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Original article

Synthesis and *in vitro* EGFR (ErbB1) tyrosine kinase inhibitory activity of 4-*N*-substituted 6-aryl-7*H*-pyrrolo[2,3-*d*]pyrimidine-4-amines

Svein Jacob Kaspersen [a], Christopher Sørum [a,1], Veronica Willassen [a], Erik Fuglseth [a], Eli Kjøbli [b], Geir Bjørkøy [b], Eirik Sundby [c], Bård Helge Hoff [a,*]

[a] Norwegian University of Science and Technology, Høgskoleringen 5, NO-7491 Trondheim, Norway
[b] Sør-Trøndelag University College, Erling Skjalgssons g 1, 7004 Trondheim, Norway
[c] Sør-Trøndelag University College, E. C. Dahls gate 2, 7004 Trondheim, Norway

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ABSTRACT

A series of 4-*N*-substituted 6-aryl-7*H*-pyrrolo[2,3-d]pyrimidine-4-amines have been synthesised, characterised and tested for their *in vitro* EGFR (ErbB1) tyrosine kinase inhibitory activity. The compounds were prepared from ethyl cyanoacetate and α-bromoacetophenones via the 2-amino-3-ethoxycarbonyl-5-aryl-pyrroles and 4-chloro-6-arylpyrrolopyrimidines. Aromatic substitution with benzylic amines was performed by conventional thermal substitution, and palladium catalysed coupling. The two methods resulted in similar yields, but the palladium coupling had the benefit of lower chemical consumption and reduced reaction times. Eight of the new compounds had IC_{50} values in the range of 2.8–9.0 nM. Four of these have a fluorine atom positioned at sites otherwise potentially susceptible to oxidative metabolism. Structural variation of the 6-aryl group indicated that the inhibitory action was only moderately sensitive to modifications in this fragment. However, the potency depended strongly on the structure of the aromatic part of the 4-amino group, and any aromatic substitution except fluorine reduced the *in vitro* activity. The cellular EGFR internalization response of selected compounds was evaluated using HeLa cells. Three fluorinated derivatives had a pronounced effect in inhibiting EGFR internalization.

1. Introduction

Tyrosine kinases (TK) are enzymes that bind ATP and catalyse the transfer of γ-phosphate to tyrosine residues on proteins, thereby regulating their activity and function. Several tyrosine kinases can be targets for cancer chemotherapy, the most important being the receptor tyrosine kinases [1]. This is a large family of receptors including among others the epidermal growth factor receptor (EGFR) [2,3], and the vascular endothelial growth factor receptor (VEGF) [4].

EGFR is a transmembrane glycoprotein and is composed of a glycosylated *N*-terminus, an extra-cellular ligand binding region, a hydrophobic transmembrane region and a C-terminal intracellular region, which contains a tyrosine kinase domain [5]. When epidermal growth factors (EGF) bind to EGFR the TK domain is activated, and this triggers a chain of different signal transduction events inside the cell that eventually leads to cell growth, proliferation and differentiation. Elevated receptor tyrosine kinase activity is often observed in malignant tumours [6]. The activity of the kinases, and thereby progression of the diseases can be reduced by administration of TK inhibitors. Several low molecular weight inhibitors have entered the marketplace as Gefitinib, Erlotinib and Lapatinib (Fig. 1), and still more are in clinical studies [7]. Their mode of action is mainly by inhibition of ATP binding in the TK domain of one or more of these growth factor receptors, resulting in inhibition of activation and subsequent downstream signalling events. The internalization, endocytosis and lysosomal degradation of EGFR are all part of a process which is dependent on ligand-induced activation of the EGF receptor [8]. Monitoring EGFR internalization therefore acts as a potential additional test of bioactivity of potential inhibitors.

EGFR-TK has previously been targeted by leads based on the pyrrolopyrimidine scaffold [9]. This led to development of PKI-166 (Fig. 1), a potent inhibitor [10,11]. The activity was found to be dependant of the stereochemistry of the 1-phenylethanamine side chain at position 4 of the pyrrolopyrimidine. AEE-788, a structurally more advanced analogue have also been studied [12,13]. While Gefitinib and Erlotinib mainly act on EGFR-TK, Lapatinib [14], PKI-

* Corresponding author. Department of Chemistry, Norwegian University of Science and Technology (NTNU), NO-7491, Norway. Tel.: +4773593973; fax: +4773594256.
E-mail address: bhoff@chem.ntnu.no (B.H. Hoff).
[1] Present address: Weifa AS, Guveveien 1, 3791 Kragerø, Norway.

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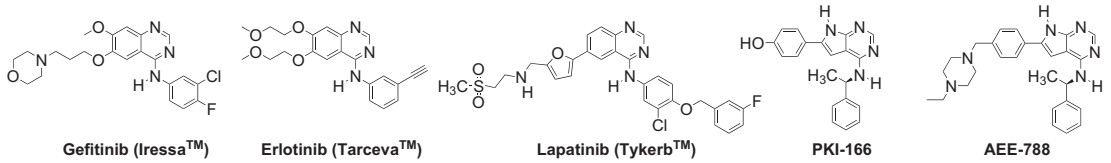


Fig. 1. The structures of EGFR-TK inhibitors.

166 [15], and AEE-788 [12] also efficiently inhibit ErbB2-TK (HER-2). AEE-788 [12] is also described as a VEGF-TK inhibitor [12]. Development of PKI-166 has been terminated, possibly due to side effects described as transaminase elevation, diarrhoea, nausea and vomiting [16,17]. However, there is limited knowledge on the bioactivity of structurally related pyrrolopyrimidines and it could be possible to modify the toxicity profile by structural alteration. As a first step new active compounds must be identified. Moreover, there is evidence that TK-inhibitors are efficient antiprotozoal agents [18–20], and that kinases are involved in developing of leprosy [21,22]. In both cases treatment can be sought by selectively blocking kinase activity. On this background we have undertaken the preparation of a series of *N*-substituted 6-aryl-7*H*-pyrrolo[2,3-d]pyrimidine-4-amines, and wish to communicate their potential as EGFR-TK (ErbB1) inhibitors.

2. Chemistry

The potential inhibitor compounds were synthesised as described in Schemes 1 and 2. Ethyl cyanoacetate (**1**) was reacted with HCl saturated ethanol to yield compound **2** as a crystalline solid [23,24]. Free basing of **2** using aq. potassium carbonate at 0 °C, followed by treatment with ammonium chloride in refluxing ethanol gave ethyl 3-amino-3-iminopropanoate hydrochloride (**3**) [24]. These steps were performed on a 75 g scale.

Based on previous reports [25–27], the aminoimidate **3** was then reacted separately with five α-bromoacetophenones, **4a**–**e**, using sodium ethoxide as base to give the pyrrolidines **5a**–**e**. The reactions could be performed at room temperature for 12 h or at 60 °C for 1.5–3 h. In gram scale, **5a**–**e** were obtained in 48–64% yield after flash chromatography or crystallisation. The reasons for the moderate yields were not investigated, however stability issues have been indicated for similar 2-amino-3-ethoxycarbonylpyrroles [25].

Conversion of **5** to **6** was performed by a condensation where formamide reacts with the 1,3-aminoester function in a formic acid/DMF mixture [27,28]. The 4-hydroxypyrrolopyrimidines **6a**–**e** precipitated from the reaction mixture upon addition of 2-propanol resulting in 54–74% yield. The chlorination of **6** to **7** was performed at 90 °C using neat $POCl_3$. The reaction was high yielding, but a drawback was the large volume in the exothermic basic quench of residual $POCl_3$. Alternatively, **7a**–**e** could be isolated by precipitation followed by careful washing.

Thermal nucleophilic aromatic substitution on **7a** using the amines **8**–**22** gave the 4-substituted pyrrolopyrimidines **23**–**37**, while **7b**–**e** were reacted with the amines **8** and **9** respectively to give **38**–**45**, Scheme 2. All the amines used were the (*R*)-enantiomers, except **12**, **14**, **16** and **22** which were racemates. The thermal amination was run with a three fold excess of amine in 1-butanol. Heating the reaction mixture at reflux for 24 h resulted in isolated yields from 48 to 87%. Attempted use of triethylamine (three equivalents) as a base, did not lower the amount of amine needed to attain full conversion.

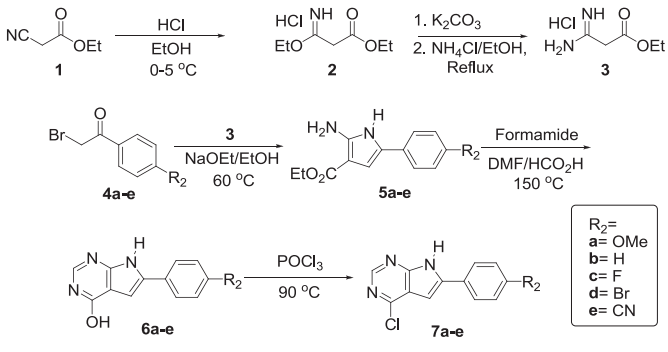
Therefore, to reduce the amount of the chiral amines, a Buchwald–Hartwig coupling was investigated for selected substrates using palladium (II) acetate and XPhos as ligand with sodium *tert*-butoxide as base (Scheme 2). The catalyst was activated by heating a solution of palladium (II) acetate and XPhos in dry *tert*-butanol containing 4 mol% distilled water for 2 min at 110 °C [29]. The Pd-catalysed reactions were performed under Schlenk conditions. Using a 1.3 fold excess of amine full conversion was obtained in less than 5 h. The results in term of yields for the two methods are compared in Table 1.

Although, more convenient in terms of chemical consumption and reaction time, also the Pd-catalysed coupling gave a mediocre 51–73% yield. The major loss in yield was related to hydrolysis of the starting materials giving **6a**–**c** (10–30% as analysed by ^{1}H NMR). These by-products could be removed by basic extraction using NaOH. The small amount of water used in the activation of the catalyst does not account for the observed level of the hydrolytic by-product, indicating that both reagent dryness and handling are crucial. Similar Pd-ligand complexes have been used in conversion of halogenated aromatics to phenols, thus the hydrolysis most likely takes place via the Pd-arene complex [30]. In the thermal amination reactions not performed under Schlenk conditions, the hydrolytic by-products were not detected. More efficient catalysts for this transformation have recently been developed [31], and work is underway in our laboratory to optimise this reaction further. All the products analysed for EGFR-TK activity in this study were however prepared by the thermal route to avoid potential palladium contaminations.

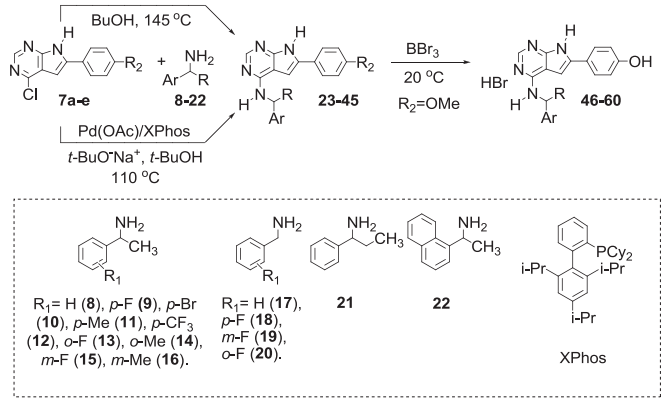
Finally, deprotection of the methyl ether function in **23**–**37** was accomplished using BBr_3 in dichloromethane. This gave a variable 26–66% yield of **46**–**60** as their hydrobromide salts. Possibly, losses in yield in the demethylation step were related to side reactions as described by Paliakov et al. [32], and by differences in the solubility of these compounds in the extractive work-up.

3. EGFR-TK inhibition and internalization

The activity of selected compounds towards EGFR-TK was investigated by IC_{50} measurements with 10 point titration using ATP concentration equal to K_m in duplicate experiments. Based on previous reported inhibition data of a series of 4-anilino derivatives [33], a hydrogen bond donor in the *meta* or *para* position of the 6-



Scheme 1. Synthetic route to the 4-chloropyrrolopyrimidines **7a**–**e**.



Scheme 2. Thermal and Pd-catalysed amination using the amines **8**–**22**. Compounds **46**–**60** were prepared by demethylation using BBr_3.

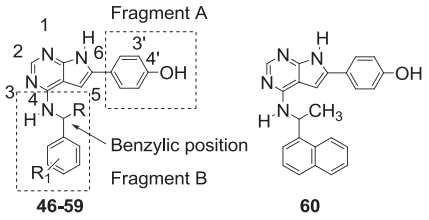


Fig. 2. Structures of the compounds tested for EGFR-TK activity and the numbering system.

aryl group (position 3′ and 4′ in fragment A, Fig. 2) was assumed to be important for efficient inhibitory properties. Therefore, keeping the 4′ phenolic group in fragment A constant, fragment B (Fig. 2) was first varied to identify possible effects on the EGFR-TK inhibitory properties. The results are summarised in Table 2.

PKI-166 (**46**), the fluorinated derivatives **47**, **51** and **53**, the benzylamine derivative **55**, and the 1-phenyl-1-propanamine derivative **59**, all gave activity in the low nanomolar range. Obviously, fluorine substitution is tolerated in the aromatic ring of fragment B, and the benzylic carbon can be substituted with a methyl or ethyl group without compromising the activity.

Introduction of more bulky groups into the *para* position of the aromatic ring (fragment B) reduced the activity considerably. This effect was most pronounced for the racemic trifluoromethyl derivative **50**. Further, the steric requirements of the inhibitors were challenged by activity measurements of the *ortho* and *meta* tolyl derivatives (Entries 7 and 9) and the 1-naphthyl containing compound **60** (Entry 16). The racemate of **52** had an IC_{50}-value of 17, indicating that the (*R*)-enantiomer would be highly active. A significant drop in activity was however observed for compound **60** containing a 1-naphthyl group in fragment B. Somewhat surprisingly, the fluorobenzylamine compounds **56**–**58** only had a moderate activity as compared to their non fluorinated parent compound **55**, and their chiral analogues **47**, **51** and **53**.

Table 1
Comparison of yields for the thermal and the Pd-catalysed amination.

Entry	Substrate	Amine	R	R_1/Ar	R_2	Pd-coupling (Yield, %)	Thermal (Yield, %)	Product
2	**7a**	*Rac*-**12**	CH_3	*p*-CF_3	OMe	71	75	(*R*)-**27**
3	**7a**	(*R*)-**21**	C_2H_5	H	OMe	47	75	(*R*)-**36**
4	**7a**	*Rac*-**22**	CH_3	$C_{10}H_7$	OMe	57	59	*Rac*-**37**
5	**7b**	(*R*)-**8**	CH_3	H	H	56	50	(*R*)-**38**
6	**7b**	(*R*)-**9**	CH_3	*p*-F	H	49	48	(*R*)-**42**
7	**7c**	(*R*)-**8**	CH_3	H	F	50	55	(*R*)-**39**
8	**7c**	(*R*)-**9**	CH_3	*p*-F	F	73	59	(*R*)-**43**

Table 2
EGFR-TK inhibitory activity (IC_{50}) of compounds **46**–**60**.

Entry	Compound	R	R_1	IC_{50} (nM)[a]	Std[b]
1	(*R*)-**46**	CH_3	H	3.7	0.6
2	(*R*)-**47**	CH_3	*p*-F	3.8	1.8
3	(*R*)-**48**	CH_3	*p*-Br	62	9
4	(*R*)-**49**	CH_3	*p*-CH_3	450	145
5	*Rac*-**50**	CH_3	*p*-CF_3	4608	3201
6	(*R*)-**51**	CH_3	*o*-F	8.0	1.1
7	*Rac*-**52**	CH_3	*o*-CH_3	17	3
8	(*R*)-**53**	CH_3	*m*-F	9.0	1.7
9	*Rac*-**54**	CH_3	*m*-CH_3	95	19
11	**55**	H	H	3.3	2.9
12	**56**	H	*p*-F	26	13
13	**57**	H	*o*-F	45	5
14	**58**	H	*m*-F	52	8
15	(*R*)-**59**	CH_2CH_3	H	4.0	0.7
16	*Rac*-**60**	CH_3	[c]	1008	806

[a] The IC_{50} values are based on dublicate measurements (2 × 10 datapoints).
[b] Standard deviation.
[c] For structure see Fig. 2.

We then went on to investigate how modifications of the R_2 group in fragment A (Fig. 3) affected inhibitory activity. In this series, position 4 of the pyrrolopyrimidine was substituted by the amines **8** (R_1 = H) and **9** (R_1 = *p*-F). The fluorine containing analogues were targeted due to the high activity of derivative **47**. The R_2 substituent was changed from a phenolic –OH to –OMe, –Br, –CN, –F and –H. The compounds tested and their *in vitro* activities are summarised in Table 3. Reference data for AEE-788 is also included for comparison [12].

Methoxy compound **23** retains good potency when compared to PKI-166 (compound **46**, Table 2, entry 1). Replacement of the phenol with unsubstituted phenyl or *p*-fluorophenyl also resulted in potent compounds, and *p*-cyanophenyl is also well tolerated. The *p*-bromophenyl derivative **40** and the fluoro-derivatives **42**–**44** (Entries 6–8) are less potent by comparison. Comparing the activity of these compounds to that of AEE-788, it is clear that the R_2–group affects the activity in a complex manner.

The cellular responses towards some of the synthesised compounds were then evaluated using a HeLa cell line derived from a cervical carcinoma. These cells express a high level of EGFR [34]. Ligand binding causes receptor dimerization, induced kinase activity and a rapid endocytosis of the receptor. To test if we could use internalization of EGFR in HeLa cells to evaluate inhibitory activity, we first performed a time study where the internalization was stopped at different time intervals, and the subcellular localization of the EGFR was determined by immunostaining. Rapid internalization of the EGFR in response to ligand binding was observed, and the presence of 500 nM PKI-166 (Compound **46**) abolished internalization for the first 10 min after stimulation (data not shown and Fig. 4). Following 15 and 20 min after EGFR activation there was a slight increase in EGFR internalization even in the presence of the inhibitor. We therefore evaluated selected compounds for their ability to interfere with internalization 10 min

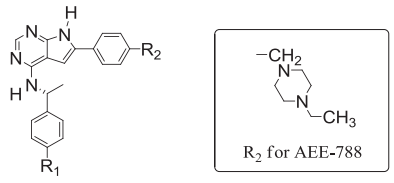


Fig. 3. Structural variations in the R_1- and R_2-group.

Table 3
Effect of modification in the 6-aryl group on EGFR-TK *in vitro* activity (IC_{50}, nM).

Entry	Compound	R_1	R_2	IC_{50} (nM)[a]	Std.[b]
1	(*R*)-**23**	H	OMe	4.7	0.8
2	(*R*)-**38**	H	H	3.3	2.9
3	(*R*)-**39**	H	F	6.6	2.0
4	(*R*)-**40**	H	Br	63	17
5	(*R*)-**41**	H	CN	12	4
6	(*R*)-**42**	*p*-F	H	33	7
7	(*R*)-**43**	*p*-F	F	27	5
8	(*R*)-**44**	*p*-F	Br	29	12
9	(*R*)-**45**	*p*-F	CN	14	2
10[c]	AEE-788	H	[d]	2.0	0.6

[a] The IC_{50} values are based on dublicate measurements (2 × 10 datapoints).
[b] Standard deviation.
[c] Data is taken from Traxler et al. [12].
[d] For structure of R_2 see Fig. 3.

after EGFR activation. Using representative microscopy images the cells were scored for having most of the EGFR located at the plasma membrane or for displaying the EGFR mainly located to intracellular vesicles. It was found that the presence of 500 nM of compound **42**, **43**, and **47** caused a potent inhibition of EGF induced receptor internalization (Fig. 4). At 500 nM, these compounds all show similar levels of inhibition of receptor internalization as compared to PKI-166 (**46**). Compound **38** and **39** displayed an intermediary effect, whereas compound **41** and **55** caused a modest effect on EGFR internalization.

4. Discussion

The structure–activity relationships identified in this study are summarised in Fig. 5.

At the benzylic carbon (R-group), hydrogen, methyl and ethyl substituents were tolerated, whereas R_1-substituents larger than fluorine in *meta* and *para* positions are not compatible with a high activity. Substitution of hydrogen by fluorine will generally increase the oxidative stability of the aromatic ring and may block CYP-450 mediated hydroxylations [35–37]. Larger variance in size and electronic properties of substituents could be tolerated in the R_2-group. PKI-166 is known to be mainly metabolised by *O*-glucuronidation [17]. The results show that a hydrogen bond donating group as R_2, is not crucial for good *in vitro* activity. Thus, several of the prepared compounds lacking the phenol functionallity might have prolonged inhibitory effect *in vivo*.

Preliminary docking studies revealed that compounds with IC_{50} values in the range of 3–86 nM, have similar conformations in the ATP binding site. Fig. 6 shows the docked structure of compound **43**, superimposed with the crystal structure complex of AEE-788 [38]. The *para* substituent on the 6-aryl group (fragment A) is directed towards the entrance of the binding pocket, explaining the minor changes in IC_{50} values upon variation of the R_2-group, whereas there is limited space for the aromatic amines at C-4 (fragment B).

The activity estimated from the internalization study does not correlate directly with activity from the *in vitro* EGFR testing. This could be due to differences in cellular transport processes, permeability, binding to other proteins or metabolic stability. The metabolic stability and the selectivity of these new compounds are the subject of ongoing studies.

5. Conclusion

A series of chiral and non-chiral 4-*N*-substituted 6-aryl-pyrrolopyrimidines have been synthesised, characterised and tested for their *in vitro* EGFR-TK inhibitor properties. Eight active derivatives were identified as possible drug candidates having IC_{50} values in the range of 2.8–9.0 nM. Four of these contain fluorine atoms at sites potentially susceptible to oxidative metabolism.

Examination of structure–activity relationships showed that substituents on the 6-aryl group (fragment A) could be varied without drastic effects on the EGFR-TK inhibition. In addition to a phenolic group, small substituents at R_2 are all well tolerated. Decreased potency was observed by introducing larger groups such as bromine. For fragment B, the unsubstituted benzylamine, as well as methyl and ethyl derivatives are all potent inhibitors, while limited substitution of the aromatic moiety is tolerated. A study of the effect of the inhibitors on the internalization process of EGFR, confirms that several of the fluorinated derivatives have high activity in HeLa cells. A benefit of the fluoro-containing pyrrolopyrimidines in a therapeutic setting could potentially be higher metabolic stability due to removal of sites for aromatic hydroxylation or *O*-glucoronidation metabolism.

6. Experimental section

6.1. General

Ethyl cyanoacetate (**1**), the α-bromoacetophenones **4a**–**c**, (*R*)-1-phenylethanamine (**8**), (*R*)-1-(4-bromophenyl)ethanamine (**10**), benzylamine (**17**), (*R*)-1-(phenyl)-1-propanamine (**21**), 1-(4-trifluoromethylphenyl)ethanone, 1-(*o*-tolyl)ethanone and 1-(*m*-tolyl)ethanone were from Fluka. BBr_3, (*R*)-1-(*p*-tolyl)ethanamine (**11**), 1-(1-naphthyl)-ethanamine (**22**), *tert*-butanol, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, palladium(II) acetate were from Sigma–Aldrich. (*R*)-1-(4-Fluorophenyl)ethanamine (**9**) was from Alfa Aesar. The α-bromoacetophenones **4d**–**e** were prepared by bromination of the corresponding acetophenones using molecular bromine. NMR spectra and high resolution mass spectra where in accordance with proposed structures. The synthesis and spectral properties of the intermediate compound **1**, **2**, **3**, **5a**, **6a**, **23**–**24**, **28**, **30**, and **33**–**35** have been described earlier [39]. Silica-gel column chromatography was performed using silica-gel 60A from Fluka, pore size 40–63 μm.

6.2. Molecular modelling

The docking was performed using a receptor modified from the 2J6M structure from RCSB Protein Data Bank [38], and AutoDock Vina [40]. The co-crystallised inhibitor (AEE788) was removed from the initial X-ray structure, water molecules were then removed and polar hydrogens and Gastieger charges were added using AutoDock Tools [41]. Ligands were optimised for the energy and geometry using MM2 force fields. In the structures of the ligands, all bonds were treated as rotatable, except for the aromatic bonds. Docking proceeded with an exhaustiveness value of 100 and a maximum output of 10 structures. Visualization was done using the PyMOL software (The PyMOL Molecular Graphics System, Version 1.3, Schrödinger, LLC).

6.3. Analyses

^1H and ^{13}C NMR spectra were recorded with Bruker Avance 400 spectrometer operating at 400 MHz and 100 MHz, respectively. ^{19}F NMR was performed on a Bruker Avance 400 or 500 operating at 376 or 470 MHz respectively. For ^1H and ^{13}C NMR chemical shifts are in ppm rel. to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. HPLC (Agilent 110-Series) with a G1379A degasser, G1311A Quatpump, G1313A ALS autosampler and a G1315D Agilent detector (230 nm) was used to determine the purity of the synthesised

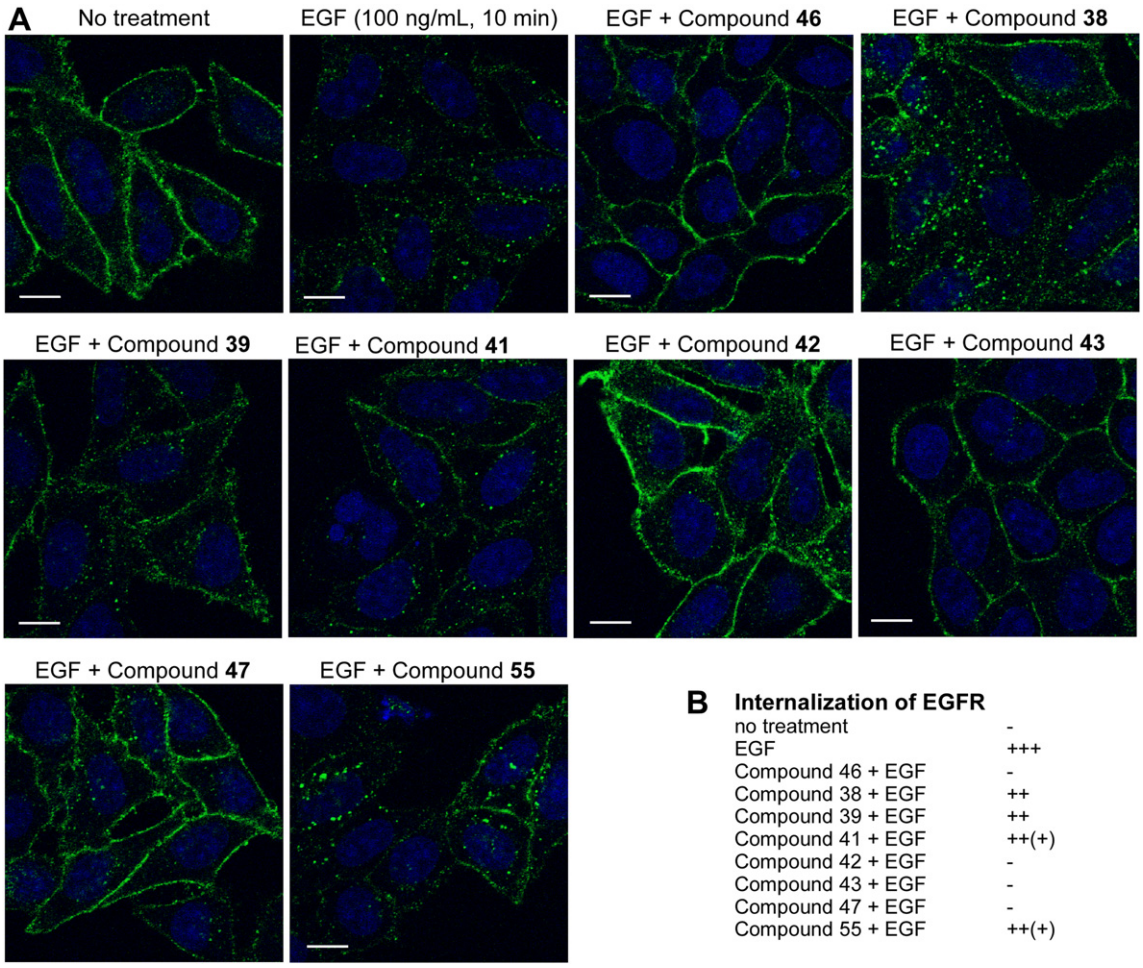


Fig. 4. EGF induced EGFR internalization is potently inhibited by compound **46**, **42**, **43** and **47**. A) Subconfluent HeLa cell cultures were starved for growth factors and left untreated or stimulated for 10 min with EGF (100 ng/mL, final concentration) in the absence or presence of the indicated compounds (500 nM, final concentration). Immunostained EGFR (green) and DNA (blue) was imaged using a Zeiss Axiovert 200 microscope with a 63× lens and a confocal detector. The images are representative for more than 500 randomly selected and manually inspected cells for each condition. Scale bar, 10 μm. B) A semi quantification of internalization was performed by scoring the location of the EGFR as "plasma membrane" or "internalized" in more than 200 randomly selected cells per condition before and following 10 min of EGF stimulation in the absence or presence of the indicated compounds (500 nM, final concentration). The study was performed in parallel as a single run, and is shown as the relative effect on internalization as determined by two independent blinded counts. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

compounds. Conditions: a Omrisphere 5 C18 (100 × 3.0 mm) column, flow rate 1.0 mL/min, elution starting with H_2O + 1% TFA/acetonitrile (98/2), linear gradient elution for 15 min ending at acetonitrile/water + 1% TFA (90/10), then 15 min isocratic elution. The software used with the HPLC was Agilent ChemStation.

Accurate mass determination (ESI) was performed on an Agilent G1969 TOF MS instrument equipped with a dual electrospray ion source, or EI (70eV) using a Finnigan MAT 95 XL. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. All melting points are uncorrected and measured by a Büchi melting point instrument. Some compounds were purified by

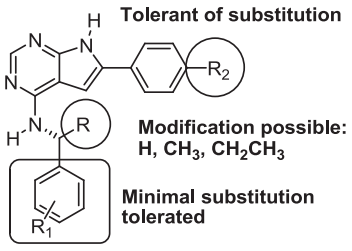


Fig. 5. Effect of structural variation on EGFR-TK activity.

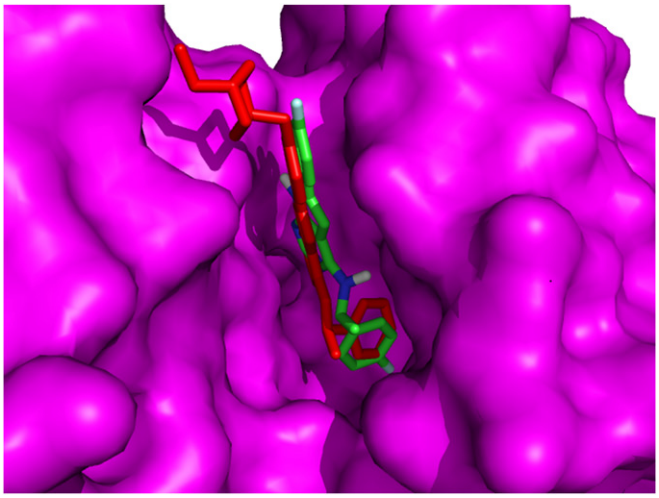


Fig. 6. Compound (*R*)-43 (green) docked in the EGFR-TK ATP binding domain, co-crystallised AEE-788 (Fig. 1) is shown in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

preparative HPLC (Agilent 110-Series) with a G1361A pump and G1328B detector. A Microsorb 100-8 C18, 250 × 21.4 mm column was used with a flow rate of 21 mL/min, elution starting with H_2O + 1% TFA/acetonitrile (98/2), linear gradient elution for 25 min ending at acetonitrile/water + 1% TFA (90/10), then 15 min isocratic elution.

6.4. In vitro EGFR (ErbB1) activity

The activity measurements of compounds towards ErbB1 was performed by Invitrogen using their Z′-LYTE® assay technology [42]. The test compounds were diluted in 1% DMSO solution, and subjected to a duplicate 10 points titration, using an ATP concentration equal to K m. The IC_{50} values were calculated from activity data with a four parameter logistic model using SigmaPlot (Windows Version 11.0 from Systat Software, Inc.)

6.5. Immunostaining and confocal microscopy analysis

HeLa cells (ATCC CCL2) were propagated as recommended by ATCC and seeded in 8-well coverglass slides (Nunc) for confocal imaging. Subconfluent cultures in normal growth medium were washed in phosphate buffer saline and incubated over night in Eagels's minimum essential medium supplemented with 0.1% fetal calf serum. The different compounds were added to 500 nM final concentration and left for 30 min at 37 °C before the cultures were placed on ice for 15 min. Recombinant EGF (Sigma) was added to the ice cold medium to 100 ng/mL final concentration and left on ice for 30 min. The medium was then replaced with warm medium supplemented with 0.1% fetal calf serum and incubated for 10 min at 37 °C in the cell incubator. Internalization was stopped by fixation of the cells by adding formaldehyde to 4% final concentration for 10 min at room temperature and the cells were permeabilized by 10 min incubation on ice in cold methanol. Unspecific binding was blocked by 30 min incubation in phosphate buffered saline supplemented with 3% goat serum followed by 30 min staining of EGFR using a 1:500 dilution of a mouse anti human EGFR antibody (sc-101, Santa Cruz Biotechnology). Unbound antibodies were removed by extensive washing in phosphate buffered saline and bound antibodies detected by 30 min incubation with a 1:1000 dilution of Alexa 488 conjugated goat anti mouse IgG antibody (Invitrogen). After extensive washing, the nuclei were visualized using the DNA dye Draq5 (Biostatus). Images were collected using a Zeiss Axiovert 200 microscope equipped with a LSM510 META confocal module and processed using Canvas 11. The effect of the different compounds on EGF induced receptor internalization was semi quantitatively determined by scoring cells for having most of the EGFR located at the plasma membrane or for displaying the EGFR mainly located to intracellular vesicles. The scoring was done by two independent blinded counts.

6.6. General procedures

6.6.1. Preparation of the pyrroles *5a–e*

The following is representative: ethyl 3-amino-3-iminopropanoate hydrochloride (**3**) (8.3 g, 50.0 mmol) and NaOEt (5.1 g, 75.0 mmol) were dissolved in abs. EtOH at 0 °C and stirred for 20 min under argon. The mixture was heated to 60 °C, and 2-bromo-1-phenylethanone (**4b**) (5.0 g, 25.0 mmol) was added portion wise over 5 min. After 1.5 h the mixture was cooled to 20 °C and the solvent was evaporated under reduced pressure. The residue was diluted with distilled water (20 mL) and extracted with EtOAc (3 × 80 mL). The organic layer was washed with water (3 × 20 mL) and brine (3 × 20 mL). The combined water fractions were back extracted with EtOAc (2 × 20 mL). The organic phases were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification was by silica-gel column chromatography (EtOAc/*n*-pentane, 7/3).

6.6.2. Preparation of the 6-aryl-7H-pyrrolo[2,3-d]pyrimidin-4-ols (*6a–e*)

The following is representative: to a solution of anhydrous DMF (28 mL), formic acid (11.3 mL), ethyl 2-amino-5-phenyl-1*H*-pyrrole-3-carboxylate (**5b**) (3.50 g, 16.57 mmol) and an excess formamide (75 mL) were added. The mixture was heated at 150 °C for 20 h. Then 2-propanol (12 mL) was added, and the mixture was cooled to 20 °C. The formed precipitate was isolated by filtration, washed with 2-propanol (10 mL) and *n*-hexane (2 × 15 mL), and dried under reduced pressure to yield a solid.

6.6.3. Preparation of the 6-aryl-4-chloro-7H-pyrrolo[2,3-d] pyrimidines (*7a–e*)

The following is representative: 6-phenyl-7*H*-pyrrolo[2,3-d] pyrimidin-4-ol (**6b**) (1.5 g, 7.43 mmol) and neat $POCl_3$ (13.3 mL) were mixed and reacted at 90 °C for 3 h. The solution was cooled with an ice-salt bath, and water (60 mL) was added. NaOH (8 M, 80 mL) was used to adjust the pH to 12. The formed precipitate was isolated by filtration, washed with water and *n*-pentane and dried to give a solid.

6.6.4. Thermal aromatic amination to *23–45*

The following is representative: 4-chloro-6-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**7a**) (275 mg, 1.06 mmol) and (*R*)-1-phenylethanamine (0.44 mL, ~3.5 mmol) were added to a dry round bottle flask containing 1-butanol (3.5 mL) under argon atmosphere. The mixture was heated at 145 °C for 24 h. The precipitate formed upon cooling to rt. was isolated by filtration, washed with diethyl ether (25 mL) and dried resulting in a solid.

6.6.5. Palladium catalysed aromatic amination

The following is representative: catalyst pre-activation: $Pd(OAc)_2$ (5 mg, 0.022 mmol), XPhos (21 mg, 0.043 mmol), sonoficated distilled water (1 μL) and *t*-BuOH (2 mL) were mixed and heated at 110 °C for 2 min, resulting in a colour change from orange to dark green indicating formation of the active catalyst.

4-Chloro-6-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**7b**) (110 mg, 0.48 mmol), sodium *tert*-butoxide (167 mg, 1.75 mmol), (*R*)-1-phenyletanamine (69 mg, 0.57 mmol) and *t*-BuOH (1 mL) were mixed under an argon atmosphere. The active catalyst was added and the mixture was heated to 110 °C for 4 h. After cooling the solvent was removed under reduced pressure, and the residue was diluted with EtOAc (20 mL) and saturated with NaOH (5%, 3 × 10 mL) to remove **6b**, After drying over $MgSO_4$ and concentration under reduced pressure 68 mg (0.22 mmol, 46%) was obtained.

6.6.6. Demethylation

The following is representative: (*R*)-6-(4-methoxyphenyl)-*N*-(1-phenylethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**23**) was dissolved in dry CH_2Cl_2 (2 mL) under argon atmosphere. BBr_3 (0.17 mL, ~1.8 mmol) in dry CH_2Cl_2 (1.5 mL) was added drop wise over 1 h at 0 °C. Then the mixture was allowed to react at 20 °C for 24 h. The reaction was quenched by addition of water (10 mL), and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The resulting residue was purified by precipitation from acetone (0.5 mL). The solid formed was isolated by filtration, washed with diethyl ether (10 mL) and dried.

6.7. Ethyl 2-amino-5-aryl-1H-pyrrole-3-carboxylate, *5a–e*

Compound **5a** was prepared as described previously [43].

*6.7.1. Ethyl 2-amino-5-phenyl-1H-pyrrole-3-carboxylate (**5b**) [25,44]*

Compound **5b** was prepared as described in Section 6.6.1. This gave 3.7 g (16.1 mmol, 64%) of a beige solid, mp. 101–104 °C, lit. [44]. 107 °C, lit. [25]. 121–122 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.72 (s, 1H, NH, H-1), 7.50–7.44 (m, 2H), 7.32–25 (m, 2H), 7.11–7.05 (m, 1H), 6.46 (d, J = 2.4, 1H, H-4), 5.65 (s, 2H, NH_2), 4.15 (q, J = 6.8, 2H), 1.25 (t, J = 6.8, 3H). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 165.4, 148.6, 132.6, 129.1 (2C), 125.4, 123.6, 122.8 (2C), 104.0, 93.9, 58.6, 15.2. HRMS (ESI): 231.1124 (calcd $C_{13}H_{14}N_2O_2$, 231.1128, M + H^+). IR (neat, cm^{-1}): 3417, 3328, 1662, 1589, 1281, 1120, 757, 691.

*6.7.2. Ethyl 2-amino-5-(4-fluorophenyl)-1H-pyrrole-3-carboxylate (**5c**)*

The compound was prepared as described in Section 6.6.1 starting with ethyl 3-amino-3-iminopropanoate hydrochloride (**3**) (7.3 g, 43.8 mmol), NaOEt (4.5 g, 66.8 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone (**4c**) (5.0 g, 23.0 mmol). The crude product was purified by silica-gel column chromatography (EtOAc/*n*-pentane, 7/3) giving 2.9 g (11.7 mmol, 51%) as a beige solid, mp. 164–166 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.72 (s, 1H, NH, H-1), 7.52–7.46 (m, 2H), 7.15–7.08 (m, 2H), 6.42 (d, J = 2.7, 1H, H-4), 5.65 (s, 2H, NH_2), 4.12 (q, J = 7.2, 2H), 1.23 (t, J = 7.2, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.4, 160.5 (d, J = 242.7), 148.6, 129.4 (d, J = 3.2), 124.7 (d, J = 7.8, 2C), 122.8, 115.8 (d, J = 20.8, 2C), 103.9, 93.9, 58.5, 15.1. ^{19}F NMR (470 MHz DMSO-d_6, C_6F_6) δ: −119.3 (m). HRMS (ESI): 249.1040 (calcd $C_{13}H_{13}N_2O_2F$, 249.1039, M + H^+). IR (neat, cm^{-1}): 3482, 3352, 1643, 1567, 1225, 1136, 1079, 834, 798, 764.

*6.7.3. Ethyl 2-amino-5-(4-bromophenyl)-1H-pyrrole-3-carboxylate (**5d**) [45]*

The compound was prepared as described in Section 6.6.1 starting with ethyl 3-amino-3-iminopropanoate hydrochloride (**3**) (8.4 g, 50.6 mmol), NaOEt (5.4 g, 79.4 mmol) and 2-bromo-1-(4-bromphenyl)ethanone (**4d**) (7.3 g, 26.3 mmol). The crude product was purified by silica-gel column chromatography (EtOAc/*n*-pentane, 1/1) giving 4.96 g (16.0 mmol, 61%) as a beige solid, mp. 256–260 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.78 (s, 1H, NH, H-1), 7.48–7.43 (m, 4H), 6.54 (d, J = 2.6, 1H, H-4), 5.72 (s, 2H, NH_2), 4.12 (q, J = 7.1, 2H), 1.24 (t, J = 7.1, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.3, 148.9, 131.9, 131.8 (2C), 124.8 (2C), 122.5, 117.6, 105.1, 94.2, 60.2, 14.5. HRMS (EI): 308.0156 (calcd $C_{13}H_{13}BrN_2O_2$, 308.0155, M^+). IR (neat, cm^{-1}): 3477, 3353, 1639, 1620, 1589, 1542, 1069, 763.

*6.7.4. Ethyl 2-amino-5-(4-cyanophenyl)-1H-pyrrole-3-carboxylate (**5e**) [46]*

The compound was prepared as described in Section 6.6.1 starting with ethyl 3-amino-3-iminopropanoate hydrochloride (**3**) (7.7 g, 46.2 mmol), NaOEt (5.4 g, 78.85 mmol) and 2-bromo-1-(4-cyanophenyl)ethanone (**4e**) (7.3 g, 32.6 mmol). The crude product was purified by crystallisation from acetonitrile giving 4.02 g (15.8 mmol, 48%) as a yellow solid, mp. 224–226 °C, lit. [46]. 228–229 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.49 (s, 1H, NH, H-1), 7.64–7.69 (m, 4H), 6.77 (s, 1H, H-4), 5.93 (s, 2H, NH_2), 4.15 (q, J = 7.1, 2H), 1.25 (t, J = 7.1, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.1, 149.8, 136.9, 133.0 (2C), 122.8 (2C), 122.0, 119.9, 108.2, 106.1, 95.0, 58.7, 15.1. HRMS (EI): 255.1003 (calcd $C_{14}H_{13}N_3O_2$, 255.1002, M^+). IR (neat, cm^{-1}): 3495, 3343, 2220, 1642, 1622, 1174, 767.

*6.8. 6-Aryl-7H-pyrrolo[2,3-d]pyrimidin-4-ol, **6a–e***

Compound **6a** was prepared as described previously [39].

*6.8.1. 6-Phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ol (**6b**) [28]*

The compound was prepared as described in Section 6.6.2. This gave 2.1 g (9.9 mmol, 65%) of a beige solid, mp > 300 °C, lit. [28]. >300 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.33 (s, 1H, NH), 11.84 (s, 1H, OH), 7.87 (s, 1H, H-2), 7.82 (m, 2H), 7.41 (m, 2H), 7.27 (m, 1H), 6.93 (s, 1H, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.2, 149.4, 143.7, 133.1, 131.4, 128.8 (2C), 127.2, 124.6 (2C), 109.1, 99.2. HRMS (ESI): 212.0821 (calcd $C_{12}H_9N_3O$, 212.0818, M + H^+). IR (neat, cm^{-1}): 2786, 1650, 1241, 900, 749, 693, 620.

*6.8.2. 6-(4-Fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (**6c**)*

The compound was prepared as described in Section 6.6.2 starting with ethyl 2-amino-5-(4-fluorophenyl-1*H*-pyrrole-3-carboxylate (**5c**) (2.78 g, 11.19 mmol) and formamide (54 mL, ~1.37 mol). This gave 1.90 g (8.29 mmol, 74%) of a beige solid, mp > 300 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.33 (s, 1H, NH, H-7), 11.84 (s, 1H, OH), 7.90–7.82 (m, 3H, H-2, C_6H_4F) 7.29–7.21 (m, 2H), 6.91 (s, 1H, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.7 (d, J = 244.5), 158.6, 149.8, 144.2, 132.6, 128.5 (d, J = 3.1), 127.0 (d, J = 8.1, 2C), 116.2 (d, J = 21.6, 2C), 109.5, 99.6. ^{19}F NMR (470 MHz DMSO-d_6, C_6F_6) δ: −116.3 (m). HRMS (ESI): 230.0725 (calcd $C_{12}H_8N_3OF$, 230.0724, M + H^+). IR (neat, cm^{-1}): 2778, 1670, 1217, 909, 839, 802, 770, 616.

*6.8.3. 6-(4-Bromophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (**6d**) [45]*

The compound was prepared as described in Section 6.6.2 starting with ethyl 2-amino-5-(4-bromophenyl-1*H*-pyrrole-3-carboxylate (**5d**) (3.66 g, 11.84 mmol) and formamide (30 mL, ~1.78 mol). This gave 2.24 g (7.72 mmol, 65%) of a brown solid, mp > 300 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.91 (br s, 2H, OH, NH, H-7), 7.89 (s, 1H, H-2), 7.79 (m, 2H), 7.60 (m, 2H), 7.00 (s, 1H, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.6, 150.0, 144.5, 132.3, 132.1, 131.1 (2C), 127.0 (2C), 120.5, 109.6, 100.4. HRMS (EI): 288.9846 (calcd $C_{12}H_8N_3OBr$, 288.9845, M^+). IR (neat, cm^{-1}): 2779, 1657, 1242, 908, 809, 764, 616.

*6.8.4. 4-(4-Hydroxy-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzonitrile (**6e**) [47]*

The compound was prepared as described in Section 6.6.2 starting with ethyl 2-amino-5-(4-cyanophenyl)-1*H*-pyrrole-3-carboxylate (**5e**) (2.66 g, 10.42 mmol) and formamide (30 mL, ~1.77 mol). This gave 1.33 g (5.63 mmol, 54%) of a grey solid, mp > 300 °C, lit. [47] >410 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.57 (br s, NH, H-7), 11.94 (br s, OH), 8.02 (m, 2H), 7.93 (d, J = 2.7, 1H, H-2), 7.86 (m, 2H), 7.21 (d, J = 2.2, 1H, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.6, 150.5, 145.2, 136.2, 133.2 (2C), 131.6, 125.3 (2C), 119.4, 109.8, 109.4, 102.8. HRMS (EI): 236.0698 (calcd $C_{13}H_8N4O$, 236.0693, M^+). IR (neat, cm^{-1}): 3112, 2862, 2231, 1652, 1078, 772.

*6.9. 6-Aryl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine, **7a–e***

Compound **7a** was prepared as described previously [39].

*6.9.1. 4-Chloro-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine (**7b**) [28]*

The compound was prepared as described in Section 6.6.3 starting from 6-phenyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-ol (**6b**) (1.57 g, 7.43 mmol) and neat $POCl_3$ (13.5 mL, 54.8 mmol). This gave 1.49 g (6.49 mmol, 87%) of a yellowish solid, mp. 255–257 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.03 (s, 1H, NH, H-7), 8.59 (s, 1H, H-2), 8.02 (m, 2H), 7.51 (m, 2H), 7.42 (m, 1H), 7.11 (d, J = 2.0, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.4, 150.9, 150.3, 140.7, 130.6, 129.5 (3C), 126.4 (2C), 118.3, 95.9. HRMS (ESI): 230.0488 (calcd $C_{12}H_8N_3Cl$, 230.0480, M + H^+). IR (neat, cm^{-1}): 3093, 2955, 2826, 1556, 1234, 983, 866, 751, 698.

*6.9.2. 4-Chloro-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine (**7c**)*

The compound was prepared as described in Section 6.6.3 starting from 6-(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ol (**6c**) (1.5 g, 6.54 mmol) and neat $POCl_3$ (11.4 mL, ~45.3 mmol). This gave 1.60 g (6.46 mmol, 99%) as a beige solid, mp. 245–247 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.98 (s, 1H, NH), 8.57 (s, 1H, H-2), 8.05 (m, 2H), 7.34 (m, 2H), 7.08 (s, 1H, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.9 (d, J = 246.9), 153.5. 150.8, 150.2, 139.8, 128.6 (d, J = 8.4, 2C), 127.3 (d, J = 3.1), 118.3, 116.4 (d, J = 21.8, 2C), 95.9. ^{19}F NMR (470 MHz DMSO-d_6, C_6F_6) δ: −113.5 (m). HRMS (ESI): 248.0388 (calcd $C_{12}H_7N_3FCl$, 248.0385, M + H^+). IR (neat, cm^{-1}): 3134, 2964, 1742, 1498, 1232, 835, 767.

*6.9.3. 6-(4-Bromophenyl)-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**7d**) [45]*

The compound was prepared as described in Section 6.6.3 starting from 6-(4-bromophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ol (**6d**) (1.55 g, 5.34 mmol) and neat $POCl_3$ (4.96 mL, ~53.2 mmol). This gave 1.46 g (4.73 mmol, 89%) of a yellow solid, mp > 300 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.09 (s, 1H, NH, H-7), 8.59 (s, 1H, H-2), 7.97 (m, 2H), 7.69 (m, 2H), 7.15 (s, 1H, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.5, 151.1, 150.5, 139.5, 132.4 (2C), 129.9, 128.3 (2C), 122.8, 118.2, 96.7. HRMS (EI): 306.9515 (calcd 306.9506, M^+). IR (neat, cm^{-1}): 3124, 2949, 1570, 1234, 869, 770.

*6.9.4. 4-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzonitrile (**7e**) [47]*

The compound was prepared as described in Section 6.6.3 starting from 4-(4-hydroxy-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)benzonitrile (**6e**) (510 mg, 2.16 mmol) and neat $POCl_3$ (5.5 mL, ~59.0 mmol). This gave 420 mg (1.65 mmol, 76%) as a yellow solid, mp > 300 °C, lit. [47]. 296–297 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.10 (s, 1H, NH, H-7), 8.64 (s, 1H, H-2), 8.22 (m, 2H), 7.96 (m, 2H), 7.37 (s, 1H, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.6, 151.7, 151.3, 138.6, 134.9, 133.4 (2C), 126.9 (2C), 119.1, 118.1, 111.5, 98.8. HRMS (EI): 254.0357 (calcd $C_{13}H_7N_4Cl$, 254.0354, M^+). IR (neat, cm^{-1}): 3126, 2956, 2228, 1570, 1238, 866, 774.

6.10. 1-Arylethanamines

*6.10.1. 1-(4-(Trifluoromethyl)phenyl)ethanamine (**12**) [48]*

A mixture of 1-(4-(trifluoromethyl)phenyl)ethanone (400 mg, 2.13 mmol), Ti(O-*i*-Pr)$_4$ (1.25 mL, ~4.25 mmol) and ammonia in EtOH (2 M, 5.30 mL, ~10.6 mmol) was stirred under argon at room temperature for 24 h $NaBH_4$ (120 mg, 3.19 mmol) was then added, and the resulting mixture was stirred for another 24 h. The pH of the reaction mixture was adjusted to pH 2 using HCl (6 M), and washed with *tert*-butyl methyl ether (TBME) (3 × 20 mL). Using NaOH (pellets) the pH was adjusted to ca 10, and the mixture was extracted with TBME (6 × 30 mL). The combined organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 210 mg (1.11 mmol, 52%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (m, 2H), 7.46 (m, 2H), 4.19 (q, J = 6.7, 1H), 1.38 (d, J = 6.7, 3H), 1.51 (s, 2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.1 (q, J = 1.1), 129.4 (q, J = 31.5), 126.5 (2C), 125.8 (q, J = 3.8, 2C), 124.6 (q, J = 270.9), 51.4, 25.1.

*6.10.2. 1-(o-Tolyl)ethanamine (**14**) [49]*

The synthesis was performed as described for **12**, starting with 1-(*o*-tolyl)ethanone (1.00 g, 7.45 mmol), Ti(O-*i*-Pr)$_4$ (4.4 mL, ~14.0 mmol), ammonia in EtOH (2 M, 18 mL, ~37.3 mmol) and $NaBH_4$ (422 mg, 11.18 mmol). The crude product was purified by silica-gel column chromatography (diethyl ether/MeOH/NEt_3, 20/5/1) yielding 0.43 g (3.18 mmol, 43%) of 1-(*o*-tolyl)ethanamine (**14**) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (m, 1H), 7.22 (m, 1H), 7.13 (m, 2H), 4.36 (q, J = 6.6, 1H), 2.35 (s, 3H), 1.65 (s, 2H, NH_2), 1.35 (d, J = 6.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.6, 134.4, 130.4, 126.4, 126.3, 124.1, 46.7, 24.5, 19.0.

*6.10.3. 1-(m-Tolyl)ethanamine (**16**) [50]*

The synthesis was performed as described for **12**, starting with 1-(*m*-tolyl)ethanone (1.00 g, 7.45 mmol), Ti(O-*i*-Pr)$_4$ (4.4 mL, ~14.0 mmol), ammonia in EtOH (2 M, 18 mL, ~37.3 mmol) and $NaBH_4$ (420 mg, 11.18 mmol). This gave after silica-gel column chromatography (diethyl ether/MeOH/NEt_3, 20/5/1) 0.81 g (5.99 mmol, 80%) of 1-(*m*-tolyl)ethanamine (**16**) as an yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (m, 1H), 7.16 (s, 1H), 7.13 (m, 1H), 7.05 (m, 1H), 4.08 (q, J = 6.7, 1H), 2.35 (s, 3H), 1.56 (s, 2H, NH_2), 1.38 (d, J = 6.7, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.7, 138.0, 128.4, 127.5, 126.4, 122.7, 51.2, 25.6, 21.3.

*6.11. Compounds **23**–**45***

The synthesis and spectroscopic properties of the 6-(4-methoxyphenyl)-***N***-(substituted)-7H-pyrrolo[2,3-*d*]pyrimidin-4-amines **23**–**24**, **28**, **30** and **33**–**35** have been described recently [39].

*6.11.1. (R)-N-(1-(4-Bromophenyl)ethyl)-6-(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**25**)*

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-(4-methoxyphenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7a**) (190 mg, 0.73 mmol) and (*R*)-1-(4-bromophenyl) ethanamine (**10**) (439 mg, 2.19 mmol). This gave 245 mg (0.58 mmol, 79%) of a white solid, mp. 271–273 °C, $[\alpha]_D^{20}$ = −333.0 (*c* 0.24, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.93 (s, 1H, NH, H-7), 8.03 (s, 1H, H-2), 7.76 (s, 1H, NH), 7.73 (m, 2H), 7.49 (m, 2H), 7.38 (m, 2H), 7.02 (m, 2H), 6.94 (d, J = 1.8, 1H, H-5), 5.44 (m, 1H), 3.80 (s, 3H), 1.51 (d, J = 7.0, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1, 155,1, 151.8, 151.7, 145.6, 134.1, 131.4 (2C), 128.8 (2C), 126.4 (2C), 124.9, 119.8, 114.9 (2C), 104.3, 94.9, 55.6, 48.8, 23.2. HRMS (EI): 422.0748 (calcd $C_{21}H_{19}Br^{79}N_4O$, 422.0737, M+). IR (neat, cm^{-1}): 3128, 2971, 1592, 1250, 830.

*6.11.2. (R)-6-(4-Methoxyphenyl)-N-(1-p-tolylethyl)-7H-pyrrolo[2,3-d] pyrimidin-4-amine (**26**)*

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-(4-metoxyphenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7a**) (203 mg, 0.78 mmol) and 1-(*p*-tolyl)ethanamine (**11**) (317 mg, 2.34 mmol). This gave 245 mg (0.68 mmol, 87%) of a white solid, mp. 260–263 °C, $[\alpha]_D^{20}$ = −343.0 (*c* 0.43, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.90 (s, 1H, NH, H-7), 8.04 (s, 1H, H-2), 7.72 (d, J = 8.6, 2H), 7.66 (d, J = 8.2, 1H, NH), 7.31 (d, J = 7.8, 2H), 7.10 (d, J = 7.7, 2H), 7.02 (d, J = 8.6, 2H), 6.95 (s, 1H, H-5), 5.45 (m, 1H), 3.80 (s, 3H), 2.25 (s, 3H), 1.51 (d, J = 6.9, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.6, 154.8, 151.3 (2C), 142.6, 135.3, 133.5, 128.7 (2C), 126.0 (2C), 125.9 (2C), 124.5, 114.4 (2C), 103.9, 94.6, 55.2, 48.4, 22.9, 20.6. HRMS (EI): 358.1784 (calcd $C_{22}H_{22}N_4O$, 358.1788, M^+). IR (neat, cm^{-1}): 3183, 2975, 1588, 1245, 830.

*6.11.3. 6-(4-Methoxyphenyl)-N-(1-(4-(trifluoromethyl)phenyl)ethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**27**)*

The compound was synthesised as described in Section 6.6.4 starting from 4-chloro-6-(4-metoxyphenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7a**) (165 mg, 0.64 mmol), and 1-(4-trifluoromethyl) phenyl)ethanamine (**12**) (157 mg, 0.83 mmol). This gave 198 mg (0.48 mmol, 75%) of a brownish solid, mp 274–277 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.95 (s, 1H, NH, H-7), 8.02 (s, 1H, H-2), 7.84 (d, J = 7.7, 1H, NH), 7.73 (d, J = 8.7, 2H), 7.65 (m, 4H), 7.02 (d, J = 8.9, 2H), 6.95 (s, 1H, H-5), 5.52 (m, 1H), 3.79 (s, 3H), 1.55 (d, J = 6.9, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1, 155.0, 151.8, 151.6, 151.0, 134.1, 127.5 (q, J = 32.1), 127.2 (2C), 126.4 (2C), 125.5 (q, J = 3.9, 2C), 124.9, 124.8 (q, J = 270.1), 114.8 (2C), 104.3, 94.9, 55.6, 49.1, 23.2. ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6) δ: −62.2 (s). HRMS (ESI): 413.1595 (calcd $C_{22}H_{19}F_3N_4O$, 413.1584, M + H^+). IR (neat, cm^{-1}): 3118, 1594, 1323, 1251, 1115, 1066, 827.

6.11.4. 6-(4-Methoxyphenyl)-N-(1-o-tolylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**29**)

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-(4-metoxyphenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7a**) (102 mg, 0.39 mmol) and 1-(*o*-tolyl)ethanamine (**14**) (214 mg, 1.58 mmol). This gave 97 mg (0.27 mmol, 69%) as a beige solid, mp > 300 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.88 (s, 1H, NH, H-7), 8.03 (s, 1H, H-2), 7.72 (d, J = 9.1, 2H) 7.71 (d, J = 8.6, 3H, NH, Ar), 7.12 (m, 3H), 7.01 (d, J = 8.3, 2H), 6.95 (s, 1H, H-5), 5.61 (m, 1H), 3.79 (s, 3H), 2.42 (s, 3H), 1.48 (d, J = 6.8, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1, 155.1, 151.8, 151.7, 144.1, 135.1, 133.9, 130.4, 126.7, 126.3 (2C), 126.4, 125.4, 124.9, 114.8 (2C), 104.3, 95.0, 55.6, 45.8, 22.1, 19.2. HRMS (ESI): 359.1850 (calcd $C_{22}H_{28}N_4O$, 359.1866, M + H^+). IR (neat, cm^{-1}): 3102, 2956, 1591, 1249, 825, 786, 752.

6.11.5. 6-(4-Methoxyphenyl)-N-(1-m-tolylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**31**)

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-(4-metoxyphenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7a**) (150 mg, 0.58 mmol) and 1-(*m*-tolyl)ethanamine (**16**) (314 mg, 2.32 mmol). This gave 141 mg (0.39 mmol, 67%) as a beige solid, mp > 300 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.90 (s, 1H, NH, H-7), 8.03 (s, 1H, H-2), 7.72 (d, J = 9.1, 2H), 7.68 (d, J = 8.9, 1H, NH), 7.15–7.26 (m, 3H), 7.01 (m, 3H), 6.95 (s, 1H, H-5), 5.45 (m, 1H), 3.79 (s, 3H), 2.27 (s, 3H), 1.50 (d, J = 6.9, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1, 155.2, 151.8 (2C), 146.0, 137.5, 133.9, 128.5, 127.5, 127.1, 126.3 (2C), 124.9, 123.6, 114.8 (2C), 104.3, 95.0, 55.6, 49.0, 23.4, 21.6. HRMS (ESI): 359.1856 (calcd $C_{22}H_{28}N_4O$, 359.1866, M + H^+). IR (neat, cm^{-1}): 3126, 2972, 1594, 1459, 1252, 825, 772, 696.

6.11.6. N-Benzyl-6-(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**32**) [27,51]

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-(4-metoxyphenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7a**) (125 mg, 0.48 mmol) and phenylmethanamine (**17**) (155 mg, 1.45 mmol). This gave 104 mg (0.31 mmol, 64%) as a white solid, mp 280–282 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.94 (s, 1H, NH, H-7), 8.10 (s, 1H, H-2), 7.94 (t, J = 5.7, 1H, NH), 7.71 (d, J = 8.5, 2H), 7.47–7.41 (m, 1H), 7.37–7.30 (m, 4H), 7.24–7.21 (m, 1H), 7.01 (d, J = 8.5, 2H), 6.86 (d, J = 2.0, 1H, H-5), 4.73 (d, J = 5.7, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1, 155.9, 151.8, 151.7, 140.8, 134.1, 128.6 (2C), 127.7 (2C), 127.0, 126.4 (2C), 124.9, 114.8 (2C), 104.3, 94.8, 55.6, 43.6. HRMS (EI): 330.1487 (calcd $C_{20}H_{18}N_4O$, 330.1475, M^+). IR (neat, cm^{-1}): 3421, 3117, 1601, 1350, 1272, 728.

6.11.7. (R)-6-(4-Methoxyphenyl)-N-(1-phenylpropyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**36**)

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-(4-metoxyphenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7a**) (178 mg, 0.69 mmol) and (*R*)-1-phenylpropan-1-amine (**21**) (295 mg, 2.18 mmol). This gave 188 mg (0.52 mmol, 75%) as a white solid, mp. 265–268 °C, $[\alpha]_D^{20}$ = −297.3 (*c* 0.61, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.89 (s, 1H, NH, H-7), 8.03 (s, 1H, H-2), 7.72 (d, J = 8.7, 2H), 7.65 (d, J = 8.6, 1H, NH), 7.42 (d, J = 7.5, 2H), 7.30 (m, 2H), 7.19 (m, 1H), 7.02 (d, J = 8.7, 2H), 6.97 (s, 1H, H-5), 5.26 (m, 1H), 3.80 (s, 3H), 1.87 (m, 2H), 0.94 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1, 155.7, 151.8 (2C), 145.1, 133.9, 128.5 (2C), 127.0 (2C), 126.9, 126.3 (2C), 124.0, 114.8 (2C), 104.4, 95.1, 55.6, 55.3, 30.1, 11.9. HRMS (EI): 358.1792 (calcd $C_{22}H_{22}N_4O$, 358.1788, M^+). IR (neat, cm^{-1}): 3128, 2963, 1590, 1247, 697.

6.11.8. 6-(4-Methoxyphenyl)-N-(1-(naphthalen-1-yl)ethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**37**)

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-(4-metoxyphenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7a**) (159 mg, 0.61 mmol) and 1-(naphthalen-1-yl) ethanamine (**22**) (314 mg, 1.83 mmol). This gave 143 mg (0.36 mmol, 59%) as a grey solid, mp. 278–280 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.93 (s, 1H, NH, H-7), 8.24 (d, J = 8.2, 1H), 8.04 (s, 1H, H-2), 7.94 (m, 1H), 7.87 (m, 1H), 7.81 (m, 1H), 7.71–7.64 (m, 3H), 7.59–7.45 (m, 3H), 7.01 (m, 2H), 6.97 (s, 1H, H-5), 6.27 (m, 1H), 3.79 (s, 3H), 1.67 (d, J = 6.8, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.7, 154.2, 151.1, 150.8, 140.7, 133.8, 133.4, 130.6, 128.6, 127.1, 126.1, 125.9 (2C), 125.52, 125.47, 124.3, 123.3, 122.2, 114.4 (2C), 103.9, 94.8, 55.2, 45.2, 21.8. HRMS (EI): 394.1789 (calcd $C_{25}H_{22}N_4O$, 394.1788, M^+). IR (neat, cm^{-1}): 3131, 1593, 1251, 828, 775.

6.11.9. (R)-6-Phenyl-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**38**)

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-phenyl-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7b**) (100 mg, 0.44 mmol) and (*R*)-1-phenylethanamine (**8**) (158 mg, 1.30 mmol). This gave 68 mg (0.22 mmol, 50%) as a pink solid, mp. 248–250 °C, $[\alpha]_D^{20}$ = −284.6 (*c* 0.40, DMSO), purity > 97% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.02 (s, 1H, NH), 8.05 (s, 1H, H-2), 7.82–7.78 (m, 3H, NH + Ar), 7.46–7.42 (m, 4H), 7.33–7.27 (m, 3H), 7.21–7.18 (m, 1H), 7.10 (s, 1H, H-5), 5.50 (m, 1H), 1.53 (d, J = 6.9, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.5, 152.2, 152.0, 145.9, 133.8, 132.2, 129.4 (2C), 128.6 (2C), 127.6, 126.9, 126.5 (2C), 124.9 (2C), 104.3, 96.5, 49.1, 23.3. HRMS (ESI): 315.1619 (calcd $C_{20}H_{18}N_4$, 315.1604, M + H^+). IR (neat, cm^{-1}): 3231, 3053, 1575, 1552, 1306, 755, 696. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

6.11.10. (R)-6-(4-Fluorophenyl)-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**39**)

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-(4-fluorophenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7c**) (148 mg, 0.60 mmol) and (*R*)-1-phenylethanamine (**8**) (218 mg, 1.80 mmol). This gave 109 mg (0.33 mmol, 55%) as a white solid, mp. 278–280 °C, $[\alpha]_D^{20}$ = −302.4 (*c* 0.50, DMSO), purity > 98% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.02 (s, 1H, NH, H-7), 8.05 (s, 1H, H-2), 7.79 (m, 3 H, NH + Ar), 7.40 (m, 2H), 7.30 (m, 4H), 7.20 (m, 1H), 7.09 (s, 1H, H-5), 5.48 (m, 1H), 1.53 d, J = 7.2, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.8 (d, J = 244.5, 1C), 155.4, 152.2, 152.0, 145.9, 132.9, 128.9 (d, J = 3.2), 128.6 (2C), 126.9, 126.8 (d, J = 9.2, 2C) 126.5 (2C), 116.3 (d, J = 20.4, 2C), 104.3, 96.4, 49.1, 23.3. ^{19}F NMR (400 MHz, DMSO-d_6, C_6F_6) δ: −116.2 (m). HRMS (ESI): 333.1516 (calcd $C_{20}H_{17}N_4F$, 333.1510, M + H^+). IR (neat, cm^{-1}): 3223, 3053, 1570, 836, 757, 697. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

6.11.11. (R)-6-(4-Bromophenyl)-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**40**)

The compound was prepared as described in Section 6.6.4 starting with 6-(4-bromophenyl)-4-chloro-7H-pyrrolo[2,3-*d*]pyrimidine (**7d**) (98 mg, 0.32 mmol) and (*R*)-1-phenylethanamine (**8**) (116 mg, 0.96 mmol). This gave 64 mg (0.16 mmol, 50%) as a white solid, mp > 300 °C, $[\alpha]_D^{20}$ = −289.6 (*c* 0.30, DMSO), purity 96% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.08 (s, 1H, NH, H-7), 8.07 (s, 1H, H-2), 7.84 (d, J = 8.2, 1H, NH), 7.72 (m, 2H), 7.64 (m, 2H), 7.43 (m, 2H), 7.30 (m, 2H), 7.19 (m, 1H), 7.14 (s, 1H, H-5), 5.51 (m, 1H), 1.53 (d, J = 7.0, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.6,

152.5, 152.1, 145.9, 132.6 (2C), 131.3, 131.5, 128.6 (2C), 126.9, 126.9 (2C), 126.5 (2C), 120.5, 104.3, 97.3, 49.1, 23.3. HRMS (EI): 392.0629 (calcd $C_{20}H_{17}N_4Br$, 392.0631, M^+). IR (neat, cm^{-1}): 3242, 3090, 2981, 1592, 821, 693.

6.11.12. (R)-4-(4–((1-Phenylethyl)amino)-7H-pyrrolo[2,3-d] pyrimidin-6-yl)benzonitrile (41) [47]

The compound was prepared as described in Section 6.6.4 starting with 4-(4-chloro-7H-pyrrolo[2,3-*d*]pyrimidin-6-yl)benzonitrile (**7e**) (75 mg, 0.29 mmol) and (*R*)-1-phenylethanamine (**8**) (107 mg, 0.88 mmol). This gave 54 mg (0.16 mmol, 55%) as a yellow solid, mp > 300 °C, lit. [47]. 333–336 °C, $[\alpha]_D^{20} = -316.4$ (*c* 0.40, DMSO), purity: 98% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.26 (s, 1H, NH, H-7), 8.11 (s, 1H, H-2), 7.98–7.88 (m, 5H), 7.43 (m, 2H), 7.33–7.29 (m, 3H), 7.19 (m, 1H, H-5), 5.51 (m, 1H), 1.54 (d, $J = 7.0$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.8, 153.2, 152.6, 145.7, 136.5, 133.4 (2C), 131.8, 128.6 (2C), 126.9, 126.5 (2C), 125.2 (2C), 119.4, 109.4, 104.5, 99.7, 49.2, 23.2. HRMS (EI): 339.1481 (calcd $C_{21}H_{17}N_5$, 339.1478, M^+). IR (neat, cm^{-1}): 3373, 3116, 2960, 2223, 1594, 1317, 702. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

*6.11.13. (R)-N-(1-(4-Fluorophenyl)ethyl)-6-phenyl-7H-pyrrolo[2,3-d] pyrimidin-4-amine (**42**)*

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-phenyl-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7b**) (100 mg, 0.44 mmol) and (*R*)-1-(4-fluorophenyl)ethanamine (**8**) (182 mg, 1.31 mmol). This gave 71 mg (0.21 mmol, 48%) as a solid, mp. 239–240 °C, $[\alpha]_D^{20} = -234.7$ (*c* 0.25, DMSO), purity > 94% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.04 (s, 1H, NH, H-7), 8.06 (s, 1H, H-2), 7.82–7.78 (m, 3H, NH + Ar), 7.48–7.42 (m, 4H), 7.31–7.27 (m, 1H), 7.15–7.08 (m, 3H, H-5+Ar), 5.49 (m, 1H), 1.53 (d, $J = 6.8$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.3 (d, $J = 243.5$), 155.4, 152.2, 152.0, 142.0 (d, $J = 2.9$), 133.9, 132.3, 129.4 (2C), 128.3 (d, $J = 8.1$, 2C), 127.7, 124.9 (2C), 115.3 (d, $J = 21.1$, 2C), 104.2, 96.5, 48.5, 23.3. ^{19}F NMR (470 MHz, DMSO-d_6, C_6F_6): −116.2 (m). HRMS (ESI): 333.1518 (calcd $C_{20}H_{17}N_4F$, 333.1510, M + H^+). IR (neat, cm^{-1}): 3110, 2964, 1591, 1508, 1225, 832, 743, 688. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

*6.11.14. (R)-6-(4-Fluorophenyl)-N-(1-(4-fluorophenyl)ethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**43**)*

The compound was prepared as described in Section 6.6.4 starting with 4-chloro-6-(4-fluorophenyl)-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7c**) (68 mg, 0.27 mmol) and (*R*)-1-(4-fluorophenyl) ethanamine (**9**) (115 mg, 0.83 mmol). This gave 57 mg (0.16 mmol, 59%) as a white solid, mp > 300 °C, $[\alpha]_D^{20} = -243.0$ (*c* 0.4, DMSO), purity > 96% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.04 (s, 1H, NH, H-7), 8.06 (s, 1H, H-2), 7.81–7.78 (m, 3H, NH + Ar), 7.47–7.44 (m, 2H), 7.32–7.27 (m, 2H), 7.15–7.10 (m, 2H), 7.03 (s, 1H, H-5), 5.49 (m, 1H), 1.53 (d, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.7 (d, $J = 244.5$), 161.2 (d, $J = 241.7$), 155.4, 152.2, 152.0, 142.1 (d, $J = 3.2$), 132.9, 128.9 (d, $J = 3.5$), 128.3 (d, $J = 7.8$, 2C), 126.9 (d, $J = 8.5$, 2C), 116.3 (d, $J = 22.2$, 2C), 115.2 (d, $J = 20.8$, 2C), 104.3, 96.4, 48.5, 23.3. ^{19}F NMR (470 MHz, DMSO-d_6, C_6F_6) δ: −116.1 (m), −118.2 (m). HRMS (ESI): 351.1422 (calcd $C_{20}H_{16}N_4F_2$, 351.1416, M + H^+). IR (neat, cm^{-1}): 3433, 3110, 2972, 1583, 1495, 1221, 832, 765.

*6.11.15. (R)-6-(4-Bromophenyl)-N-(1-(4-fluorophenyl)ethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**44**)*

The compound was prepared as described in Section 6.6.4 starting with 6-(4-bromophenyl)-4-chloro-7*H*-pyrrolo-[2,3-*d*]-pyrimidine (**7d**) (88 mg, 0.29 mmol) and (*R*)-1-(4-fluorphenyl) ethanamine (**9**) (119 mg, 0.86 mmol). This gave 72 mg (0.18 mmol, 62%) as a white solid, mp > 300 °C, $[\alpha]_D^{20} = -266.4$ (*c* 0.20, DMSO), purity > 95% (by HPLC) ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.09 (s, 1H, NH, H-7), 8.07 (s, 1H, H-2), 7.84 (d, $J = 8.1$, 1H, NH), 7.72 (m, 2H), 7.64 (m, 2H), 7.45 (m, 2H), 7.12 (m, 3H, NH + Ar), 5.49 (m, 1H), 1.52 (d, $J = 7.0$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.3 (d, $J = 241.7$), 155.5, 152.5, 152.1, 142.0 (d, $J = 2.8$), 132.7, 132.3 (2C), 131.5, 128.4 (d, $J = 8.0$, 2C), 126.9 (2C), 120.6, 115.3 (d, $J = 21.1$, 2C), 104.3, 97.2, 48.6, 23.3. ^{19}F NMR (470 MHz, DMSO-d_6, C_6F_6) δ: −116.7 (m). HRMS (EI): 410.0550 (calcd $C_{20}H_{16}N_4Br$, 410.0537, M^+). IR (neat, cm^{-1}): 3237, 3094, 2987, 1592, 1509, 1223, 824.

*6.11.16. (R)-4-(4-((1-(4-Fluorophenyl)ethyl)amino)-7H-pyrrolo[2,3-d] pyrimidin-6-yl)benzonitrile (**45**)*

The compound was prepared as described in Section 6.6.4 starting with 4-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)benzonitrile (**7e**) (64 mg, 0.25 mmol) and (*R*)-1-(4-fluorophenyl)ethanamine (**9**) (105 mg, 0.75 mmol). This gave 67 mg (0.19 mmol, 76%) as a solid, mp > 300 °C, $[\alpha]_D^{20} = -249.8$ (*c* 0.20, DMSO), purity > 97% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.26 (s, 1H, NH, H-7), 8.10 (s, 1H, H-2), 7.99–7.89 (m, 5H), 7.50–7.42 (m, 3H), 7.31 (s, 1H, H-5), 7.16–7.13 (m, 2H), 5.50 (m, 1H), 1.53 (d, $J = 6.5$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.4 (d, $J = 243.2$), 153.3, 152.6, 149.5, 141.9 (d, $J = 2.9$), 136.4, 133.4 (2C), 131.9, 128.4 (d, $J = 7.8$, 2C), 125.3 (2C), 119.7, 115.3 (d, $J = 21.5$, 2C), 109.4, 104.5, 99.7, 48.6, 23.6. ^{19}F NMR (470 MHz, DMSO-d_6, C_6F_6) δ: −118.1 (m). HRMS (EI): 357.1383 (calcd $C_{21}H_{16}N_5F$, 357.1384, M^+). IR (neat, cm^{-1}): 3389, 3122, 2979, 2223, 1594, 1322, 698. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

*6.11.17. (R)-4-(4-((1-Phenylethyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol hydrobromide (**46**) [27,33]*

The compound was synthesised as described in Section 6.6.6 starting from (*R*)-6-(4-methoxyphenyl)-*N*-(1-phenylethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**23**) (61 mg, 0.18 mmol) and BBr_3 (0.17 mL, 1.8 mmol). This gave 40 mg, (0.10 mmol, 54%) of a white solid, mp > 300 °C, purity > 99% (by HPLC), $[\alpha]_D^{20} = -207.9$ (*c* 0.11, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.98 (s, 1H, NH, H-7), 9.83 (br s, 1H, OH), 9.55 (br s, 1H, NH), 8.30 (s, 1H, H-2), 7.66 (m, 2H), 7.50–7.48 (m, 2H), 7.39 (m, 2H), 7.32–7.29 (m, 1H), 7.24 (s, 1H, H-5), 6.89 (m, 2H), 5.37 (m, 1H), 1.66 (d, $J = 6.5$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.0, 148.8 (2C), 142.3, 141.9, 137.6, 128.6 (2C), 127.5, 126.7 (2C), 126.1 (2C), 121.2, 116.0 (2C), 102.9, 96.6, 50.9, 22.3. HRMS (ESI): 331.1555 (calcd $C_{20}H_{18}N_4O$ 331.1553, M + H^+). IR (neat, cm^{-1}): 3135, 1647, 1495, 758, 702.

*6.11.18. (R)-4-(4-((1-(4-Fluorophenyl)ethyl)amino)-7H-pyrrolo[2,3-d] pyrimidin-6-yl)phenol hydrobromide (**47**) [27]*

The compound was synthesised as described in Section 6.6.6 starting from (*R*)-*N*-(1-(4-fluorophenyl)ethyl)-6-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**24**) (149 mg, 0.41 mmol) and BBr_3 (0.40 mL, 4.2 mmol). This gave 75 mg (0.17 mmol, 43%) of a white solid, mp > 300 °C, $[\alpha]_D^{20} = -142.2$ (*c* 0.12, DMSO), purity > 99% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.97 (s, 1H, NH, H-7), 9.82 (br s, 1H, OH), 9.51 (br s, 1H, NH), 8.31 (s, 1H, H-2), 7.65 (m, 2H), 7.56–7.52 (m, 2H), 7.25–7.20 (m, 3H, H-5, Ar), 6.89 (m, 2H), 5.39 (m, 1H), 1.65 (d, $J = 6.7$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.5 (d, $J = 243.4$), 158.0, 148.6 (2C), 142.5, 138.2, 137.5, 128.2 (d, $J = 7.0$, 2C), 126.7 (2C), 121.3, 116.0 (2C), 115.4 (d, $J = 22.1$, 2C), 102.9, 96.6, 50.2, 22.4. ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6) δ: −114.6 (m). HRMS (ESI): 349.1465 (calcd $C_{20}H_{17}FN_4O$, 349.1459, M + H^+). IR (neat, cm^{-1}): 3122, 1647, 1223, 835, 748.

*6.11.19. (R)-4-(4-((1-(4-Bromophenyl)ethyl)amino)-7H-pyrrolo[2,3-d] pyrimidin-6-yl)phenol hydrobromide (**48**)*

The compound was synthesised as described in Section 6.6.6 starting from (*R*)-*N*-(1-(4-bromophenyl)ethyl)-6-(4-methoxyphenyl)-

7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**25**) (144 mg, 0.34 mmol) and BBr_3 (322 μL, 3.40 mmol). This gave 80 mg (0.16 mmol, 48%) of a white solid, mp. 267–270 °C, $[\alpha]_D^{20} = -216.2$ (*c* 0.44, DMSO), purity > 97% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.94 (s, 1H, NH, H-7), 9.82 (br s, 1H, OH), 9.47 (br s, 1H, NH), 8.29 (s, 1H, H-2), 7.65 (m, 2H), 7.58 (m, 2H), 7.44 (m, 2H), 7.16 (s, 1H, H-5), 6.88 (m, 2H), 5.37 (m, 1H), 1.63 (d, $J = 6.6$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.4, 149.6, 148.2, 142.5, 142.1, 137.9, 131.9 (2C), 128.9 (2C), 127.2 (2C), 121.7, 121.0, 116.4 (2C), 103.4, 96.8, 50.8, 22.7. HRMS (EI): 408.0582 (calcd $C_{20}H_{17}Br^{79}N_4O$, 408.0580, M^+). IR (neat, cm^{-1}): 3135, 1645, 1613, 1493, 761.

6.11.20. (R)-4-(4-((1-(p-Tolyl)ethyl)amino)-7H-pyrrolo[2,3-d] pyrimidin-6-yl)phenol hydrobromide (**49**)

The compound was synthesised as described in Section 6.6.6 starting from (*R*)-6-(4-methoxyphenyl)-*N*-(1-(*p*-tolyl)ethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**26**) (87 mg, 0.24 mmol) and BBr_3 (231 μL, 2.44 mmol). This gave 47 mg, (0.11 mmol, 46%) of a white solid, mp > 300 °C, $[\alpha]_D^{20} = -247.0$ (*c* 0.20, DMSO), purity > 96% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.77 (s, 1H, NH, H-7), 9.59 (s, 1H, OH), 8.97 (s, 1H, NH), 8.23 (s, 1H, H-2), 7.58 (d, $J = 8.4$, 2H), 7.29 (m, 3H, H-5+Ar), 7.10 (d, $J = 7.8$, 2H), 6.87–6.81 (m, 2H), 5.44 (m, 1H), 2.25 (s, 3H), 1.51 (d, $J = 6.8$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.4, 155.2, 150.8 (2C), 142.4, 135.9, 133.4, 128.5 (2C), 126.3 (2C), 126.1 (2C), 124.3, 114.3 (2C), 103.8, 94.6, 53.2, 22.8, 20.5 HRMS (EI): 344.1634 (calcd $C_{21}H_{20}N_4O$, 344.1632, M^+). IR (neat, cm^{-1}): 3183, 1614, 1278, 833, 763. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

6.11.21. 4-(4-((1-(4-(Trifluoromethyl)phenyl)ethyl)amino)-7H-pyrrolo [2,3-d]pyrimidin-6-yl)phenol hydrobromide (**50**)

The compound was synthesised as described in Section 6.6.6 starting with 6-(4-methoxyphenyl)-*N*-(1-(4-(trifluoromethyl) phenyl)ethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**27**) (176 mg, 0.43 mmol) and BBr_3 (410 μL, 4.30 mmol). This gave 99 mg, (0.21 mmol, 48%) as a beige solid, mp. 256 °C, purity > 96% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.01 (s, 1H, NH, H-7), 9.84 (br s, 1H, OH), 9.63 (br s, 1H, NH), 8.31 (s, 1H, H-2), 7.98 (d, $J = 8.2$, 2H), 7.65 (m, 4H), 7.25 (s, 1H, H-5), 6.89 (d, $J = 6.9$, 2H), 5.47 (m, 1H), 1.67 (d, $J = 7.5$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.6, 154.1, 150.7, 147.8, 142.7, 138.1, 129.9 (2C), 127.2 (q, $J = 3.2$, 2C), 127.1 (q, $J = 32.0$), 126.9 (2C), 124.6 (q, $J = 270.6$), 121.4, 116.3 (2C), 103.2, 96.6, 48.9, 22.6. ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6) δ: −61.9 (s) HRMS (ESI): 399.1410 (calcd $C_{21}H_{17}N_4OF_3$, 399.1427, M + H^+). IR (neat, cm^{-1}): 3150, 1609, 1277, 761, 620. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

6.11.22. (R)-4-(4-((1-(2-Fluorophenyl)ethyl)amino)-7H-pyrrolo[2,3-d] pyrimidin-6-yl)phenol hydrobromide (**51**)

The compound was synthesised as described in Section 6.6.6 starting from (*R*)-*N*-(1-(2-fluorophenyl)ethyl)-6-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**28**) (218 mg, 0.60 mmol) and BBr_3 (580 μL, 6.0 mmol). This gave 101 mg, (0.24 mmol, 39%) of a colourless solid, mp > 300 °C, $[\alpha]_D^{20} = -177.6°$ (*c* 0.13, DMSO), purity > 99% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.91 (br s, 1H, NH, H-7), 9.82 (br s, 1H, OH), 9.36 (br s, 1H, NH), 8.30 (s, 1H, H-2), 7.66–7.64 (m, 2H), 7.50–7.46 (m, 1H), 7.41–7.35 (m, 1H), 7.27–7.21 (m, 3H, H-5+Ar), 6.87 (m, 2H), 5.58 (m, 1H), 1.65 (d, $J = 6.7$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.8 (d, $J = 244.5$), 158.0, 149.2, 147.5, 142.7, 137.6, 129.7 (d, $J = 8.0$), 128.8 (d, $J = 13.1$), 126.8 (3C), 124.7 (d, $J = 2.3$), 121.2, 116.0 (2C), 115.7 (d, $J = 21.1$), 103.0, 96.5, 45.8, 20.8. ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6) δ: −116.5 (m). HRMS (ESI): 349.1465 (calcd $C_{20}H_{17}FN_4O$, 349.1459, M + H^+). IR (neat, cm^{-1}): 3133, 1648, 1589, 758, 699.

6.11.23. -(4-((1-(o-Tolyl)ethyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol hydrobromide (**52**)

The compound was synthesised as described in Section 6.6.6 starting from (**29**) (97 mg, 0.27 mmol) and BBr_3 (270 μL, 2.70 mmol). This gave 41 mg, (0.10 mmol, 36%) of a white solid, mp > 300 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.51 (s, 1H, NH, H-7), 9.85 (s, 1H, OH), 8.79 (br s, 1H, NH), 8.20 (s, 1H, H-2), 7.61 (d, $J = 8.6$, 2H), 7.46 (m, 1H), 7.32 (s, 1H, H-5), 7.19–7.18 (m, 4H), 7.07 (m, 1H), 6.86 (d, $J = 8.7$, 2H), 5.57 (m, 1H), 2.41 (s, 3H), 1.56 (d, $J = 6.6$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.5, 151.7 (2C), 149.7, 142.1, 137.2, 136.1, 131.3, 127.9, 127.3 (2C), 127.0, 125.7, 122.8, 116.7 (2C), 104.2, 96.6, 47.9, 22.0, 19.7. HRMS (EI): 344.1632 (calcd $C_{21}H_{20}N_4O$, 344.1632, M^+). IR (neat, cm^{-1}): 3417, 3132, 1647, 1597, 1224, 758. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

6.11.24. (R)-4-(4-((1-(3-Fluorophenyl)ethyl)amino)-7H-pyrrolo[2,3-d] pyrimidin-6-yl)phenol hydrobromide (**53**)

The compound was synthesised as described in Section 6.6.6 starting from (*R*)-*N*-(1-(3-fluorophenyl)ethyl)-6-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**30**) (176 mg, 0.49 mmol) and BBr_3 (470 μL, 4.9 mmol). This gave 123 mg, (0.29 mmol, 58%) of an off-white solid, mp > 300 °C, $[\alpha]_D^{20} = -195.2$ (*c* 0.13, DMSO), purity > 99% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 12.95 (s, 1H, NH, H-7), 9.84 (br s, 1H, OH), 9.52 (br, 1H, NH), 8.29 (s, 1H, H-2), 7.66 (d, $J = 8.7$, 2H), 7.46–7.40 (m, 1H), 7.38–7.33 (m, 2H), 7.23 (s, 1H, H-5), 7.15–7.11 (m, 1H), 6.89 (d, $J = 8.7$, 2H), 5.45 (m, 1H), 1.65 (d, $J = 6.8$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.2 (d, $J = 244.5$), 158.0, 148.3 (2C), 145.3, 142.8, 137.4, 130.6 (d, $J = 8.0$), 126.7 (2C), 122.2, 121.3, 115.9 (2C), 114.3 (d, $J = 21.1$), 113.2 (d, $J = 22.1$), 103.0, 96.5, 50.4, 22.3. ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6) δ: −112.2 (m). HRMS (ESI): 349.1466 (calcd $C_{20}H_{17}FN_4O$, 349.1459, M + H^+). IR (neat, cm^{-1}): 3133, 1648, 1589, 758, 699.

6.11.25. 4-(4-((1-(m-Tolyl)ethyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol hydrobromide (**54**)

The compound was synthesised as described in Section 6.6.6 starting from 6-(4-methoxyphenyl)-*N*-(1-*m*-tolylethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**31**) (121 mg, 0.34 mmol) and BBr_3 (320 μL, 3.39 mmol). This gave 96 mg (0.23 mmol, 66%) as a beige solid, mp. 248–249 °C, purity > 95% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.59 (s, 1H, NH, H-7), 9.78 (br s, 1H, OH), 8.91 (br s, NH), 8.21 (s, 1H, H-2), 7.64 (d, $J = 8.6$, 2H), 7.27 (s, 1H), 7.24 (m, 2H), 7.10 (s, 1H, H-5), 7.07 (m, 1H), 6.86 (d, $J = 8.9$, 2H), 5.36 (m, 1H), 2.29 (s, 3H), 1.58 (d, $J = 6.9$, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.6, 155.4, 149.2 (2C), 143.6, 137.9, 136.7, 128.8, 128.2, 127.1, 126.9 (2C), 123.5, 122.2, 116.3 (2C), 103.7, 96.0, 50.4, 23.0, 21.2. HRMS (ESI): 345.1712 (calcd $C_{21}H_{20}N_4O$, 345.1710, M + H^+). IR (neat, cm^{-1}): 3110, 1599, 1497, 1274, 832, 761, 700. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

6.11.26. 4-(4-(Benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol hydrobromide (**55**) [27,52]

The compound was synthesised as described in Section 6.6.6 starting from *N*-benzyl-6-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*] pyrimidin-4-amine (**32**) (79 mg, 0.24 mmol) and BBr_3 (220 μL, 2.28 mmol). This gave 46 mg (0.12 mmol, 48%) of an off-white solid, mp > 300 °C, purity: 99% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.06 (s, 1H, NH, H-7), 9.65 (s, 1H, OH), 9.24 (s, 1H, NH), 8.13 (s, 1H, H-2), 7.60 (d, $J = 8.2$, 2H), 7.38–7.31 (m, 4H), 7.26–7.23 (m, 1H), 6.84–6.82 (m, 3H, H-5+Ar), 4.74 (d, $J = 5.3$, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.6 (2C), 151.1, 147.3, 140.1, 135.3, 128.8 (2C), 127.7 (2C), 127.2, 126.6 (2C), 123.0, 116.2 (2C), 104.1, 64.6, 43.9. HRMS (EI): 316.1320 (calcd $C_{19}H_{16}N_4O$, 316.1319, M^+). IR (neat, cm^{-1}): 3421, 3117, 1601, 1350, 1272, 728.

*6.11.27. 4-(4-((4-Fluorobenzyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol hydrobromide (**56**)*

The compound was synthesised as described in Section 6.6.6 starting from *N*-(4-fluorobenzyl)-6-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**33**) (168 mg, 0.48 mmol) and BBr_3 (0.47 mL, 4.9 mmol). This gave 114 mg (0.27 mmol, 57%) of an off-white solid, mp 274–276 °C, purity: 98% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.01 (s, 1H, NH, H-7), 9.81 (br, 1H, OH), 9.76 (br, 1H, NH), 8.35 (s, 1H, H-2), 7.65 (d, J = 8.7, 2H), 7.51–7.48 (m, 2H), 7.27–7.21 (m, 2H), 7.14 (d, J = 2.0, 1H, H-5), 6.88 (d, J = 8.7, 2H), 4.77 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.7 (d, J = 243.4), 158.0, 149.4, 147.5, 142.1, 137.6, 132.7, 129.7 (d, J = 8.0, 2C), 126.8 (2C), 121.2, 116.0 (2C), 115.4 (d, J = 21.1, 2C), 102.8, 96.5, 44.2. ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6) δ: −114.3 (m). HRMS (ESI): 335.1303 (calcd $C_{19}H_{15}FN_4O$, 335.1303, M + H^+). IR (neat, cm^{-1}): 3150, 1652, 1221, 758.

*6.11.28. 4-(4-((3-Fluorobenzyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol hydrobromide (**57**)*

The compound was synthesised as described in Section 6.6.6 starting from *N*-(3-fluorobenzyl)-6-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**34**) (139 mg, 0.40 mmol) and BBr_3 (0.39 mL, 4.00 mmol). This gave 44 mg (0.11 mmol, 26%) of an off-white solid, mp. 271–273 °C, purity > 99% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.73 (br, 1H, NH, H-7), 9.78 (s, 1H, OH), 9.31 (br s, 1H, NH), 8.29 (s, 1H, H-2), 7.64 (d, J = 8.7, 2H), 7.46–7.40 (m, 1H), 7.27–7.25 (m, 2H), 7.17–7.12 (m, 1H), 7.04 (s, 1H, H-5), 6.87 (d, J = 8.7, 2H), 4.82 (d, J = 4.9, 2H) ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.1 (d, J = 243.4), 158.0, 149.6, 147.4, 142.2, 139.6, 137.7, 130.7 (d, J = 8.0), 126.8 (2C), 123.5, 121.2, 116.0 (2C), 114.5 (d, J = 21.1), 114.4 (d, J = 21.1), 103.0, 96.4, 44.3. ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6) δ: −112.5 (m). HRMS (ESI): 335.1305 (calcd $C_{19}H_{16}FN_4O$, 335.1303, M + H^+). IR (neat, cm^{-1}): 3133, 1609, 1496, 757.

*6.11.29. 4-(4-((2-Fluorobenzyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol hydrobromide (**58**)*

The compound was synthesised as described in Section 6.6.6 starting from *N*-(2-fluorobenzyl)-6-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**35**) (157 mg, 0.45 mmol) and BBr_3 (0.44 mL, 4.6 mmol). This gave 83 mg (0.20 mmol, 44%) of a colourless solid, mp. 284–285 °C, purity: 98% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.94 (br, 1H, NH, H-7), 9.82 (br s, 1H, OH), 9.60 (br s, 1H, NH), 8.35 (s, 1H, H-2), 7.64 (d, J = 8.7, 2H), 7.48–7.45 (m, 1H), 7.44–7.40 (m, 1H), 7.31–7.29 (m, 1H), 7.27–7.21 (m, 1H), 7.11 (s, 1H, H-5), 6.88 (d, J = 8.7, 2H), 4.86 (d, J = 3.5, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.4 (d, J = 245.5), 158.0, 149.8, 147.4, 142.4, 137.6, 130.0 (d, J = 7.0), 129.6, 126.8 (2C), 124.7, 123.5 (d, J = 13.1), 121.2, 116.0 (2C), 115.5 (d, J = 21.1), 103.0, 96.3, 39.5. ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6) δ: −117.1 (s). HRMS (ESI): 335.1306 (calcd $C_{19}H_{16}FN_4O$, 335.1303, M + H^+). IR (neat, cm^{-1}): 3128, 1645, 1492, 758.

*6.11.30. (R)-4-(4-((1-Phenylpropyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol hydrobromide (**59**)*

The compound was synthesised as described in Section 6.6.6 starting from (*R*)-6-(4-methoxyphenyl)-*N*-(1-phenylpropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**36**) (98 mg, 0.27 mmol) and BBr_3 (0.26 mL, 2.77 mmol). This gave 46 mg, (0.11 mmol, 40%) of a colourless solid, mp > 300 °C, $[\alpha]_D^{20}$ = −197.3 (*c* 0.23, DMSO), purity: 96% (by HPLC), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.56 (s, 1H, NH, H-7), 9.87 (br s, 1H, OH), 8.90 (br s, 1H, NH) 8.19 (s, 1H, H-2), 7.64–7.62 (m, 2H), 7.50–7.48 (m, 2H), 7.37–7.33 (m, 2H), 7.27–7.23 (m, 1H), 7.15 (s, 1H, H-5), 6.88–6.85 (m, 2H), 5.24 (m, 1H), 1.88 (m, 2H), 0.94 (t, J = 7.3, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.1, 155.3, 151.4 (2C), 144.3, 133.2, 128.5 (2C), 127.6, 127.0 (2C), 126.4 (2C), 124.7, 116.3 (2C), 104.5, 96.1, 55.7, 30.0, 11.6. HRMS (EI): 344.1630 (calcd $C_{21}H_{20}N_4O$, 344.1632, M^+). IR (neat, cm^{-1}): 3417, 3110, 2981, 1586, 1234.

*6.11.31. 4-(4-((1-(Naphthalen-1-yl)ethyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol hydrobromide (**60**)*

The compound was synthesised as described in Section 6.6.6 starting from 6-(4-methoxyphenyl)-*N*-(1-(naphthalen-1-yl)ethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**37**) (113 mg, 0.29 mmol) and BBr_3 (3 mL, 3 mmol). This gave 65 mg, (0.16 mmol, 54%) as a grey solid, mp > 300 °C, purity: 97% (by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.98 (s, 1H, NH, H-7), 9.82 (br s, 1H, OH), 9.55 (br s, 1H, NH), 8.30 (s, 1H), 8.14 (s, 1H), 8.00 (m, 1H), 7.91 (m, 1H), 7.64–7.57 (m, 5H), 7.54–7.50 (m, 1H), 7.26 (s, 1H, H-5), 6.89–6.87 (m, 2H), 6.09 (m, 1H), 1.78 (d, J = 6.5, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 156.9, 154.5, 151,2, 151.1, 141.0, 134.0, 133.4, 130.6, 128.6, 127.0, 126.1, 126.0 (2C), 125.5 (2C), 123.3, 122.9, 122.2, 115.7 (2C), 103.9, 94.0, 52.4, 21.8. HRMS (EI): 380.1634 (calcd $C_{24}H_{20}N_4O$, 380.1632, M^+). IR (neat, cm^{-1}): 3126, 1646, 1613, 1494, 1176, 761. A 20 mg sample was purified by preparative HPLC for the *in vitro* studies.

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