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^{1}H,^{13}C and ^{19}F NMR data of *N*-substituted 6-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amines in DMSO-d_6

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Chemical shift assignment of seven *N*-substituted 6-(4-methoxyphenyl)-7*H*-pyrrolo[2, 3-*d*]pyrimidin-4-amines, six of which are fluorinated, have been performed based on ^{1}H, ^{13}C, ^{19}F, and 2D COSY, HMBC and HSQC experiments.

Keywords: NMR; ^{1}H; ^{13}C; ^{19}F; 7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amines

Introduction

Tyrosine kinases (TKs) are enzymes that bind ATP and catalyse the transfer of γ-phosphate to hydroxy groups of tyrosine residues in proteins, regulating their activity and function. Several TKs can be targets for cancer chemotherapy, the most important being the receptor tyrosine kinases (RTKs).[1] This is a large family of receptors including the epidermal growth factor receptor (EGFR)[2,3] and the vascular endothelial growth factor receptor among others.[4] Pyrrolopyrimidines have shown promising properties as TK inhibitors.[5–8]

Further, there is evidence that such compounds or analogues have prospects of becoming efficient antiprotozoal agents.[9] Another interesting finding is that the ErbB2 TK is involved in developing leprosy and that the breakdown of myelin causing the disease can be blocked by kinase inhibitors.[10,11] With this background, we have undertaken the synthesis and characterisation of seven pyrrolopyrimidines and present herein their NMR spectroscopic properties.

Result and Discussion

The 7*H*-pyrrolo[2, 3-*d*]pyrimidines were synthesised in multiple steps by a previously described route (Scheme 1).[8]

Four of the compounds contain a (*R*)-1-arylethanamine structural unit, **8a–d**, at position 4 of the pyrimidine ring, whereas for compounds **9b–d** the position has been substituted with *para-*, *meta-* and *ortho*-fluorobenzylamine. The compounds **8a** and **8b** have been prepared previously, but only ^{1}H NMR data of **8a** is available in the literature.[8] The structures of the molecules investigated by NMR spectroscopy and the numbering system are given in Fig. 1.

DMSO-d_6 was chosen as a solvent for all NMR experiments of compounds **8a–d** and **9b–d**, due to superior solubility of the compounds in comparison to other solvents. The NMR assignments of the compounds **8a–d** and **9b–d** were based on the data obtained from 1D ^{1}H, ^{13}C, ^{19}F and various 2D experiments.

The ^{1}H chemical shifts are shown in Table 1, the resolved ^{1}H coupling constants are presented in Table 2, the ^{13}C chemical shifts are given in Table 3, and the ^{19}F chemical shifts and the $^{13}C–^{19}F$ coupling constants observed by ^{13}C NMR spectroscopy are given in Table 4.

The shift values of the three pyrrolopyrimidine protons (H-2, H-5 and H-7) were mainly depending on benzylic moiety in position 4, and not the fluorine substitution pattern. The H-2 proton appeared as a singlet residing at 8.04–8.11 ppm. The proton H-5 appeared at 6.84–6.98 ppm as doublets and couplings were observed to the pyrrole protons H-7. Broadening of the H-5 and H-7 signals was pronounced. The coupling between H-5 and H-7 could not be detected by ^{1}H NMR for compound **8b**, although its presence was evidenced by COSY. The proton signals from the 4-methoxyphenyl group, which is distant from the structural variations, had only small differences in shift values for compounds **8a–d** and **9b–d**. The amine proton H-15 appeared as a doublet in the derivatives **8a–d** and as a triplet for compounds **9b–d**. Assignment of proton shifts for the aromatic part of the benzylamine unit was aided by COSY, HMBC and HSQC, and by $^{13}C–^{19}F$ coupling constants from ^{13}C NMR. Owing to fluorine coupling, complex splitting patterns were observed in ^{1}H NMR.

The ^{13}C NMR spectra data (Table 3) showed only minor variation in the pyrrolopyrimidine and the 4-methoxyphenyl units over the series. Assignment of the pyrrolopyrimidine carbons was aided by HMBC, and the most important HMBC correlations are shown in Fig. 2. The carbons C-2 and C-8 had almost identical shift values (151.3–151.8), and the assignments were also aided by

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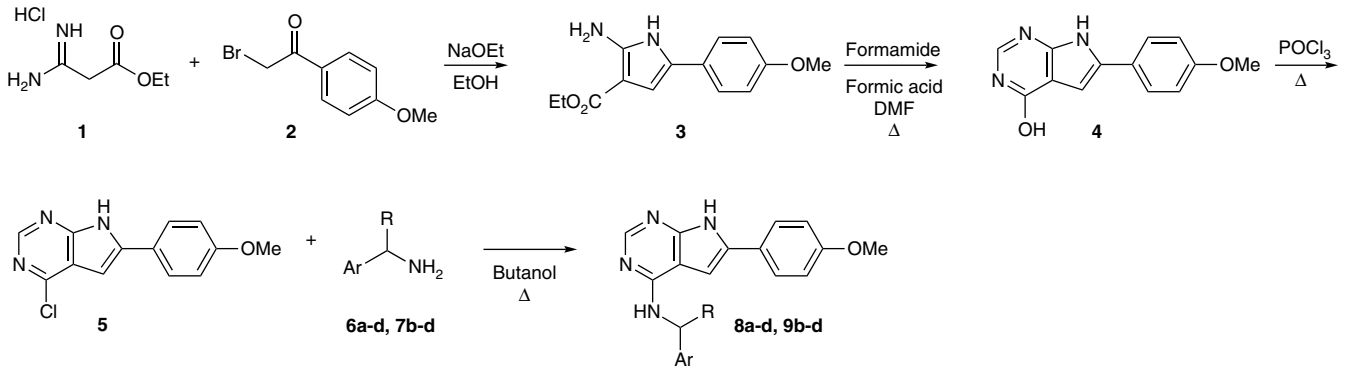

Scheme 1. Synthetic route to the target compounds **8a–d** and **9b–d**. Ar = C_6H_5 (**a**), *p*-F-C_6H_4 (**b**), *m*-F-C_6H_4 (**c**), *o*-F-C_6H_4 (**d**), R = CH_3 (**6** and **8**) and H (**7** and **9**).

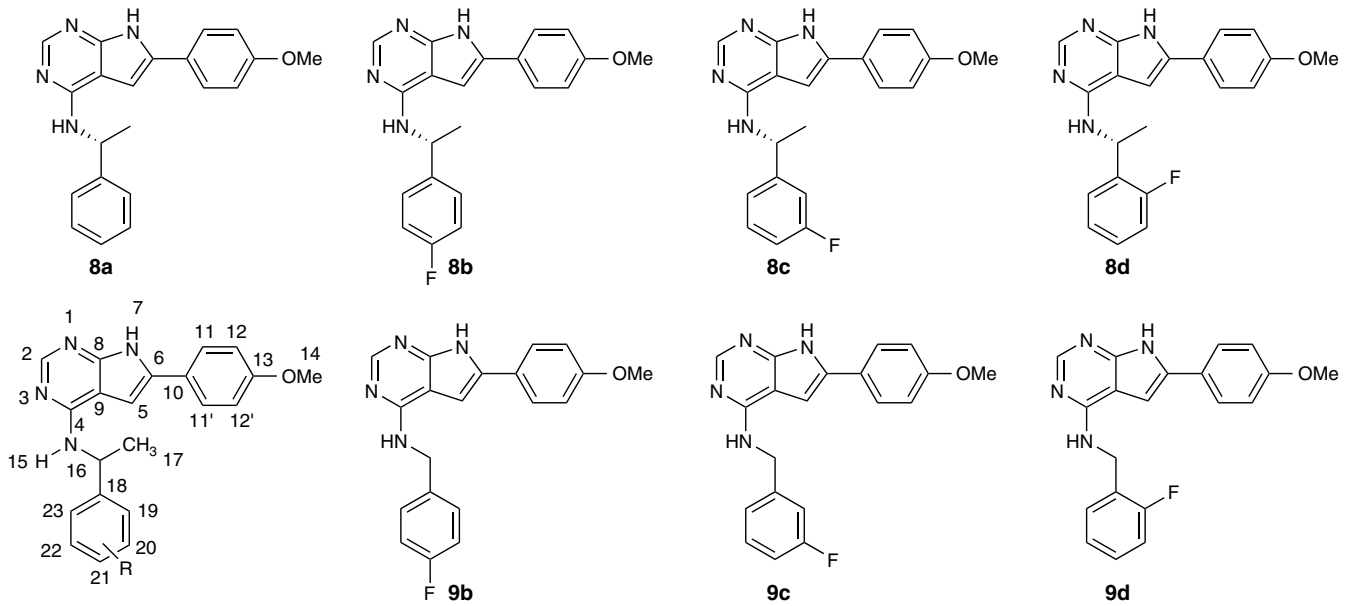

Figure 1. Structure of the compounds in the study.

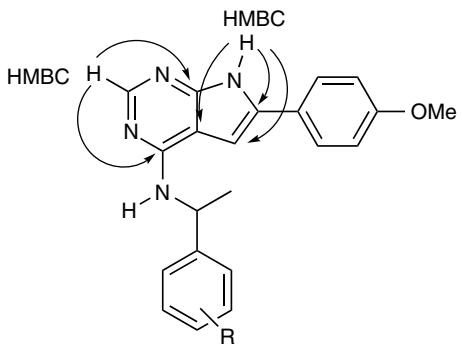

Figure 2. HMBC correlations in the pyrrolopyrimidine substructure.

HSQC showing correlation between C-2 and the attached proton (8.03–8.11 ppm).

The carbon at the stereogenic centre (C-16) in compounds **8a–d** and the benzylic carbon (C-16) in **9b–d** had shift values depending on the substitution pattern. Fluorine induced a shielding effect, being most pronounced for the *ortho*-substituted derivatives, **8d** and **9d**.

The ^{13}C NMR spectroscopic shifts of the aromatic carbons C-18 to C-23 experienced the usual shielding/deshielding effect caused by fluorine. For compounds **8b–d**, the aromatic carbons directly attached to the fluorine were deshielded by 33.6–34.2 ppm. The carbons in *ortho* position to the fluorine were shielded by 13.0–13.5 ppm, the carbons in *meta* position were deshielded by 1.1–3.3 ppm and those being in *para* position were shielded by 3.8–3.9 ppm, all compared with the parent compound **8a**.

The ^{19}F chemical shifts (Table 4) were also dependant on the position of the fluorine atom. The highest ^{19}F chemical shifts were observed for the *ortho*-substituted derivatives **8d** and **9d**, whereas the *meta*-substituted derivative had the lowest ^{19}F chemical shifts.

The $^{13}C-^{19}F$ coupling constants as detected by ^{13}C NMR are shown in Table 4. The $^{1}J_{CF}$ coupling constants varied between 241.6 and 244.7 Hz, with the *ortho*-derivatives **8d** and **9d** having the highest coupling constants. The $^{2}J_{CF}$ and $^{3}J_{CF}$ coupling constants were within the expected range, except for the derivatives **8d** and **9d**, where lower value of the coupling constant was observed for the $^{2}J_{CF}$ coupling to C-18 and $^{3}J_{CF}$ coupling to C-23.

Table 1. ^{1}H NMR chemical shifts (δ, ppm) of **8a–d** and **9b–d** in DMSO-d_6 at 298 K

	8a	8b	8c	8d	9b	9c	9d
Pyrrolopyrimidine							
H-2	8.04 (s)	8.04 (s)	8.04 (s)	8.03 (s)	8.10 (s)	8.11 (s)	8.10 (s)
H-5	6.96 (br, d)	6.94 (s)	6.94 (d)	6.98 (br, d)	6.84 (d)	6.86 (d)	6.88 (d)
H-7 (NH)	11.91 (br, s)	11.92 (s)	11.94 (s)	11.94 (br, d)	11.96 (s)	11.99 (s)	11.98 (s)
6-(4-methoxyphenyl)							
H-11 and H-11′	7.73 (d)	7.72 (d)	7.73 (d)	7.73 (d)	7.71 (d)	7.73 (d)	7.72 (d)
H-12 and H-12′	7.02 (d)	7.02 (d)	7.02 (d)	7.03 (d)	7.02 (d)	7.02 (d)	7.02 (d)
H-14 (OMe)	3.80 (s)	3.80 (s)	3.80 (s)	3.80 (s)	3.79 (s)	3.79 (s)	3.79 (s)
4-Amino group							
H-15 (NH)	7.73 (d)	7.72[a]	7.76 (d)	7.79 (d)	7.95 (t)	7.99 (t)	7.92 (t)
H-16	5.50 (m)	5.48 (m)	5.49 (m)	5.71 (m)	4.71 (d)	4.75 (d)	4.77 (d)
H-17	1.53 (d)	1.52 (d)	1.53 (d)	1.53 (d)	–	–	–
H-19	7.45 (m)	7.46 (m)	7.23 (m)	–	7.40 (m)	7.16 (m)	–
H-20	7.30 (m)	7.12 (m)	–	7.11–7.18 (m)	7.14 (m)	–	7.20
H-21	7.19 (m)	–	7.00 (m)	7.26 (m)	–	7.07 (m)	7.30
H-22	7.30 (m)	7.12 (m)	7.32–7.37 (m)	7.11–7.18 (m)	7.14 (t)	7.36 (m)	7.15
H-23	7.45 (m)	7.46 (m)	7.32–7.37 (m)	7.47 (m)	7.40 (m)	7.20 (m)	7.41

[a] Signal interferes with signals from protons H-11/H-11′.

Table 2. Resolved coupling constants (Hz) for **8a–d** and **9b–d** in DMSO-d_6 at 298 K

	8a	8b	8c	8d	9b	9c	9d
J							
H-5, H-7	1.8	[a]	1.9	1.4	1.3	1.9	1.3
H-11, H-12	8.8	8.6	8.8	8.8	8.7	8.8	8.7
H-15, H-16	8.7	NR[b]	8.3	7.8	5.8	5.9	5.7
H-16, H-17	7.1	7.1	7.1	NA	NA	NA	NA

[a] Both signals appeared as singlets.
[b] Not resolved due to overlapping with H-11/H-11′.

Table 3. ^{13}C NMR chemical shifts (δ, ppm) of **8a–d** and **9b–d** in DMSO-d_6 at 298 K

	8a	8b	8c	8d	9b	9c	9d
Pyrrolopyrimidine							
C-2	151.3	151.3	151.3	151.3	151.3	151.2	151.8
C-4	154.8	154.7	154.7	154.5	155.4	155.3	155.8
C-5	94.6	94.5	94.5	94.5	94.3	94.2	94.7
C-6	133.5	133.6	133.7	133.7	133.7	133.9	134.2
C-8	151.4	151.4	151.4	151.4	151.4	151.3	151.8
C-9	103.9	103.9	103.9	104.0	103.9	103.9	104.4
6-(4-Methoxyphenyl)							
C-10	124.5	124.5	124.5	124.4	124.4	124.4	124.8
C-11 and C-11′	125.9	125.9	126.0	125.9	125.9	126.0	126.4
C-12 and C-12′	114.4	114.4	114.5	114.4	114.4	114.4	114.9
C-13	158.6	158.7	158.7	158.7	158.7	158.7	159.1
C-14 (OMe)	55.2	55.2	55.2	55.2	55.2	55.2	55.6
4-Amino group							
C-16	50.0	48.1	48.4	43.2	42.4	42.7	37.4
C-17	22.9	22.9	22.8	21.9	–	–	–
C-18	145.6	141.7	148.9	132.5	136.5	143.6	127.3
C-19	126.0	127.9	112.7	159.6	129.1	113.7	160.6
C-20	128.1	114.8	162.3	115.1	114.9	162.2	115.4
C-21	126.7	160.9	113.2	128.3	161.1	113.3	129.1
C-22	128.1	114.8	130.1	124.3	114.9	130.2	124.7
C-23	126.0	127.9	122.2	127.1	129.1	123.1	129.8

Experimental

NMR spectroscopy

All NMR data were recorded using a Bruker Avance DPX 400 spectrometer (XWIN-NMR 3.5 software) operating at a proton frequency of 400.13 MHz. A 5 mm dual probe equipped with z-gradient was used for 1D and 2D ^{1}H and ^{13}C observing experiments, whereas a 5 mm QNP probe was used for ^{19}F NMR. The samples containing a solution of 15 mg of substances **8a–d** and **9b–d** in DMSO-d_6 were measured at 298 K. For ^{1}H and ^{13}C experiments, solvent signals were used as reference. Reference compound for ^{19}F NMR was hexafluorobenzene. Following 1D and 2D pulse, sequences from the Bruker user library were used for the NMR experiments:

^{1}H 1D (400 MHz): $\pi/2$ pulse for ^{1}H 11.5 µs, spectral width 8 kHz, acquisition time 3.96 s, relaxation delay 1.0 s, the 16-transient free-induction decay was collected with 64 K data points.

^{13}C 1D (100 MHz): $\pi/2$ pulse for ^{13}C 9.0 µs, spectral width 23 kHz, acquisition time 2.83 s, WALTZ proton decoupling during acquisition, relaxation delay 0.5 s, the 5600-transient free-induction decay was collected with 128 K data points.

DEPT135 (100 MHz): $\pi/2$ pulse for ^{13}C 9.50 µs, spectral width 24 kHz, acquisition time 1.37 s, WALTZ proton decoupling during acquisition, relaxation delay 2.0 s, the 1400-transient free-induction decay was collected with 64 K data points.

DEPT90 (100 MHz): $\pi/2$ pulse for ^{13}C 7.40 µs, spectral width 22 kHz, acquisition time 0.74 s, WALTZ proton decoupling during acquisition, relaxation delay 1.8 s, the 1400-transient free-induction decay was collected with 32 K data points.

Table 4. ^{19}F chemical shift (δ, ppm) and $^{13}C-^{19}F$ coupling constants (Hz) resolved for **8b–d** and **9b–d** in DMSO-d_6 at 298 K

	8b	8c	8d	9b	9c	9d
^{19}F (δ)	−116.2	−113.0	−119.2	−115.6	−113.1	−118.5
$^{1}J_{CF}$	241.6 (C-21)	242.4 (C-20)	243.7 (C-19)	242.9 (C-21)	242.7 (C-20)	244.7 (C-19)
$^{2}J_{CF}$	21.2 (C-20)	21.5 (C-19)	14.1 (C-18)	21.2 (C-20)	21.5 (C-19)	14.8 (C-18)
$^{2}J_{CF}$	21.2 (C-22)	21.2 (21)	21.6 (C-20)	21.2 (C-22)	20.8 (21)	21.2 (C-20)
$^{3}J_{CF}$	8.1 (C-19)	6.7 (C-18)	8.1 (C-21)	8.1 (C-19)	7.1 (C-18)	7.8 (C-21)
$^{3}J_{CF}$	8.1 (C-23)	8.5 (C-22)	4.6 (C-23)	8.1 (C-23)	8.1 (C-22)	4.6 (C-23)
$^{4}J_{CF}$	3.2 (C-18)	2.5 (C-23)	3.5 (C-22)	2.5 (C-18)	2.5 (C-23)	3.5 (C-22)

Hexafluorobenzene was used as internal standard in the ^{19}F experiments.

HSQC (400/100 MHz) – 2D $^{1}H/^{13}C$ correlation via double inept transfer, phase sensitive using echo/antiecho-TPPI gradient selection, with decoupling during acquisition, using trim pulses in inept transfer: $\pi/2$ pulse for ^{1}H 10.5 µs, spectral width in F_2 5 kHz, carrier at 7 ppm, acquisition time 0.20 s, relaxation delay 1.0 s, 16 transients per increment, 128 complex data points in F_1, spectral width in F_1 22 kHz, decoupler at 110 ppm, GARP decoupling, linear prediction in F_1 up to 1 K complex data points.

HMBC (400/100 MHz) – 2D $^{1}H/^{13}C$ correlation via heteronuclear zero and double quantum coherence, optimised for long-range couplings, no decoupling during acquisition, using gradient pulses for selection: $\pi/2$ pulse for ^{1}H 10.5 µs, spectral width in F_2 5 kHz, carrier at 7 ppm, acquisition time 0.10 s, relaxation delay 0.9 s, 32 transients per increment, 256 complex data points in F_1, spectral width in F_1 22 kHz, decoupler at 110 ppm, linear prediction in F_1 up to 1 K real data points.

$^{1}H,^{1}H$ COSY (400 MHz) – 2D homonuclear shift correlation, using gradient pulses for selection: $\pi/2$ pulse for ^{1}H 9.25 µs, spectral width in F_2 5 kHz, carrier at 7 ppm, acquisition time 0.20 s, relaxation delay 0.75 s, 12 transients per increment, 256 complex data points in F_1, spectral width in F_1 5 kHz, zero filling in F_1 up to 1 K complex data points.

^{19}F 1D (376 MHz): $\pi/2$ pulse for ^{19}F 12.0 µs, spectral width 75 kHz, acquisition time 0.44 s, relaxation delay 3.0 s, carrier at −100 ppm, the 16-transient free-induction decay was collected with 64 K data points.

Synthesis

(*R*)-1-Phenylethanamine (**6a**), ethyl cyanoacetate and 2-bromo-1-(4-methoxyphenyl)ethanone (**2**) were from Fluka. (*R*)-1-(4-Fluorophenyl)ethanamine (**6b**) and 2-fluorobenzylamine (**7d**) were from Alfa Aesar. (*R*)-1-(3-Fluorophenyl)ethanamine (**6c**) and (*R*)-(2-fluorophenyl)ethanamine (**6d**) were from Apollo Scientific, whereas 4-fluorobenzylamine (**7b**), 3-fluorobenzylamine (**7c**) and phosphorus oxychloride were from Sigma-Aldrich. Accurate mass determination (ESI) was performed on an Agilent G1969 TOF MS instrument equipped with a dual electrospray ion source. Samples were injected into the MS using an Agilent 1100 series HPLC, and analysis was performed as a direct injection analysis without any chromatography. All melting points are uncorrected and measured by a Büchi melting point instrument. Optical rotations were measured using sodium D line at 589 nm on a Perkin-Elmer 243 B polarimeter. Synthesis of ethyl amidinoacetate hydrochloride (**1**)[12,13]: Compound **1** was synthesised as previously described,[12,13] starting with ethyl cyanoacetate (18.16 g, 160.55 mmol). This yielded 22.99 g (137.99 mmol, 86%) of **1** as a colourless solid, mp 105–107 °C (Ref. [12], 104 °C) ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.22 (s, 2H), 8.95 (s, 2H), 4.15 (q, 2H), 3.64 (s, 2H), 1.22 (t, 3H) ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.7, 164.2, 61.8, 38.0, 14.4. Synthesis of 2-amino-3-carboxethyl-5-(4-methoxyphenyl)-pyrrole (**3**)[8,14]: Compound **1** (13.87 g, 83.25 mmol) and absolute ethanol (60 mL) were mixed under an argon atmosphere at 0 °C. Sodium ethoxide (5.92 g, 86.99 mmol) was then added and the mixture was allowed to stir for 15 min before allowed to heating at 20 °C. 2-Bromo-1-(4-methoxyphenyl)ethanone (**2**) (10.78 g, 47.06 mmol) was then added and the temperature was adjusted to 60 °C. After 1 h, the solvent was evaporated at reduced pressure and the residue taken up in water (30 mL) and EtOAc (70 mL). The water fraction was removed and the organic layer was washed three times with water (3 × 20 mL) and brine (30 mL). The combined water fractions were back extracted with EtOAc (2 × 50 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (*n*-hexane/EtOAc, 4/6). The obtained residue was triturated with diethyl ether (25 mL) and *n*-hexane (45 mL). The beige solid obtained was isolated by filtration and washed with *n*-hexane (60 mL), giving 9.47 g (36.38 mmol, 77%), mp 146–147 °C (Ref. [14], 141–142 °C). ^{1}H NMR corresponded well with the reported data.[8] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.63 (s, 1H), 7.41(d, 2H), 6.89 (d, 2H), 6.31 (d, 1H), 5.60 (s, 2H), 4.13 (q, 2H), 3.74, (s, 3H), 1.24 (t, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.0, 157.1, 147.8, 125.2, 123.8 (2C), 123.3, 114.1 (2C), 101.8, 93.1, 58.0, 55.0, 14.7. Synthesis of 4-hydroxy-6-(4-metoxyphenyl)-7*H*-pyrrolo-[2.3-*d*]-pyrimidine (**4**)[8,14]: anhydrous DMF (20 mL), formic acid (24 mL), formamide (76 mL) and **3** (13.01 g, 49.99 mmol) were mixed and reacted under argon at 150 °C for 19 h. *i*-PrOH (20 mL) was added and the mixture was cooled to 20 °C. The precipitate formed was isolated by filtration, washed with *i*-PrOH (30 mL) and *n*-hexane (3 × 10 mL), and dried under reduced pressure. This yielded 7.79 g (32.29 mmol, 65%) of an off-white solid, mp >300 °C (Ref. [8], >300 °C). ^{1}H NMR corresponded well with the reported data.[8] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.22 (s, br, 1H), 11.81 (s, br, 1H), 7.85 (s, 1H), 7.76 (d, 2H), 6.98 (d, 2H), 6.79 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1, 158.5, 149.5, 143.7, 133.7, 126.4 (2C), 124.6, 114.7 (2C), 109.5, 98.2, 55.6. Synthesis of compound **5**[8,14]: Under a nitrogen atmosphere compound **4** (1.74 g, 7.21 mmol) and phosphorus oxychloride (13.5 mL, 53.50 mmol) were mixed and heated at reflux for 2.5 h. Then the mixture was quenched by the addition of ice (200 mL), and the pH of the solution was adjusted to pH 7 using NaOH (8 M, 75 mL). The mixture was extracted using EtOAc (4 × 400 mL), and the combined organic extracts were washed with brine (2 × 200 mL).

Drying over $MgSO_4$ and concentration in vacuum yielded 1.83 g (7.06 mmol, 98%) of a yellow solid, mp 248–249 °C (Ref. [14] 248–249 °C). ^{1}H NMR corresponded well with the reported data.[8] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.90 (s, 1H), 8.55 (s, 1H), 7.95 (m, 2H), 7.06 (m, 2H), 6.96 (d, J = 2.1, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.0, 153.0, 150.0, 149.2, 140.5, 127.5 (2C), 122.7, 118.0, 114.5 (2C), 94.0, 55.3. Synthesis of **8a**[8,15]: Under an argon atmosphere, compound **5** (275 mg, 1.06 mmol), 1-butanol (3.5 mL) and (*R*)-1-phenylethanamine (**6a**) (486 mg, 4.01 mmol) were mixed and reacted at 145 °C for 24 h. Upon cooling the reaction mixture to 20 °C, a precipitate was formed, which was isolated by filtration and washed with diethyl ether (25 mL). This yielded 260 mg (0.75 mmol, 71%) of a white solid, mp 218–220 °C, $[\alpha]_D^{22} = -353.3$ (c = 0.11, DMSO), HRMS (ESI, *m/z*): *m/z* 345.1715 (calcd $C_{21}H_{21}N_4O^+$, M+H$^+$, 345.1710). Synthesis of **8b**[8]: Synthesis was performed as described for **8a**, starting with **5** (142 mg, 0.55 mmol), and (*R*)-1-(4-fluorophenyl)ethanamine (**6b**) (308 mg, 2.22 mmol). This yielded 133 mg (0.37 mmol, 67%) of an off-white solid, mp 234–236 °C, $[\alpha]_D^{22} = -315.9$ (c = 0.16, DMSO), HRMS (ESI, *m/z*): *m/z* 363.1630 (calcd $C_{21}H_{20}FN_4O^+$, M+H$^+$, 363.1616). Synthesis of **8c**: Synthesis was performed as described for **8a**, starting with **5** (229 mg, 0.88 mmol) and (*R*)-(3-fluorophenyl)ethanamine (**6c**) (431 mg, 3.10 mmol). This yielded 236 mg (0.65 mmol, 74%) of a slight yellowish solid, mp 235–236 °C, $[\alpha]_D^{22} = -347.3$ (c = 0.13, DMSO), HRMS (ESI, *m/z*): 363.1613 (calc. $C_{21}H_{20}FN_4O^+$, M+H$^+$, 363.1616). Synthesis of **8d**: Synthesis was performed as described for **8a**, starting with **5** (186 mg, 0.72 mmol) and (*R*)-(2-fluorophenyl)ethanamine (**6d**) (401 mg, 2.88 mmol). This yielded 183 mg (0.50 mmol, 70%) of an off-white solid, mp 217–219 °C, $[\alpha]_D^{22} = -375.9$ (c = 0.13, DMSO), HRMS (ESI, *m/z*): 363.1615 (calcd $C_{21}H_{20}FN_4O^+$, M+H$^+$, 363.1616). Synthesis of **9b**: Compound **5** (178 mg, 0.69 mmol), 4-fluorobenzylamine (**7b**) (198 mg, 1.51 mmol) and 1-butanol (3.0 mL) were mixed and reacted at 145 °C under an argon atmosphere for 24 h. Upon cooling the reaction mixture to 20 °C, a precipitate was formed, which was isolated by filtration and washed with diethyl ether (15 mL). The material obtained was suspended in saturated K_2CO_3 (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic fraction was washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuum. This yielded 187 mg, (0.54 mmol, 78%) of a slightly yellowish solid, mp 290–292 °C, HRMS (ESI, *m/z*): 349.1460 (calcd $C_{20}H_{18}FN_4O^+$, M+H$^+$, 349.1459). Synthesis of **9c**: Synthesis was performed as described for **9b** starting with **5** (97 mg, 0.37 mmol), 3-fluorobenzylamine (**7c**) (140 mg, 1.12 mmol). This yielded 98 mg (0.28 mmol, 76%) of an off-white solid, mp 284–285 °C, HRMS (ESI, *m/z*): 349.1455 (calcd $C_{20}H_{18}FN_4O^+$, M+H$^+$, 349.1459). Synthesis of **9d**: Synthesis was performed as described for **9b**, starting with **5** (186 mg, 0.72 mmol) and 2-fluorobenzylamine **7d** (270 mg, 2.16 mmol) This yielded 183 mg (0.53 mmol, 73%) of an off-white solid, mp 234–235 °C, HRMS (ESI, *m/z*): 349.1452 (calcd $C_{20}H_{18}FN_4O^+$, M+H$^+$, 349.1459).

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