707.3188, found 707.3201; HRMS (ESI): *m/z* calcd for $C_{39}H_{42}N_6NaO_7$ $[M+Na]^+$ 729.3007, found 729.2999.

4.11. Representative procedure for the synthesis of pyrimidinyl aminoesters 14a–b

N^{α}-Boc-(*S*)-tyrosine methyl ester **4b** (1.2 equiv) was dissolved in dry DMF (2.5 mL/mmol) under a nitrogen atmosphere. NaH (1.2 equiv) was added and the resulting mixture was stirred at room temperature for 15 min. Then, the appropriate sulfone **7a–b** (1.0 equiv) was added as a DMF solution (1 mL/mmol) and the resulting reaction was stirred at room temperature. 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 10:1–1:1) to afford pyrimidinyl aminoesters **14a–b**.

*4.11.1. (S)-Methyl 3-(2-(4-(2-(S)-tert-butoxycarbonylamino-2-methoxycarbonylethyl)phenoxy)pyrimidinin-4-yloxy)-2-(tritylamino)propanoate (**14a**).* Synthesised according to general procedure from sulfone derivative **12a** (119 mg, 0.2 mmol), N^{α}-Boc-(*S*)-tyrosine methyl ester **4b** (70.9 mg, 0.24 mmol) and NaH (6 mg, 0.24 mmol), 107 mg (73%) of compound **14a** was obtained as a colourless solid. Mp 90–91 °C. TLC: R_f=0.49 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{26}$ +46.77 (*c*=0.41, MeOH). IR (ATR): 3045 (w), 2949 (w), 2927 (w), 1738 (m), 1711 (m), 1572 (s), 1503 (w), 1444 (m), 1381 (s), 1339 (m), 1271 (s), 1206 (s), 1162 (s), 1048 (m), 1025 (m), 816 (w), 744 (w), 704 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=1.35 (s, 9H, C(CH_3)$_3$), 2.79 (d, *J*=12 Hz, 1H, N*H*), 3.03–3.06 (m, 2H, CH_2), 3.12 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.65–3.71 (m, 1H, C*H*-α_{serine}), 4.42 (dd, *J*=10.0 Hz, *J*′=6.0 Hz, 1H, OCH_2), 4.46–4.47 (m, 1H, C*H*-$\alpha_{tyrosine}$), 4.61 (dd, *J*=10.0 Hz, *J*′=6.0 Hz, 1H, OCH_2), 4.92 (br, 1H, N*H*), 6.38 (d, *J*=6.0 Hz,

1H, $H(5)_{pym}$), 7.01–7.23 (m, 13H, CH_{Aryl}), 7.41–7.46 (m, 6H, CH_{Aryl}), 8.36 (d, J=6.0 Hz, 1H, $H(6)_{pym}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=29.0 (q, 3C), 38 (t), 52.6 (q), 52.9 (q), 55.1 (d), 56.3 (d), 69.2 (t), 71.7 (s), 80.7 (s), 104.2 (d), 122.4, 127.2, 128.6, 129.4, 131.1 (d, 19C), 133.8 (s), 146.3 (s, 3C), 152.6 (s), 159.5 (d), 165.5, 171.8, 172.9, 173.6 (s, 5C). MS (ESI) m/z: 733 $[M+H]^+$. HRMS (ESI): m/z calcd for $C_{42}H_{44}N_4NaO_8$ $[M+Na]^+$ 755.3051, found 755.3018.

*4.11.2. (S)-Methyl 3-(2-(4-(2-(S)-tert-butoxycarbonylamino-2-methoxycarbonylethyl)phenoxy)-6-methylpyrimidinin-4-yloxy)-2-(tritylamino)propanoate (**14b**).* Synthesised according to general procedure from sulfone derivative **12b** (121 mg, 0.2 mmol), N^{α}-Boc-(*S*)-tyrosine methyl ester **4b** (70.9 mg, 0.24 mmol) and NaH (6 mg, 0.24 mmol), 60 mg (40%) of compound **14b** was obtained as a colourless oil. TLC: R_f=0.41 (*n*-hexane/ethyl acetate, 1:1). $[\alpha]_D^{27}$ −72.69 (c=0.18, MeOH). IR (ATR): 3441 (w), 3359 (w), 3042 (w), 2976 (w), 2952 (w), 1738 (m), 1712 (m), 1596 (s), 1564 (m) 1505 (m), 1446 (w), 1362 (s), 1343 (s), 1246 (w), 1210 (s), 1164 (s), 1079 (w), 908 (m), 728 (s), 706 (s) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.46 (s, 9H, $C(CH_3)_3$), 2.37 (s, 3H, CH_3), 2.89 (br, 1H, N*H*), 3.13–3.16 (m, 2H, CH_2), 3.21 (s, 3H, OCH_3), 3.71–3.74 (m, 1H, C*H*-α_{serine}), 3.74 (s, 3H, OCH_3), 4.43 (dd, J=10.6 Hz, J'=6.0 Hz, 1H, OCH_2), 4.59 (dd, J=10.6 Hz, J'=5.0 Hz, 1H, OCH_2), 4.71–4.61 (m, 1H, C*H*-$\alpha_{tyrosine}$), 5.32 (br, 1H, N*H*), 6.35 (s, 1H, $H(5)_{pym}$), 7.11–7.33 (m, 13H, CH_{Aryl}), 7.50–7.54 (m, 6H, CH_{Aryl}). ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.3 (q), 28.9 (q, 3C), 38.5 (t), 52.5 (q), 52.8 (q), 55.1 (d), 56.3 (d), 68.9 (t), 71.6 (s), 80.6 (s), 102.4 (d), 122.2, 127.1, 128.5, 129.4, 130.7 (d, 19C), 133.8 (s), 146.3 (s, 3C), 152.7 (s), 155.7 (s), 164.8 (s), 170.6 (s), 171.9 (s), 172.8 (s), 173.6 (s). MS (ESI) m/z: 747 $[M+H]^+$. HRMS (ESI): m/z calcd for $C_{43}H_{46}N_4NaO_8$ $[M+Na]^+$ 769.3208, found 769.3197.

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Supplementary data

Representative ^{1}H and ^{13}C NMR spectra of synthesised compounds, X-ray crystallographic details of compounds **5c**, **5f** and **12b** and representative HPLC and MS (ESI) of dipeptides **8**. CCDC-724139, CCDC-724138, and CCDC-724137 contain the supplementary data for compounds **5c**, **5f** and **12b**, respectively. 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.2009.11.077.

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