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Pyrrolo-dihydropteridines via a cascade reaction consisting of iminium cyclization and O–N Smiles rearrangement

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ABSTRACT

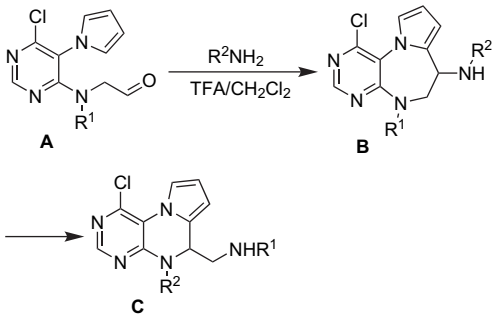
The reactions of 5-pyrrolyl-pyrimidinyloxyacetaldehyde or methyl ketone with primary amines yielded hydroxymethylpyrrolopteridine derivatives via a cascade of iminium cyclization and O–N Smiles rearrangement. The present cascade exhibited a different profile compared to the previously reported ones, which consisted of N–N Smiles rearrangement. Lewis acid ($TiCl_4$) under carefully controlled conditions was employed to suppress the competing formation of imine dimers to give the desired heterocycles. A plausible mechanism involving the iminium cyclization and Smiles rearrangement is proposed. This methodology has been used to generate a series of 6-hydroxymethylpyrrolo[1,2-*f*]pteridine derivatives with potential biological activities.

1. Introduction

Pyrimidine moiety, as a structural component of several key biomolecules, has been widely explored in designing privileged structures in medicinal chemistry and has attracted much great attention of organic and medicinal chemists.[1] Its fused bicyclic analogs, pteridines, have been reported to exhibit a variety of biological activities and constitute the backbones of several marketed drugs. For example, methotrexate (MTX) is used as an anti-tumor agent and triamterene as diuretics. In addition, some pteridine derivatives are reported to have potent inhibitory activity against biological targets.[2] Despite interesting biological activities exhibited by pteridines, few methodologies are available for the synthesis of pyrrolo[1,2-*f*]pteridines.[3] Therefore, efficient synthetic methods to access pyrrolo[1,2-*f*]pteridines are desired.

Tandem reactions are often developed as efficient strategies in the synthesis of complex organic molecules, since they enable multiple transformations via a series of cascade reactions.[4] For example, tandem reactions have been applied to the synthesis of a number of important nitrogen-containing natural products.[4b,5] The success of tandem reactions provides the impetus to new synthetic strategies that combine existing reactions into new single-operation tandem reactions. Iminium cyclization reactions have been widely used for C–C bond formation to build various nitrogen ring systems. As an attractive strategy, both *endo*-cyclizations and *exo*-cyclizations have been reported.[6] Another important reaction often reported in the synthesis of condensed heterocyclic systems is the Smiles rearrangement.[7] We have successfully combined the iminium cyclization reaction with a N–N Smiles rearrangement reaction and developed an unique cascade reaction to efficiently access pyrrolo[1,2-*f*]pteridines (Scheme 1).[3c]

As a result of our investigation on the scope of this new cascade reaction, we have demonstrated that this strategy can be extended to a similar pyridine system with an O–N Smiles rearrangement.[8] To further explore the scope of these types of cascade reactions, it is logical to investigate the potential of combining iminium cyclization reactions with an O–N Smiles rearrangement within a pyrimidine system as outlined in Scheme 2. Herein, the results from such investigations are reported.



Scheme 1. Tandem iminium cyclization and N–N Smiles rearrangement.

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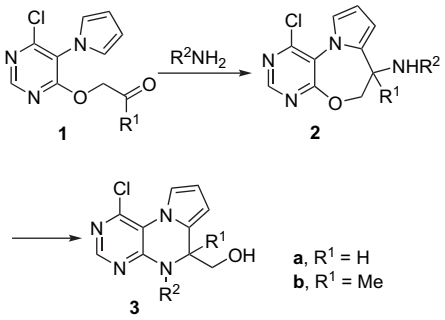
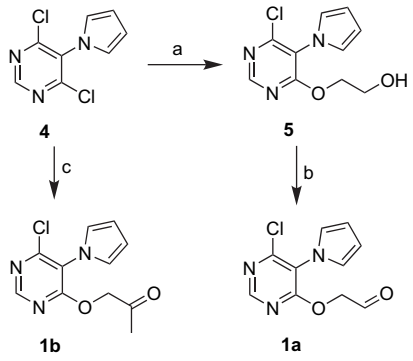


Scheme 2. Tandem iminium cyclization and O–N Smiles rearrangement.

2. Results and discussion

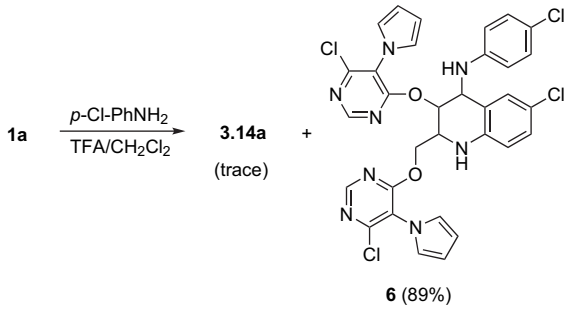
The starting aldehyde **1a** and ketone **1b** were prepared from 4,6-dichloro-5-pyrrolylpyrimidine **4** according to a procedure analogous to its nitrogen analogue (Scheme 3).[3c] Nucleophilic substitution of dichloropyrimidine **4** by ethyleneglycol in the presence of K_2CO_3 in DMF afforded **5** in 80% yield. Alcohol **5** was oxidized by Parikh–Doering oxidation[9] to its corresponding aldehyde **1a** in 67% yield. Aldehyde **1a** was surprisingly stable to silica gel column chromatography purification. In contrast, the corresponding amino aldehyde (compound **A** in Scheme 1) readily cyclized to form a diazepine on a silica gel column. Starting ketone **1b** was synthesized through nucleophilic substitution of dichloropyrimidine **4** by hydroxyacetone in 77% yield.



Scheme 3. Synthesis of starting materials **1**. Reagents and conditions: (a) $HO(CH_2)_2OH$, K_2CO_3, $MgSO_4$, DMF, room temperature, 12 h, 80%; (b) $Pyr{\cdot}SO_3$, $DMSO/CH_2Cl_2$ (1:1), room temperature, 35 min, 67%; (c) $HOCH_2COCH_3$, K_2CO_3, $MgSO_4$, DMF, room temperature, 7 h, 77%.

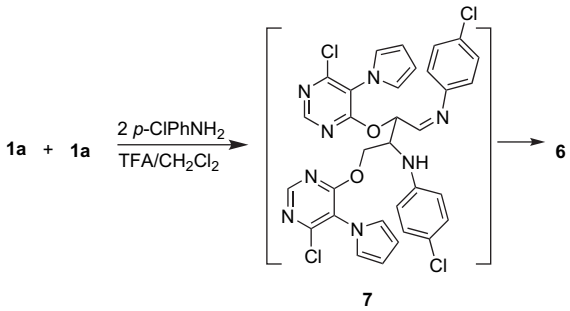
Initially, pyrimidine aldehyde **1a** was treated with *p*-chloroaniline under our previously reported TFA reaction condition.[3c] Unfortunately, only trace amount of the desired 6-hydroxymethylpyrrolo[1,2-*f*]pteridine **3.14a** was observed by LC–MS, but instead a product with higher molecular weight ($M+Na^+=715.0$) was obtained. Extensive characterization by MS, NMR, and HRMS confirmed the by-product as the diastereoisomeric mixture of compound **6**, a 1,2,3,4-tetrahydroquinoline derivative (Scheme 4).

The formation of compound **6** could be attributed to iminium cyclization of intermediate **7** derived from aldol condensation of two molecules of **1a** followed by Michael addition and formation of imine with aniline under the strong acidic condition of TFA (Scheme 5). This rationalization was supported by the fact that the employment of *p*-nitroaniline completely suppressed the formation of corresponding by-product to give the desired product **3.17a** in 86% yield since the strong electron-withdrawing nitro group deactivated the phenyl ring of aniline as an acceptor of the iminium ion, which also indicated that the last step was irreversible. The



Scheme 4. Tandem reaction with *p*-chloroaniline promoted by TFA.

formation of 1,2,3,4-tetrahydroquinoline from aliphatic aldehydes and arylamines has been precedented in the literature.[10]



Scheme 5. Proposed path to structure **6**.

The above results prompted us to search for milder reaction conditions. Thus, various acids and solvents were screened for the reactions of aldehyde **1a** and *p*-chloroaniline to accommodate electron-rich anilines, and the results are summarized in Table 1.

Since Smiles rearrangement was reported to occur in the presence of protic acids,[11] other protic acids, such as AcOH and TsOH

Table 1
Optimization results in conversion of **1a** to **3.14a**

Entry	Solvent	Temp (°C)	Time (h)	Acid (equiv)	**3.14a**/**6**[a]
1	CH_2Cl_2	24	0.25	TFA (0.6)	5:95
2	CH_2Cl_2	24	3.0	AcOH (0.6)	2:98
3	CH_2Cl_2	24	3.0	TsOH (0.04)	1:99
4	CH_2Cl_2	24	0.25	$BF_3{\cdot}Et_2O$ (0.7)	5:95
5	Dioxane	24	0.25	$BF_3{\cdot}Et_2O$ (0.7)	2:98
6	THF	24	0.25	$BF_3{\cdot}Et_2O$ (0.7)	1:99
7	Toluene	24	0.25	$BF_3{\cdot}Et_2O$ (0.7)	1:99
8	CH_3CN	24	0.25	$BF_3{\cdot}Et_2O$ (0.7)	22:78[b]
9	CH_3CN	24	1.5	TFA (0.6)	6:94
10	CH_3CN	24	0.6	$ZnCl_2$ (0.05)	N.R.[c]
11	CH_3CN	24	0.25	$SnCl_4$ (0.8)	6:94
12	CH_3CN	24	0.6	$FeCl_3$ (0.04)	5:95
13	CH_3CN	24	0.6	TMSCl (0.4)	14:86
14	CH_3CN	24	0.6	TfOTMS (0.3)	13:87
15	CH_3CN	24	1.0	$TiCl_4$ (1.0)	43:56
16	CH_3CN	0	0.6	$TiCl_4$ (1.0)	51:49
17	CH_3CN	−15 to 24	1.5	$TiCl_4$ (1.0)	72:28
18	CH_3CN	50	0.25	$TiCl_4$ (1.0)	45:55
19	CH_3CN	−15 to 24	1.5	$TiCl_4$ (1.0)[d]	45:55
20	**CH_3CN**	**−15 to 24**	**4.0**	**$TiCl_4$ (2.4)**	**100:0**[e]

[a] Ratio of products was estimated based on the peak areas of LC–ELSD. This ratio is only a reflection of conversions, but not the conversion ratio since the molecular weights of the two compounds are different and the peak areas of LC–ELSD may not be linear to the weights.

[b] The desired product **3.14a** was isolated in 26% yield.

[c] The reaction was heated to reflux for 2 h after stirring for 0.6 h at 24 °C and LC–ELSD showed the ratio of **3.14a**/**6** to be 2:98.

[d] $MgSO_4$ was added to trap moisture.

[e] The desired product **3.14a** was isolated in 70% yield.

were also investigated. However, these Brönsted acids did not lead to any improvement over the TFA condition (entries 1–3, Table 1). Lewis acids are generally viewed as milder alternatives to protic acids such as TFA, and they have been shown to promote iminium cyclization reactions such as Pictet–Spengler reactions.[12] To test the effectiveness of Lewis acids, the combination of $BF_3 \cdot Et_2O$ with various solvents was studied (entry 4–8, Table 1). We were encouraged by the combination of $BF_3 \cdot Et_2O$ as the catalyst and acetonitrile as the solvent, in which more desired product **3.14a** was generated compared to the ones with other solvents (entry 8 vs entries 4–7, Table 1) or the one of TFA and acetonitrile (entry 8 vs entry 9). More importantly, 26% yield of desired product **3.14a** was isolated. These results prompted us to screen other Lewis acids using acetonitrile as the solvent. Thus, a number of Lewis acids ($ZnCl_2$, $SnCl_4$, $FeCl_3$, TMSCl, TfOTMS, and $TiCl_4$) were investigated (entries 10–15). Among them, $TiCl_4$ (1.0 equiv) promoted the cascade reaction more effectively than $BF_3 \cdot Et_2O$ (entry 15 vs entry 8, Table 1). Finally, the $TiCl_4$-promoted cascade reaction in CH_3CN was further optimized at various reaction temperatures and with the stoichiometry of $TiCl_4$ (entries 16–20, Table 1). The by-product **6** was completely suppressed by using 2.4 equiv $TiCl_4$ at −15 °C (entry 20, Table 1), and the desired rearrangement product **3.14a** was isolated in 70% yield. It is also noted that no intermediate oxazepine **2.14a** was observed (Scheme 2), which indicated that O–N Smiles rearrangement was indeed faster than the N–N version as expected.

To explore the scope of this cascade reaction, a number of amines were studied under the above optimized reaction conditions using $TiCl_4$ as the promoter. The results are summarized in Table 2.

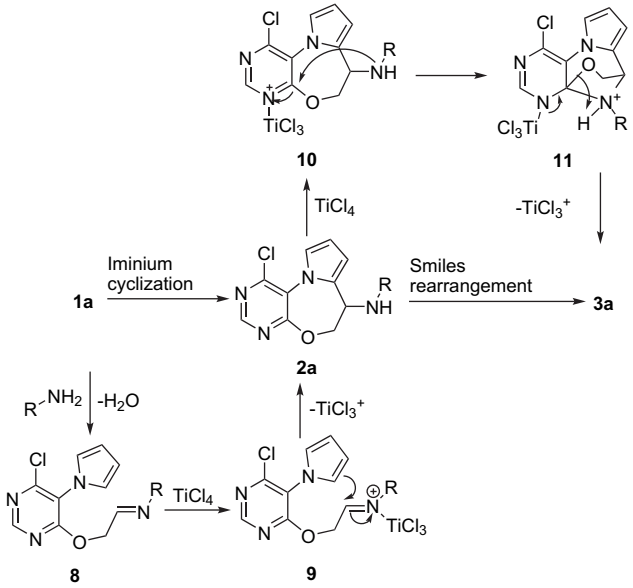
As disclosed in Table 2, various amines ranging from ammonia to aliphatic and aromatic amines are compatible to this reaction conditions to produce the expected pyrrolo[1,2-*f*]pteridines **3** in moderate to good yields when R^1=H (Scheme 2). Higher product yields were obtained when aromatic amines with an electron-withdrawing group were employed. Higher yields were obtained with benzylamine and *n*-butylamine compared to cyclohexylamine and isopropylamine. The presence of an *ortho* substituent of the aromatic amine led to lower yields of the final products **3** compared to the corresponding *meta*- and *para*-substituted analogs. These results indicate that the steric effect of substrate amine is important in this cascade of reactions. However, the reaction of *ortho*-MeO substituted aniline did generate the desired product **3.9a** (entry 9) compared to *ortho*-Cl substitution that failed to produce **3.8a** (entry 8), which indicated that this tandem reaction is sensitive to electronic effects at the *ortho* position. In addition, ketone **1b** gave only 18% of the desired product **3.7b** under reflux conditions and no pre-Smiles rearrangement intermediate **2.7b** was obtained. This result is consistent with an iminium cyclization as the rate determining step since a ketone is less reactive than an aldehyde in the imine formation.[13]

Table 2
The $TiCl_4$-promoted cascade reactions (Scheme 2)

Entry	Compd	R^1	R^2	Time (h)	Yield[a] (%)
1	**3.1a**	H	Bn	12	60
2	**3.2a**	H	H[b]	12	32
3	**3.3a**	H	Me[c]	5.0	48
4	**3.4a**	H	*n*-Bu	7.5	40
5	**3.5a**	H	Cyclohexyl	10	22
6	**3.6a**	H	*i*-Pr	12	12
7	**3.7a**	H	Ph	4.0	55
8	**3.8a**	H	*o*-ClPh	4.0	Trace
9	**3.9a**	H	*o*-MeOPh	4.0	25
10	**3.10a**	H	*o*-MePh	4.0	23[d]
11	**3.11a**	H	*m*-MePh	4.0	53
12	**3.12a**	H	*p*-MePh	4.0	50
13	**3.13a**	H	*p*-MeOPh	4.0	38
14	**3.14a**	H	*p*-ClPh	12	70
15	**3.15a**	H	*p*-BrPh	4.0	71
16	**3.16a**	H	*p*-FPh	4.0	52
17	**3.17a**	H	*p*-NO_2Ph	4.0	73
18	**3.7b**	Me	Ph	5.0[e]	18

[a] All reactions were performed on 0.5 mmol scale using 2.4 equiv $TiCl_4$ in acetonitrile at −15 to 24 °C.
[b] Ammonia/methanol was used.
[c] Methylamine alcohol solution (27–32%) was used.
[d] About 23% of atropisomer was observed by ^{1}H NMR conclusion.
[e] Refluxed.

A plausible mechanism involving Lewis acid promoted iminium cyclization and Smiles rearrangement for the above tandem process is outlined in Scheme 6. Pyrimidine aldehyde **1a** could react with an amine in presence of $TiCl_4$ to give an imine **8**, which could be coordinated by Ti^{4+} to form iminium ion-intermediate **9**. Electrophilic substitution of intermediate **9** at the electron-rich C-2 of the pyrrole ring could produce oxazepine **2a**.[14] Subsequently, intramolecular attack of the C-6 by the resulting secondary amine, which could be activated by the coordination of Ti^{4+} to N^1 of the pyrimidine ring, forming a bridged ring intermediate **11**. Finally, intermediate **11** could undergo an intramolecular rearrangement with loss of Ti^{4+} to yield pyrrolo[1,2-*f*]pteridine **3a**. This mechanism is consistent with the facts that Smiles rearrangement could be effected under various conditions (such as in the presence of a protic acid or a base or under thermal conditions)[11a] and iminium cyclization could be promoted by a Lewis acid.[12]



Scheme 6. Proposed mechanism for the iminium cyclization and O–N Smiles rearrangement.

The 4-Cl group in compound **3** was added by design to provide an entry to introduce an additional diversity point. For this purpose, compound **3.14a** was selected as representative example to examine their reactivity toward various nucleophiles as shown in Table 3. As expected, compounds **12** were obtained in good to excellent yields.

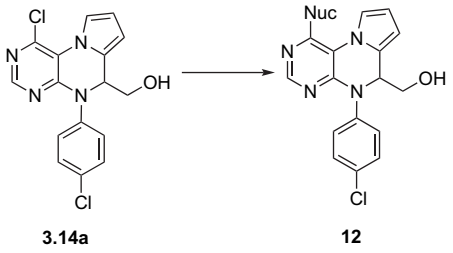


Table 3
Substitution with various nucleophiles

Entry	Compd	Nucleophile	Time (h)	Yield (%)
1	**12.1**	Pyrrolidin-1-yl[a]	10	98
2	**12.2**	PhS[a]	4.0	85
3	**12.3**	*n*-BuO[b]	20	59

[a] Reaction was conducted in the presence of K_2CO_3 in DMF.
[b] Reaction was conducted in butan-1-ol with NaH as the base.

In summary, the tandem iminium cyclization and O–N Smiles rearrangement of pyrrolopyrimidinyloxyacetaldehyde or methyl ketone and amines have been thoroughly investigated. The present cascade with O–N Smiles rearrangement exhibits a different reaction profile compared to the one with N–N Smiles rearrangement. While the previously reported TFA promoted conditions might lead to the formation of imine dimers, $TiCl_4$ under carefully controlled conditions can completely suppress the dimer formation to give the desired pyrrolo[1,2-*f*]pteridine **3** in high yield. A plausible mechanism involving iminium cyclization and Smiles rearrangement promoted by $TiCl_4$ is proposed. In this cascade process, a Lewis acid ($TiCl_4$) promotes both an electrophilic substitution to an aromatic ring (iminium cyclization) and a nucleophilic replacement (Smiles rearrangement). The utility of this reaction sequence is demonstrated via the preparation of novel 6-hydroxymethylpyrrolo[1,2-*f*]pteridine derivatives, which may have potential biological activities.

3. Experimental

3.1. General considerations

Acetonitrile (CH_3CN) was dried with CaH_2 and distilled. Dichloromethane (DCM) was dried with P_2O_5 and distilled. All other commercial reagents were used as received without purification. Melting points were uncorrected. Mass spectra and HPLC data were recorded on a LC/MS system with ELSD. The ^1H and ^{13}C NMR data were obtained on a 300 MHz NMR spectrometer with TMS as the internal standard and $CDCl_3$ as the solvent unless otherwise stated. Multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doubled doublet; br, broad. Coupling constants (*J* values) are quoted in hertz.

*3.1.1. 4,6-Dichloro-5-pyrrol-1-yl-pyrimidine **4***

To a stirred solution of 4,6-dichloro-5-aminopyrimidine (15.0 g, 92.02 mmol) in acetic acid (150 mL), 2,5-dimethoxy tetrahydrofuran (11.9 mL, 92.02 mmol) was added. The resulting solution was stirred for 1 h at reflux. Then acetic acid was evaporated and the residue was diluted with DCM and washed with water. The organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (petroleum ether/EtOAc 20:1, v/v) afforded 15.3 g (78%) of **4** as a white solid. Mp: 120–122 °C; ^1H NMR: δ=8.80 (s, 1H), 6.74 (t, 2H, *J*=2.4), 6.45 (t, 2H, *J*=2.1); MS (ESI): *m*/*z* 214.0 [M+H$^+$].

*3.1.2. 4-Chloro-6-hydroxylethoxyl-5-pyrrol-1-yl-pyrimidine **5***

To a stirred solution of 4,6-dichloro-5-pyrrol-1-yl-pyrimidine (4.0 g, 18.78 mmol) and ethyleneglycol (11.5 mL, 205.68 mmol) in DMF (150 mL) was added $MgSO_4$ (0.75 g, 6.25 mmol) followed by K_2CO_3 (3.89 g, 28.19 mmol). The resulting solution was stirred for 12 h at ambient temperature, water (200 mL) was added, and extracted with EtOAc (4×100 mL). The combined organic layers were washed with water (3×80 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc 4:1, v/v) to afford 3.59 g (80%) of **5** as a white solid. Mp: 46–47 °C; ^1H NMR: δ=8.53 (s, 1H), 6.77 (t, 2H, *J*=2.1), 6.37 (t, 2H, *J*=2.1), 4.54 (t, 2H, *J*=4.5), 3.88 (d, 2H, *J*=3.0), 2.25 (s, 2H); ^{13}C NMR: δ=165.5, 157.2, 155.4, 122.0, 109.9, 109.7, 69.9, 60.8; MS (ESI): *m*/*z* 240.0 [M+H$^+$].

*3.1.3. 2-(4-Chloro-5-(1H-pyrrol-1-yl)pyrimidin-6-yloxy) acetaldehyde **1a***

4-Chloro-6-hydroxylethoxyl-5-pyrrol-1-yl-pyrimidine **5** (3.0 g, 12.55 mmol) in 50 mL of DMSO/DCM (1:1) was treated with TEA (17.6 mL, 125.52 mmol). A solution of SO_3-pyridine (12.05 g, 75.31 mmol) in 60 mL DMSO was added and the mixture was stirred for 35 min at ambient temperature. The reaction solution was then diluted with 10% citric acid (250 mL) and extracted with DCM (4×150 mL). The combined organic layers were washed with 10% citric acid (100 mL), water (3×80 mL) followed by drying ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography twice (petroleum ether/EtOAc 4:1, v/v and DCM) to afford 2.0 g (67%) of **1a** as a white solid. Mp: 48–50 °C; ^1H NMR: δ=9.67 (s, 1H), 8.49 (s, 1H), 6.84 (t, 2H, *J*=1.8), 6.40 (t, 2H, *J*=1.8), 5.06 (s, 2H); ^{13}C NMR: δ=194.5, 164.4, 157.7, 155.1, 122.0, 110.1, 109.7, 71.3.

*3.1.4. (4-Chloro-5-(1H-pyrrol-1-yl)pyrimidin-6-yloxy) acetone **1b***

To a stirred solution of 4,6-dichloro-5-pyrrol-1-yl-pyrimidine (213 mg, 1.0 mmol) and hydroxyacetone (0.114 mL, 1.5 mmol) in DMF (2 mL) was added $MgSO_4$ (48 mg, 0.4 mmol) followed by K_2CO_3 (207 mg, 1.5 mmol). The resulting solution was stirred for 7 h at ambient temperature. Water (10 mL) was added and extracted with EtOAc (3×10 mL). The combined organic layers were washed with water (3×8 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc 2:1, v/v) to afford 192 mg (77%) of **1b** as a white solid. Mp: 60–61 °C; ^1H NMR: δ=8.46 (s, 1H), 6.85 (t, 2H, *J*=2.4), 6.39 (t, 2H, *J*=2.4), 5.03 (s, 2H), 2.19 (s, 3H); ^{13}C NMR: δ=200.6, 164.5, 157.4, 155.1, 122.0, 121.1, 109.9, 70.9, 25.9; MS (ESI): *m*/*z* 252.0 [M+H$^+$].

*3.1.5. 2-((6-Chloro-5-(1H-pyrrol-1-yl)pyrimidin-4-yloxy)methyl)-6-chloro-3-((6-chloro-5-(1H-pyrrol-1-yl)pyrimidin-4-yl)methyl)-N-(4-chlorophenyl)-1,2,3,4-tetrahydroquinolin-4-amine **6***

To a stirred solution of 2-(4-chloro-5-(1*H*-pyrrol-1-yl)pyrimidin-6-yloxy)acetaldehyde **1a** (300 mg, 1.27 mmol) in DCM (40 mL) was added *p*-chloroaniline (177 mg, 1.39 mmol) and TFA (136 μL), and the mixture was stirred for 15 min at ambient temperature. The reaction solution was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc=4:1, v/v) afforded 384 mg (89%) of **6**. MS (ESI): *m*/*z* 715.0 [M+Na$^+$]. ^1H NMR indicated the ratio of two isomers of **6** to be 2:1 (**6.1**/**6.2**). Compound **6** was further purified by column chromatography (DCM) to afford 80 mg of **6.1** as a white solid (mp: 104–106 °C) and 295 mg of mixture (**6.1**, **6.2**). Compound **6.1**: ^1H NMR: δ=8.64 (s, 1H), 8.46 (s, 1H), 7.21 (d, 2H, *J*=8.7), 7.13–7.07 (m, 2H), 6.89 (d, 2H, *J*=8.7), 6.65 (t, 2H, *J*=2.1), 6.50 (d, 1H, *J*=8.4), 6.37 (t, 2H, *J*=2.1), 6.33 (t, 2H, *J*=2.1), 6.16 (t, 2H, *J*=2.1), 5.51 (s, 1H), 4.59 (t, 1H, *J*=4.5), 4.53–4.48 (m, 1H), 4.30–4.24 (m, 1H), 4.06–4.02 (m, 2H), 3.71 (d, 1H, *J*=5.4); ^{13}C NMR: δ=164.8, 164.1, 157.3, 157.1, 155.4, 154.9, 144.2, 140.8, 130.2, 129.5, 129.3, 123.2, 122.5, 121.8, 121.75, 121.70, 121.2, 118.7, 115.9, 114.1, 110.2, 109.7, 70.5, 67.5, 52.0, 48.5; HRMS (ESI-Q-TOF): calcd for $C_{32}H_{24}Cl_4N_8O_2$: 393.0854 [M+H$^+$], found: 693.0848.

3.2. General procedure for the synthesis of 6-hydroxymethylpyrrolo[1,2-*f*]pteridine 3

To a stirred solution of 2-(4-chloro-5-(1*H*-pyrrol-1-yl)pyrimidin-6-yloxy)acetaldehyde **1a** (119 mg, 0.5 mmol) in CH_3CN

(18 mL) was added the appropriate amine (0.55 mmol), then cooled to −15 °C, and $TiCl_4$ (132 μL, 1.2 mmol) was added dropwise. The reaction was held at this temperature for 1 h and then allowed to warm slowly to 24 °C. After complete consumption of the starting material **1a** by TLC, the solvent was removed in vacuo and the residue was diluted with DCM (40 mL), which was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by flash chromatography (DCM/EtOAc=10:1 or 5:1, v/v) afforded the desired products.

3.2.1. 5-Benzyl-1-chloro-5,6-dihydro-6-hydroxylmethyl pyrrolo[1,2-f]pteridine ***3.1a***

Yield 60%, mp: 162–163 °C. ^{1}H NMR: δ=8.19 (s, 1H), 7.97 (dd, 1H, J_1=3.0, J_2=1.5), 7.36–7.28 (m, 5H), 6.39 (t, 1H, J=3.3), 6.07 (dd, 1H, J_1=3.3, J_2=1.5), 5.61 (d, 1H, J=15.3), 4.70 (t, 1H, J=5.1), 4.54 (d, 1H, J=15.6), 3.71–3.67 (m, 2H), 1.69 (t, 1H, J=6.6) (D_2O exchangeable); ^{13}C NMR: δ=154.1, 152.1, 142.3, 136.2, 128.8, 127.8, 125.4, 119.9, 116.1, 111.5, 109.8, 106.2, 64.2, 56.1, 50.5; MS (ESI): *m*/*z* 327.0 [M+H$^+$]. Anal. Calcd for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.15. Found: C, 62.49; H, 4.54; N, 17.11.

3.2.2. 1-Chloro-5,6-dihydro-6-hydroxylmethylpyrrolo-[1,2-f]pteridine ***3.2a***

Yield 32%, mp: 214–216 °C. ^{1}H NMR (DMSO-d_6): δ=8.36 (br, 1H), 8.02 (s, 1H), 7.85 (dd, 1H, J_1=3.3, J_2=1.5), 6.36 (t, 1H, J=3.3), 6.16 (dd, 1H, J_1=3.9, J_2=1.2), 5.04 (br, 1H), 4.69 (dd, 1H, J_1=7.2, J_2=4.5), 3.63–3.53 (m, 2H); ^{13}C NMR (DMSO-d_6): δ=155.5, 152.2, 140.6, 127.2, 118.4, 114.4, 111.2, 105.8, 65.6, 51.4; MS (ESI): *m*/*z* 237.0 [M+H$^+$].

3.2.3. 1-Chloro-5,6-dihydro-5-methyl-6-hydroxylmethyl pyrrolo[1,2-f]pteridine ***3.3a***

Yield 48%, mp: 175–176 °C. ^{1}H NMR: δ=8.17 (s, 1H), 7.97 (dd, 1H, J_1=3.0, J_2=1.2), 6.41 (t, 1H, J=3.3), 6.16 (d, 1H, J=2.7), 4.72 (t, 1H, J=5.1), 3.82–3.76 (m, 2H), 3.31 (s, 3H), 1.72 (t, 1H, J=6.6); ^{13}C NMR (DMSO-d_6): δ=154.6, 151.8, 140.1, 127.5, 118.4, 115.9, 111.3, 105.3, 63.4, 58.6, 35.4; MS (ESI): *m*/*z* 251.0 [M+H$^+$]. Anal. Calcd for $C_{11}H_{11}ClN_4O$: C, 52.70; H, 4.42; N, 22.35. Found: C, 52.75; H, 4.37; N, 22.19.

3.2.4. 5-(n-Butyl)-1-chloro-5,6-dihydro-6-hydroxylmethyl pyrrolo[1,2-f]pteridine ***3.4a***

Yield 40%, mp: 89–90 °C. ^{1}H NMR: δ=8.13 (s, 1H), 7.94 (dd, 1H, J_1=3.3, J_2=1.2), 6.40 (t, 1H, J=3.3), 6.15–6.14 (m, 1H), 4.74–4.71 (m, 1H), 4.36–4.27 (m, 1H), 3.78–3.63 (m, 2H), 3.26–3.16 (m, 1H), 1.83 (br, 1H), 1.71–1.60 (m, 2H), 1.39–1.32 (m, 2H), 0.94 (t, 3H, J=7.5); ^{13}C NMR: δ=153.7, 152.1, 141.9, 125.3, 119.9, 115.9, 111.4, 106.2, 64.3, 57.2, 47.7, 29.6, 20.0, 13.8; MS (ESI): *m*/*z* 293.1 [M+H$^+$].

3.2.5. 1-Chloro-5-cyclohexyl-5,6-dihydro-6-hydroxylmethyl pyrrolo[1,2-f]pteridine ***3.5a***

Yield 22%, mp: 151–153 °C. ^{1}H NMR: δ=8.18 (s, 1H), 7.89 (d, 1H, J=1.8), 6.40 (t, 1H, J=3.3), 6.13 (d, 1H, J=2.4), 4.80 (dd, 1H, J_1=8.4, J_2=4.5), 4.60–4.54 (m, 1H), 3.67–3.62 (m, 1H), 3.47–3.41 (m, 1H), 2.08 (d, 1H, J=9.3), 1.92–1.84 (m, 2H), 1.75–1.43 (m, 7H), 1.26–1.16 (m, 1H); ^{13}C NMR: δ=153.9, 152.0, 142.6, 126.1, 119.9, 116.1, 111.5, 105.9, 64.7, 57.2, 52.1, 31.8, 30.7, 25.9, 25.8, 25.4; MS (ESI): *m*/*z* 319.0 [M+H$^+$].

3.2.6. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(iso-propyl)pyrrolo[1,2-f]pteridine ***3.6a***

Yield 12%, mp: 139–141 °C. ^{1}H NMR: δ=8.18 (s, 1H), 7.90 (dd, 1H, J_1=3.0, J_2=1.2), 6.41 (t, 1H, J=3.3), 6.15 (d, 1H, J=2.4), 4.92–4.85 (m, 1H), 4.83–4.78 (m, 1H), 3.72–3.65 (m, 1H), 3.51–3.43 (m, 1H), 1.69–1.64 (m, 1H), 1.41 (d, 3H, J=6.9), 1.33 (d, 3H, J=6.6); ^{13}C NMR: δ=153.9, 152.0, 142.5, 126.1, 119.9, 116.6, 111.5, 106.0, 64.9, 52.0, 49.3, 21.4, 20.3; MS (ESI): *m*/*z* 279.0 [M+H$^+$].

3.2.7. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-phenyl pyrrolo[1,2-f]pteridine ***3.7a***

Yield 55%, mp: 185–187 °C. ^{1}H NMR: δ=8.10 (s, 1H), 8.03 (d, 1H, J=1.8), 7.51–7.34 (m, 5H), 6.47 (t, 1H, J=3.3), 6.18 (d, 1H, J=2.4), 5.05 (t, 1H, J=4.8), 3.88–3.73 (m, 2H), 1.78 (t, 1H, J=6.6); ^{13}C NMR: δ=153.9, 152.0, 143.2, 141.4, 129.6, 127.6, 127.2, 125.5, 120.1, 116.5, 111.8, 106.5, 64.0, 60.2; MS (ESI): *m*/*z* 313.0 [M+H$^+$].

3.2.8. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(2-methoxyl phenyl)pyrrolo[1,2-f]pteridine ***3.9a***

Yield 25%, mp: 159–161 °C. ^{1}H NMR: δ=8.07 (dd, 1H, J_1=3.3, J_2=1.8), 8.03 (s, 1H), 7.42 (t, 1H, J=8.1), 7.28 (br, 1H), 7.11 (t, 2H, J=7.8), 6.46 (t, 1H, J=3.3), 6.16 (d, 1H, J=3.0), 5.01 (t, 1H, J=3.9), 3.86 (s, 3H), 3.73 (s, 2H), 3.00 (br, 1H); ^{13}C NMR: δ=151.9, 142.5, 129.9, 126.1, 122.0, 121.9, 119.9, 116.0, 112.8, 111.7, 110.1, 109.8, 106.1, 64.9, 60.6, 56.1; MS (ESI): *m*/*z* 343.0 [M+H$^+$].

3.2.9. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(2-methyl phenyl)pyrrolo[1,2-f]pteridine ***3.10a***

Yield 23%. ^{1}H NMR: δ=8.13 (dd, 0.38H, J_1=3.3, J_2=1.5), 8.06 (s, 1H), 8.06 (d, 1H, J=1.8), 7.35–7.31 (m, 4.57H), 7.22–7.19 (m, 0.43H), 6.50–6.46 (m, 1.21H), 6.20 (d, 1.24H, J=3.6), 5.16 (d, 0.36H, J=3.3), 4.77 (t, 0.83H, J=4.8), 3.86–3.81 (m, 2.14H), 3.74–3.70 (m, 0.41H), 2.26 (s, 1.21H), 2.14 (s, 2.62H), 1.70–1.62 (m, 1.28H); MS (ESI): *m*/*z* 327.0 [M+H$^+$].

3.2.10. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(3-methyl phenyl)pyrrolo[1,2-f]pteridine ***3.11a***

Yield 53%, mp: 160–161 °C. ^{1}H NMR: δ=8.09 (s, 1H), 8.01 (dd, 1H, J_1=3.3, J_2=1.5), 7.36 (t, 1H, J=8.1), 7.18–7.16 (m, 3H), 6.45 (t, 1H, J=3.9), 6.17 (dd, 1H, J_1=2.7, J_2=0.9), 5.02 (t, 1H, J=5.1), 3.82–3.75 (m, 2H), 2.39 (s, 3H), 1.84 (s, 1H); ^{13}C NMR: δ=153.9, 152.0, 142.9, 141.3, 139.7, 129.3, 128.5, 127.7, 125.6, 124.3, 120.0, 116.4, 111.7, 106.4, 64.0, 60.2, 21.4; MS (ESI): *m*/*z* 327.0 [M+H$^+$]. Anal. Calcd for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.15. Found: C, 62.45; H, 4.56; N, 16.99.

3.2.11. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(4-methyl phenyl)pyrrolo[1,2-f]pteridine ***3.12a***

Yield 50%, mp: 136–138 °C. ^{1}H NMR: δ=8.08 (s, 1H), 8.02 (dd, 1H, J_1=3.0, J_2=1.5), 7.31–7.23 (m, 4H), 6.46 (t, 1H, J=3.3), 6.18 (dd, 1H, J_1=3.9, J_2=0.9), 5.01 (t, 1H, J=5.1), 3.83–3.76 (m, 2H), 2.40 (s, 3H), 1.78 (t, 1H, J=6.6); ^{13}C NMR: δ=154.1, 152.0, 142.9, 138.6, 137.7, 130.3, 127.2, 125.5, 120.0, 116.2, 111.7, 106.4, 64.0, 60.2, 21.1; MS (ESI): *m*/*z* 327.0 [M+H$^+$].

3.2.12. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(4-methoxyl phenyl)pyrrolo[1,2-f]pteridine ***3.13a***

Yield 38%, mp: 141–142 °C. ^{1}H NMR: δ=8.08 (s, 1H), 8.03 (dd, 1H, J_1=3.3, J_2=1.5), 7.30–7.26 (m, 2H), 7.02–6.99 (m, 2H), 6.46 (t, 1H, J=3.0), 6.18 (dd, 1H, J_1=3.6, J_2=1.5), 4.98 (dd, 1H, J_1=5.1, J_2=3.6), 3.85 (s, 3H), 3.82 (br, 2H), 1.77 (s, 1H); ^{13}C NMR: δ=158.8, 154.3, 151.9, 142.6, 133.8, 128.9, 125.6, 119.9, 116.1, 114.8, 111.6, 106.3, 64.0, 60.5, 55.4; MS (ESI): *m*/*z* 343.0 [M+H$^+$].

3.2.13. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(4-chloro phenyl)pyrrolo[1,2-f]pteridine ***3.14a***

Yield 70%, mp: 158–159 °C. ^{1}H NMR: δ=8.10 (s, 1H), 8.01 (d, 1H, J=1.8), 7.44 (d, 2H, J=8.7), 7.34 (d, 1H, J=8.7), 6.46 (t, 1H, J=3.3), 6.18 (d, 1H, J=2.7), 5.02 (t, 1H, J=4.8), 3.85–3.73 (m, 2H), 1.90 (br, 1H); ^{13}C NMR: δ=153.8, 151.7, 143.0, 139.9, 133.1, 129.7, 128.6, 125.5, 120.0, 116.7, 111.8, 106.5, 64.0, 60.2; MS (ESI): *m*/*z* 346.9 [M+H$^+$].

3.2.14. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(4-bromo phenyl)pyrrolo[1,2-f]pteridine ***3.15a***

Yield 71%, mp: 102–103 °C. ^{1}H NMR: δ=8.12 (s, 1H), 8.02 (dd, 1H, J_1=3.0, J_2=1.5), 7.62–7.57 (m, 2H), 7.32–7.28 (m, 2H), 6.47 (t, 1H,

J=3.3), 6.19 (dd, 1H, J_1=3.6, J_2=1.5), 5.03 (t, 1H, J=4.8), 3.83–3.74 (m, 2H), 1.76 (t, 1H, J=6.6); ^{13}C NMR: δ=153.6, 151.7, 143.2, 140.5, 132.6, 128.8, 125.6, 121.0, 119.9, 116.8, 111.8, 106.5, 64.0, 60.1; MS (ESI): m/z 390.9 [M+H$^+$].

3.2.15. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(4-fluoro phenyl)pyrrolo[1,2-f]pteridine **3.16a**

Yield 52%, mp: 229–230 °C. ^{1}H NMR (DMSO-d_6): δ=8.04 (s, 1H), 7.89 (dd, 1H, J_1=3.0, J_2=1.5), 7.53–7.49 (m, 2H), 7.34–7.28 (m, 2H), 6.44 (t, 1H, J=3.0), 6.18 (dd, 1H, J_1=3.3, J_2=1.5), 5.23 (t, 1H, J=5.1), 5.10 (t, 1H, J=3.3), 3.67–3.64 (m, 1H), 3.57–3.52 (m, 1H); ^{13}C NMR (DMSO-d_6): δ=162.2, 158.9, 154.2, 151.3, 141.5, 137.7, 129.9, 129.8, 127.6, 118.6, 116.3, 116.0, 115.7, 111.5, 105.6, 63.4, 59.9; MS (ESI): m/z 331.0 [M+H$^+$].

3.2.16. 1-Chloro-5,6-dihydro-6-hydroxylmethyl-5-(4-nitro phenyl)pyrrolo[1,2-f]pteridine **3.17a**

(a) *Procedure 1*. To a stirred solution of 2-(4-chloro-5-(1*H*-pyrrol-1-yl)pyrimidin-6-yloxy)acetaldehyde **1a** (119 mg, 0.5 mmol) in DCM (18 mL) was added *p*-nitroaniline (76 mg, 0.55 mmol) and TFA (68 μL). The mixture was stirred for 15 min, then washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (DCM/EtOAc=10:1, v/v) to afford 154 mg (86%) of the desired products **3.17a** as a yellow solid.

(b) *Procedure 2*. General procedure for the synthesis of 6-hydroxymethylpyrrolo[1,2-*f*]pteridine 3. Yield 73%, mp: 173–174 °C. ^{1}H NMR: δ=8.30 (d, 1H, J=7.2), 8.27 (s, 1H), 7.98 (dd, 1H, J_1=3.3, J_2=1.5), 7.64 (d, 1H, J=6.9), 6.47 (t, 1H, J=3.3), 6.22 (dd, 1H, J_1=3.3, J_2=0.9), 5.23 (t, 1H, J=5.4), 3.88–3.81 (m, 2H), 1.82 (t, 1H, J=6.3); ^{13}C NMR (DMSO-d_6): δ=153.1, 151.7, 148.2, 143.7, 143.6, 127.6, 124.9, 124.3, 119.0, 118.5, 111.6, 106.2, 63.7, 58.6; MS (ESI): m/z 358.0 [M+H$^+$].

3.2.17. 1-Chloro-5,6-dihydro-6-methyl-6-hydroxylmethyl-5-phenyl pyrrolo[1,2-f]pteridine **3.7b**

To a stirred solution of 2-(4-chloro-5-(1*H*-pyrrol-1-yl)pyrimidin-6-yloxy)acetone **1b** (126 mg, 0.5 mmol) in CH_3CN (18 mL) was added aniline (53 μL, 0.55 mmol) at ambient temperature, then $TiCl_4$ (132 μL, 1.2 mmol) was added dropwise. The resulting solution was stirred for 9 h at reflux. The solvent was removed in vacuo and the residue was diluted with DCM (40 mL), washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc=4:1, v/v) afforded the desired products to afford 30 mg (18%) of **3.7b** as a coffee solid. Mp: 198–200 °C. ^{1}H NMR: δ=8.06 (dd, 1H, J_1=3.0, J_2=1.5), 8.04 (s, 1H), 7.53–7.46 (m, 3H), 7.35 (d, 1H, J=7.8), 7.15 (d, 1H, J=7.5), 6.47 (t, 1H, J=3.3), 6.19 (dd, 1H, J_1=3.6, J_2=1.2), 3.74 (t, 1H, J=5.7), 1.77 (t, 1H, J=6.6), 1.44 (s, 3H); ^{13}C NMR: δ=151.8, 142.1, 138.0, 130.9, 130.7, 130.4, 129.5, 129.4, 128.5, 119.9, 111.4, 105.5, 68.9, 61.2, 22.7; MS (ESI): m/z 327.0 [M+H$^+$].

3.2.18. 5,6-Dihydro-6-hydroxylmethyl-5-(4-chlorophenyl)-1-(pyrrolidin-1-yl)pyrrolo[1,2-f]pteridine **12.1**

To a stirred solution of 1-chloro-5,6-dihydro-6-hydroxylmethyl-5-(4-chlorophenyl)pyrrolo[1,2-*f*]pteridine **3.14a** (52 mg, 0.15 mmol) and pyrrolidine (37 μL, 0.45 mmol) in DMF (1 mL) was added K_2CO_3 (31 mg, 0.225 mmol). The resulting solution was stirred for 6 h at ambient temperature, water (20 mL) was added, and extracted with DCM (3×10 mL). The combined organic layers were washed with water (3×8 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (DCM/Et_2O 40:1, v/v) to afford 56 mg (98%) of **12.1** as a yellow solid. Mp: 170–171 °C. ^{1}H NMR: δ=8.03 (s, 1H), 7.37–7.30 (m, 4H), 7.11 (d, 1H, J=1.5), 6.34 (t, 1H, J=3.0), 6.00 (dd, 1H, J=3.0), 5.00 (t, 1H, J=6.9), 3.93–3.72 (m, 4H), 3.17 (br, 2H), 2.62 (br, 1H), 2.02–1.84 (m, 4H); MS (ESI): m/z 382.1 [M+H$^+$].

3.2.19. 5,6-Dihydro-6-hydroxylmethyl-5-(4-chlorophenyl)-1-(phenylthio)pyrrolo[1,2-f]pteridine **12.2**

To a stirred solution of 1-chloro-5,6-dihydro-6-hydroxylmethyl-5-(4-chlorophenyl)pyrrolo[1,2-*f*]pteridine **3.14a** (52 mg, 0.15 mmol) and thiophenol (46 μL, 0.45 mmol) in DMF (1 mL) was added K_2CO_3 (31 mg, 0.225 mmol). The resulting solution was stirred for 6 h at ambient temperature, water (20 mL) was added, and extracted with EtOAc (3×10 mL). The combined organic layers were washed with water (3×8 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc 4:1, v/v) to afford 54 mg (85%) of **12.2** as a yellow solid. Mp: 186–188 °C. ^{1}H NMR (DMSO-d_6): δ=8.00 (s, 1H), 7.82 (t, 1H, J=1.5), 7.57–7.44 (m, 9H), 6.43 (t, 1H, J=3.3), 6.16 (d, 1H, J=3.6), 5.27 (t, 1H, J=5.1), 5.12 (t, 1H, J=4.2), 3.62–3.53 (m, 2H); ^{13}C NMR (DMSO-d_6): δ=151.7, 151.6, 150.4, 141.2, 135.0, 130.1, 129.3, 129.2, 128.8, 128.5, 128.3, 127.8, 118.4, 116.8, 111.2, 105.5, 63.2, 59.3; MS (ESI): m/z 421.2 [M+H$^+$].

3.2.20. 1-Butoxy-5,6-dihydro-6-hydroxylmethyl-5-(4-chloro phenyl)pyrrolo[1,2-f]pteridine **12.3**

To a stirred solution of 1-chloro-5,6-dihydro-6-hydroxylmethyl-5-(4-chlorophenyl)pyrrolo[1,2-*f*]pteridine **3.14a** (52 mg, 0.15 mmol) in *n*-BuOH (1 mL) was added NaH (18 mg, 0.45 mmol). The resulting solution was stirred for 24 h at ambient temperature, the solvent was evaporated in vacuo, water (20 mL) was added, and extracted with EtOAc (2×10 mL). The combined organic layers were washed with water (2×8 mL) followed by drying ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (DCM/Et_2O 40:1, v/v) to afford 34 mg (59%) of **12.3** as a white solid. Mp: 126–127 °C. ^{1}H NMR: δ=8.08 (s, 1H), 7.78 (s, 1H), 7.40–7.26 (m, 4H), 6.37 (t, 1H, J=2.7), 6.12 (s, 1H), 5.50 (t, 1H, J=5.1), 4.57–4.46 (m, 2H), 3.82–3.64 (m, 2H), 1.91–1.84 (m, 2H), 1.59–1.52 (m, 2H), 1.02 (t, 1H, J=6.9); MS (ESI): m/z 385.1 [M+H$^+$].

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.002.

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