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Trifluoroacetic acid-mediated nucleophilic substitution / Smiles rearrangement cascade reaction: An alternative approach to constructing pyrrole-fused dihydropteridines

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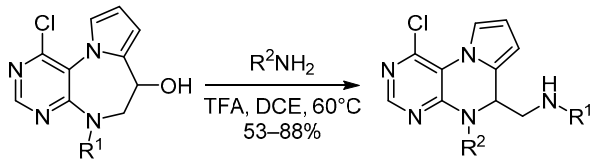


R^1 = Me, Bn; R^2 = *p*-ClC_6H_4, *p*-$O_2NC_6H_4$, *p*-NCC_6H_4, *p*-FC_6H_4, *m*,*p*-$Cl_2C_6H_3$, *p*-BrC_6H_4, *m*-ClC_6H_4, Ph, *p*-MeC_6H_4, *m*-MeC_6H_4, *p*-$MeOC_6H_4$, *o*-$MeOC_6H_4$, *p*-ClC_6H_4

A trifluoroacetic acid-mediated cascade reaction involving nucleophilic substitution and Smiles rearrangement is described. The reaction of hydroxydihydrodiazepines with primary amines led to amino-substituted dihydrodiazepines, which readily underwent Smiles rearrangement to give pyrrolo[1,2-*f*]pteridine derivatives.

Keywords: dihydrodiazepines, pyrimidines, pyrrolo[1,2-*f*]pteridines, cascade reactions, nucleophilic substitution, Smiles rearrangement.

Cascade reactions have been of interest for organic synthesis because they offer convenient and economical methods for the preparation of various organic molecules.[1] Smiles rearrangement is a type of intramolecular nucleophilic aromatic substitution, which has become a powerful synthetic method.[2] To date, several cascade reactions involving Smiles rearrangement have been reported. For example, the Ugi–Smiles rearrangement cascade reaction was developed by Kaïm's group;[3] a Smiles rearrangement / nucleophilic substitution cascade reaction was reported by the groups of Guillaumet,[4] Shin,[5] and Ma;[6] an Ullmann coupling / Smiles rearrangement / nucleophilic substitution cascade reaction was achieved by Snieckus's group.[7]

In the past years, we reported a new cascade reaction entailing an iminium cyclization followed by a Smiles rearrangement in *N*-pyrrolopyrimidine and analogous systems.[8] As depicted in Scheme 1, the reaction of aldehydes **2** with a primary amine yielded an *exo* iminium cyclization products, dihydrodiazepines **4**, under acidic conditions; subsequently, dihydrodiazepines **4** underwent Smiles rearrangement to produce pteridine derivatives **5**. It is noteworthy that the aldehydes **2** were unstable and readily cyclized to give the hydroxydihydrodiazepines **3** during purification on a silica gel column.[8a] Thus it was considered that hydroxydihydrodiazepines **3** may serve as stable analogs of aldehydes **2** and can participate directly in a cascade reaction under acidic conditions.

As part of our continuing efforts to provide further insights into synthetically useful reactions[8d] and to develop new cascade reactions involving Smiles rearrangement, we speculated that the reaction of hydroxydihydrodiazepine **3** and primary amines may offer an alternative approach to pteridine derivatives **5** *via* a cascade reaction involving nucleophilic substitution[9] / Smiles rearrangement under acidic conditions (Scheme 1). Herein, the preliminary results of the studies are reported.

Our studies began with the preparation of key precursor, hydroxydihydrodiazepine **3**, from amino alcohol **1** by a sequence of oxidation/cyclization processes. The oxidation of compounds **1** under the Parikh–Doering conditions cleanly generated aldehydes **2**, which were extracted from aqueous solutions. Considering the reaction workup, 2-iodobenzoic acid (IBX) was regarded as an ideal oxidant, as simple filtration of the reaction mixture provided the aldehydes **2**.[10] The oxidation of compound **1a** with IBX followed by cyclization was investigated, and results are summarized in Table 1. First, solvents (EtOAc, MeCN, and 1,2-dichloroethane (DCE)) were investigated in the presence of TFA (entries 1–3). The best reaction solvent was DCE, giving the desired product **3a** in 50% yield

Scheme 1

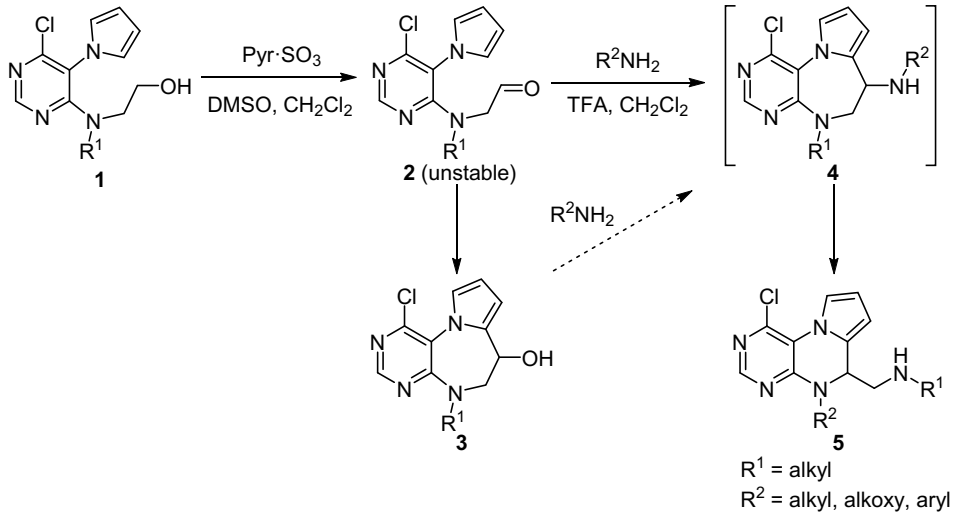
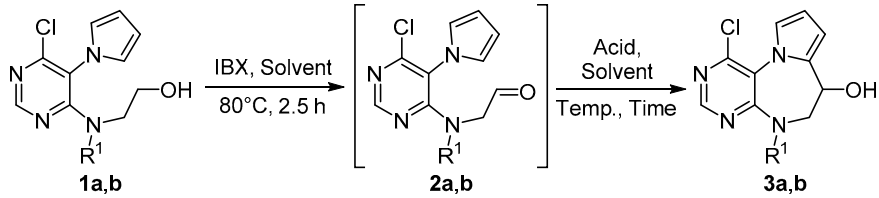


Table 1. Optimization of the oxidation and cyclization conditions



Entry	Product	R^1	Solvent	Acid (equiv)	Temp., °C	c_2, M*	Time, h	Yield, %
1	**3a**	Me	EtOAc	TFA (0.5)	80	0.025	1.0	37
2	**3a**	Me	MeCN	TFA (0.5)	80	0.025	2.5	21
3	**3a**	Me	DCE	TFA (0.5)	80	0.025	0.5	50
4	**3a**	Me	DCE	TsOH (0.5)	80	0.025	1.5	20
5	**3a**	Me	DCE	AcOH (0.5)	80	0.025	0.5	34
6	**3a**	Me	DCE	TFA (0.25)	80	0.025	0.5	43
7	**3a**	Me	DCE	TFA (1.0)	80	0.025	0.5	39
8	**3a**	Me	DCE	TFA (0.5)	60	0.025	1.5	30
9	**3a**	Me	DCE	TFA (0.5)	25	0.025	1.5	27
10	**3a**	Me	DCE	TFA (0.5)	80	0.01	0.5	71
11	**3a**	Me	DCE	TFA (0.5)	80	0.005	0.5	67
12	**3b**	Bn	DCE	TFA (0.5)	80	0.01	0.2	65

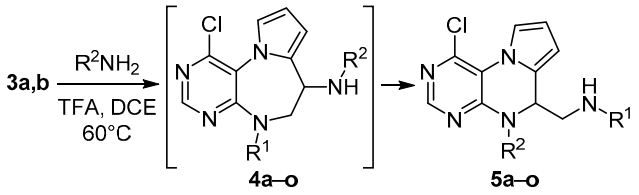
* c_2 – the concentration of compound **2** based on assumed 100% conversion of amino alcohol **1** to aldehyde **2**.

(entry 3). Other acids, including TsOH and AcOH, were also screened, but neither produced a higher yield of compound **3a** (entries 4 and 5). The amount of TFA was varied, but these changes did not improve the yield (entries 6 and 7). Finally, the reaction conditions were further optimized with regard to the reaction temperature and the concentration of aldehyde **2a** (entries 8–11), and the desired product **3a** was obtained in 71% yield by using 0.01 M concentration of compound **2a** at 80°C temperature (entry 10). Moreover, a 65% yield of compound **3b** was also obtained under these optimal conditions (entry 12).

Initially, hydroxydihydrodiazepine **3a** was treated with 4-chloroaniline under our previously reported reaction conditions,[8d] giving an 83% yield of the desired product **5a** (entry 1, Table 2). It was noteworthy that no aldehyde **2a** was detected in the reaction mixture by both LC-MS and thin-layer chromatography analysis during the cascade reaction. Therefore, the results confirmed that diazepine **4a** was indeed produced *via* direct amine substitution of the hydroxyl group in compound **3a** (S_N1 mechanism),[8d] not iminium cyclization of aldehyde **2a** with 4-chloroaniline. The scope of this new cascade reaction was further investigated with hydroxydiazepines **3a**,**b** and various amines, and the results are summarized in Table 2.

As shown in Table 2, aromatic amines effectively participated in the current reaction and produced the desired products in good to high yields (entries 1–12). The reaction appeared to be somewhat sensitive to electronic effects in

Table 2. Cascade reactions of compounds **3***



Entry	R^1	R^2	Time, h	Product	Yield, %
1	Me	*p*-ClC_6H_4	9	**5a**	83
2	Me	*p*-$O_2NC_6H_4$	2	**5b**	57
3	Me	*p*-NCC_6H_4	5.5	**5c**	67
4	Me	*p*-FC_6H_4	8	**5d**	78
5	Me	*m*,*p*-$Cl_2C_6H_3$	8	**5e**	85
6	Me	*p*-BrC_6H_4	9	**5f**	88
7	Me	*m*-ClC_6H_4	9	**5g**	79
8	Me	Ph	13	**5h**	79
9	Me	*p*-MeC_6H_4	15	**5i**	78
10	Me	*m*-MeC_6H_4	15	**5j**	80
11	Me	*p*-$MeOC_6H_4$	18	**5k**	53
12	Me	*o*-$MeOC_6H_4$	22	**5l**	66
13	Me	*n*-Bu	23	**5m**	0
14	Me	*i*-Pr	23	**5n**	0
15	Bn	*p*-ClC_6H_4	11	**5o**	85

* Intermediates **4** could be detected in the reaction mixture by mass spectroscopy and thin-layer chromatography analysis during the reaction.

the aromatic amines. When either a moderate electron-withdrawing or a mild electron-donating group (Cl, F, Br, H and Me; entries 1 and 4–10) was present in the aromatic amine, higher yields were obtained compared to those aromatic amines with either a strong electron-withdrawing group (R^2 = *p*-NO_2 or *p*-CN; entry 2 or 3) or a strong electron-donating group (R^2 = *p*-MeO, entry 11). On the other hand, the reaction proceeded faster with aromatic amines having an electron-withdrawing group compared to those with an electron-donating group (entries 2–7 *vs* entries 9–12). In contrast, aliphatic amines failed in this reaction (entries 13 and 14). In addition, when hydroxydihydrodiazepine **3b** was treated with 4-chloroaniline, 85% yield of the desired product **5o** was obtained (entry 15). The structures of compounds **5** were determined based on the 6-CH proton at 5.02−5.26 ppm (double doublet) in ^{1}H NMR spectra and the comparison of their ^{1}H NMR spectra with analogues reported in the literature.[8a]

In conclusion, a new cascade reaction involving nucleophilic substitution and Smiles rearrangement was developed. The utility of this reaction sequence has been demonstrated by the synthesis of pyrrolo[1,2-*f*]pteridine derivatives. Futhermore, the proposed method represents a promising approach that could be extended to the synthesis of other practically relevant molecules.

Experimental

^{1}H and ^{13}C NMR data were acquired on a Varian Mercury 300 NMR spectrometer (300 and 75 MHz, respectively). TMS was used as internal standard and the solvent was $CDCl_3$, unless otherwise stated. HRMS analysis was performed on an Agilent 1290-micrOTOF-Q II mass spectrometer. Melting points were determined on an XT5 melting point apparatus and are uncorrected. All commercial reagents were purchased from Energy Chemical and Sigma-Aldrich, and used without additional purification.

Synthesis of compounds 3a,b (General method). IBX (2.52 g, 9 mmol) was added to a stirred solution of compound **1a**,**b** (3 mmol) in DCE (42 ml). The reaction mixture was stirred for 2.5 h at 80°C. When the solution was cooled to 0°C, the precipitate was filtered off. The resulting clear solution was then diluted with DCE to give a solution of crude aldehyde **2** in DCE (300 ml). TFA (112 µl, 1.5 mmol) was then added to the solution. The mixture was stirred for the appropriate time at 80°C, then washed with saturated aqueous Na_2CO_3 solution, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. Purification by flash chromatography (petroleum ether–EtOAc, 10:1 to 1:1) afforded the desired products **3a**,**b**.

1-Chloro-5-methyl-6,7-dihydro-5*H*-pyrimido[4,5-*b*]-pyrrolo[1,2-*d*][1,4]diazepin-7-ol (3a). Yield 533 mg (71%), white solid, mp 139–141°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.02 (3H, s, CH_3); 3.61 (1H, dd, *J* = 12.6, *J* = 4.8) and 3.75 (1H, dd, *J* = 12.6, *J* = 2.7, $NC\underline{H}_2CHOH$); 4.90 (1H, dd, *J* = 4.8, *J* = 2.7, $NCH_2C\underline{H}OH$); 6.10 (1H, dd, *J* = 3.3, *J* = 1.8, H Ar); 6.13 (1H, t, *J* = 3.3, H Ar); 6.98 (1H, dd, *J* = 2.7, *J* = 1.8, H Ar); 8.29 (1H, s, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 39.8; 62.7; 63.8; 105.6; 108.3; 118.8; 123.6; 134.3; 150.3; 152.9; 158.3. Found, *m*/*z*: 251.0699 $[M+H]^+$. $C_{11}H_{12}ClN_4O$. Calculated, *m*/*z*: 251.0694.

5-Benzyl-1-chloro-6,7-dihydro-5*H*-pyrimido[4,5-*b*]-pyrrolo[1,2-*d*][1,4]diazepin-7-ol (3b). Yield 637 mg (65%), white solid, mp 171–173°C (171–173°C[8a]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.68–3.82 (2H, m, $NC\underline{H}_2CHOH$); 4.67 (1H, d, *J* = 15.6) and 5.12 (1H, d, *J* = 15.3, $NC\underline{H}_2Ph$); 5.00 (1H, dd, *J* = 5.1, *J* = 2.1, $NCH_2C\underline{H}OH$); 6.16 (1H, dd, *J* = 3.3, *J* = 1.5, H Ar); 6.23 (1H, t, *J* = 3.3, H Ar); 7.01 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 7.24–7.36 (5H, m, H Ar); 8.25 (1H, s, H Ar).

Synthesis of 5,6-dihydropyrrolo[1,2-*f*]pteridines 5a–l,o (General method). The appropriate amine (0.6 mmol) was added to a stirred solution of compound **3** (0.5 mmol) in DCE (20 ml), followed by TFA (78 µl, 1.05 mmol). The mixture was stirred for the appropriate time at 60°C, then washed with saturated aqueous Na_2CO_3 solution, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. Purification by flash chromatography (4:1 to 2:1 petroleum ether–EtOAc, v/v) afforded the desired products.

1-[1-Chloro-5-(4-chlorophenyl)-5,6-dihydropyrrolo-[1,2-*f*]pteridin-6-yl]-*N*-methylmethanamine (5a). Yield 150 mg (83%). Pale-yellow solid. Mp 86–87°C (86–87°C[8a]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, s, NCH_3); 2.76–2.93 (2H, m, NCH_2); 5.04 (1H, dd, *J* = 7.5, *J* = 4.2,

NCH); 6.16 (1H, dd, *J* = 3.3, *J* = 1.2, H Ar); 6.44 (1H, t, *J* = 3.3, H Ar); 7.33 (2H, d, *J* = 8.7, H Ar); 7.43 (2H, d, *J* = 8.7, H Ar); 7.98 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 8.13 (1H, s, H Ar).

1-[1-Chloro-5-(4-nitrophenyl)-5,6-dihydropyrrolo[1,2-*f*]-pteridin-6-yl]-*N*-methylmethanamine (5b). Yield 106 mg (57%). Yellow solid. Mp 128–130°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, NCH_3); 2.83 (1H, dd, *J* = 12.0, *J* = 8.4) and 2.99 (1H, dd, *J* = 12.0, *J* = 4.8, NCH_2); 5.24–5.29 (1H, m, NCH); 6.21 (1H, d, *J* = 3.3, H Ar); 6.45 (1H, t, *J* = 3.3, H Ar); 7.62 (2H, d, *J* = 9.0, H Ar); 7.94 (1H, dd, *J* = 3.0, *J* = 1.2, H Ar); 8.25–8.31 (3H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.4; 54.5; 57.8; 107.1; 112.1; 118.6; 120.1; 124.3; 124.9; 126.5; 144.7; 145.2; 147.7; 152.0; 152.7. Found, *m/z*: 371.1025 $[M+H]^+$. $C_{17}H_{16}ClN_6O_2$. Calculated, *m/z*: 371.1018.

4-{1-Chloro-6-[(methylamino)methyl]pyrrolo[1,2-*f*]-pteridin-5(6*H*)-yl}benzonitrile (5c). Yield 118 mg (67%). Pale-yellow solid. Mp 154–155°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, NCH_3); 2.80 (1H, dd, *J* = 12.3, *J* = 7.8) and 2.94 (1H, dd, *J* = 12.0, *J* = 5.1, NCH_2); 5.17 (1H, dd, *J* = 7.8, *J* = 5.1, NCH); 6.18 (1H, dd, *J* = 3.6, *J* = 1.2, H Ar); 6.44 (1H, t, *J* = 3.3, H Ar); 7.56 (2H, d, *J* = 9.0, H Ar); 7.71 (2H, d, *J* = 9.0, H Ar); 7.94 (1H, dd, *J* = 3.3, *J* = 1.5, H Ar); 8.24 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.3; 54.5; 57.9; 106.7; 109.0; 111.9; 118.1; 118.4; 119.8; 125.0; 126.5; 133.1; 144.7; 145.9; 151.8; 152.6. Found, *m/z*: 351.1127 $[M+H]^+$. $C_{18}H_{16}ClN_6$. Calculated, *m/z*: 351.1119.

1-[1-Chloro-5-(4-fluorophenyl)-5,6-dihydropyrrolo-[1,2-*f*]pteridin-6-yl]-*N*-methylmethanamine (5d). Yield 134 mg (78%). Pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, s, NCH_3); 2.79 (1H, dd, *J* = 12.0, *J* = 7.8) and 2.99 (1H, dd, *J* = 12.0, *J* = 4.2, NCH_2); 5.11 (1H, dd, *J* = 8.4, *J* = 4.2, NCH); 6.23 (1H, d, *J* = 2.4, H Ar); 6.42 (1H, t, *J* = 3.3, H Ar); 7.11–7.17 (2H, m, H Ar); 7.32–7.36 (2H, m, H Ar); 7.97 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 8.10 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.4; 54.7; 59.1; 106.5; 111.9; 116.4; 116.7; 120.1; 126.5; 129.3; 129.4; 137.7; 143.4; 152.1; 153.9; 159.9; 163.2. Found, *m/z*: 344.1078 $[M+H]^+$. $C_{17}H_{16}ClFN_5$. Calculated, *m/z*: 344.1073.

1-[1-Chloro-5-(3,4-dichlorophenyl)-5,6-dihydropyrrolo-[1,2-*f*]pteridin-6-yl]-*N*-methylmethanamine (5e). Yield 167 mg (85%). Pale-yellow solid. Mp 102–104°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, NCH_3); 2.78 (1H, dd, *J* = 12.0, *J* = 7.5) and 2.91 (1H, dd, *J* = 12.0, *J* = 4.5, NCH_2); 5.06 (1H, dd, *J* = 7.5, *J* = 4.5, NCH); 6.17 (1H, dd, *J* = 3.3, *J* = 1.2, H Ar); 6.44 (1H, t, *J* = 3.3, H Ar); 7.25–7.30 (1H, m, H Ar); 7.52 (1H, d, *J* = 8.7, H Ar); 7.55 (1H, d, *J* = 2.4, H Ar); 7.96 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 8.17 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.3; 54.6; 58.6; 106.6; 110.3; 111.9; 117.1; 119.9; 126.0; 126.2; 128.5; 130.9; 133.1; 141.0; 143.8; 151.9; 153.1. Found, *m/z*: 394.0391 $[M+H]^+$. $C_{17}H_{15}Cl_3N_5$. Calculated, *m/z*: 394.0388.

1-[5-(4-Bromophenyl)-1-chloro-5,6-dihydropyrrolo-[1,2-*f*]pteridin-6-yl]-*N*-methylmethanamine (5f). Yield 178 mg (88%). Pale-yellow solid. Mp 68–70°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, NCH_3); 2.79 (1H, dd, *J* = 11.7, *J* = 7.8) and 2.93 (1H, dd, *J* = 11.7, *J* = 4.2, NCH_2); 5.08 (1H, dd, *J* = 7.5, *J* = 4.2, NCH); 6.18 (1H, dd, *J* = 3.3, *J* = 1.2, H Ar); 6.44 (1H, t, *J* = 3.3, H Ar); 7.28 (2H, d, *J* = 9.0, H Ar); 7.58 (2H, d, *J* = 8.7, H Ar); 7.97 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 8.14 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.4; 54.5; 58.6; 106.5; 111.8; 116.8; 119.9; 120.8; 126.3; 128.5; 132.6; 140.7; 143.5; 152.0; 153.4. Found, *m/z*: 404.0282 $[M+H]^+$. $C_{17}H_{16}BrClN_5$. Calculated, *m/z*: 404.0272.

1-[1-Chloro-5-(3-chlorophenyl)-5,6-dihydropyrrolo-[1,2-*f*]pteridin-6-yl]-*N*-methylmethanamine (5g). Yield 142 mg (79%). Pale-yellow solid. Mp 86–88°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, NCH_3); 2.79 (1H, dd, *J* = 11.7, *J* = 8.1) and 2.93 (1H, dd, *J* = 12.0, *J* = 4.2, NCH_2); 5.08 (1H, dd, *J* = 8.4, *J* = 3.9, NCH); 6.15–6.20 (1H, m, H Ar); 6.44 (1H, t, *J* = 3.3, H Ar); 7.28–7.32 (2H, m, H Ar); 7.36–7.43 (2H, m, H Ar); 7.96–7.97 (1H, m, H Ar); 8.16 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.3; 54.5; 58.5; 106.6; 111.8; 117.0; 119.9; 124.7; 126.3; 126.8; 127.3; 130.3; 134.8; 142.8; 143.7; 152.0; 153.3. Found, *m/z*: 360.0779 $[M+H]^+$. $C_{17}H_{16}Cl_2N_5$. Calculated, *m/z*: 360.0777.

1-(1-Chloro-5-phenyl-5,6-dihydropyrrolo[1,2-*f*]pteridin-6-yl)-*N*-methylmethanamine (5h). Yield 129 mg (79%). Pale-yellow solid. Mp 130–132°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, NCH_3); 2.81 (1H, dd, *J* = 11.7, *J* = 8.1) and 2.94 (1H, dd, *J* = 11.7, *J* = 4.2, NCH_2); 5.08 (1H, dd, *J* = 7.8, *J* = 4.2, NCH); 6.17 (1H, dd, *J* = 3.3, *J* = 1.2, H Ar); 6.44 (1H, t, *J* = 3.3, H Ar); 7.32–7.37 (3H, m, H Ar); 7.44–7.51 (2H, m, H Ar); 7.98 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 8.13 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.4; 54.6; 58.8; 106.4; 111.7; 116.6; 119.9; 126.5; 126.9; 127.4; 129.5; 141.7; 143.3; 152.1; 153.7. Found, *m/z*: 326.1172 $[M+H]^+$. $C_{17}H_{17}ClN_5$. Calculated, *m/z*: 326.1167.

1-[1-Chloro-5-(*p*-tolyl)-5,6-dihydropyrrolo[1,2-*f*]pteridin-6-yl]-*N*-methylmethanamine (5i). Yield 133 mg (78%). Pale-yellow solid. Mp 122–124°C (122–124°C[8a]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, NCH_3); 2.39 (3H, s, $C\underline{H}_3C_6H_4$); 2.78–3.01 (2H, m, NCH_2); 5.06–5.13 (1H, m, NCH); 6.19 (1H, d, , *J* = 3.0, H Ar); 6.43 (1H, t, *J* = 3.3, H Ar); 7.22–7.30 (4H, m, H Ar); 7.98 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 8.11 (1H, s, H Ar).

1-[1-Chloro-5-(*m*-tolyl)-5,6-dihydropyrrolo[1,2-*f*]-pteridin-6-yl]-*N*-methylmethanamine (5j). Yield 136 mg (80%). Pale-yellow solid. Mp 56–58°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, NCH_3); 2.39 (3H, s, $C\underline{H}_3C_6H_4$); 2.81 (1H, dd, *J* = 11.7, *J* = 8.1) and 2.96 (1H, dd, *J* = 11.7, *J* = 3.9, NCH_2); 5.08 (1H, dd, *J* = 7.8, *J* = 3.9, NCH); 6.15–6.21 (1H, m, H Ar); 6.44 (1H, t, *J* = 3.3, H Ar); 7.13–7.19 (3H, m, H Ar); 7.32–7.38 (1H, m, H Ar); 7.97 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 8.13 (1H, s, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.9; 36.2; 54.8; 58.2; 105.8; 111.7; 116.2; 118.8; 124.1; 127.4; 127.5; 127.8; 128.9; 138.7; 141.7; 141.8; 151.6; 153.7. Found, *m/z*: 340.1331 $[M+H]^+$. $C_{18}H_{19}ClN_5$. Calculated, *m/z*: 340.1323.

1-[1-Chloro-5-(4-methoxyphenyl)-5,6-dihydropyrrolo-[1,2-*f*]pteridin-6-yl]-*N*-methylmethanamine (5k). Yield 94 mg (53%). Pale-yellow solid. Mp 104–106°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, s, NCH_3); 2.81 (1H, dd, *J* = 11.7, *J* = 8.1) and 2.95 (1H, dd, *J* = 11.7, *J* = 4.2, NCH_2); 3.84 (3H, s, OCH_3); 5.04 (1H, dd, *J* = 7.8, *J* = 4.2,

NCH); 6.18–6.20 (1H, m, H Ar); 6.44 (1H, t, *J* = 3.3, H Ar); 6.99 (2H, d, *J* = 9.0, H Ar); 7.28 (2H, d, *J* = 8.7, H Ar); 7.98 (1H, dd, *J* = 3.0, *J* = 1.2, H Ar); 8.10 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.3; 54.6; 55.6; 59.1; 106.4; 111.8; 115.0; 116.4; 120.1; 126.5; 128.9; 134.4; 143.1; 152.2; 154.2; 158.9. Found, *m*/*z*: 356.1282 $[M+H]^+$. $C_{18}H_{19}ClN_5O$. Calculated, *m*/*z*: 356.1273.

1-[1-Chloro-5-(2-methoxyphenyl)-5,6-dihydropyrrolo-[1,2-*f*]pteridin-6-yl]-*N*-methylmethanamine (5l). Yield 117 mg (66%). Pale-yellow solid. Mp 99–100°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, NCH_3); 2.79 (1H, dd, *J* = 12.0, *J* = 7.2) and 2.86 (1H, dd, *J* = 12.0, *J* = 3.9, NCH_2); 3.79 (3H, s, OCH_3); 4.99–5.04 (1H, m, NCH); 6.16 (1H, dd, *J* = 3.3, *J* = 1.2, H Ar); 6.43 (1H, t, *J* = 3.3, H Ar); 7.03–7.10 (2H, m, H Ar); 7.29–7.43 (2H, m, H Ar); 8.01 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 8.05 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.2; 54.5; 55.6; 57.0; 106.0; 111.5; 112.4; 115.7; 119.7; 120.9; 124.8; 126.5; 128.7; 129.5; 130.9; 142.3; 151.8; 153.7. Found, *m*/*z*: 356.1280 $[M+H]^+$. $C_{18}H_{19}ClN_5O$. Calculated, *m*/*z*: 356.1273.

***N*-Benzyl-1-[1-chloro-5-(4-chlorophenyl)-5,6-dihydro-pyrrolo[1,2-*f*]pteridin-6-yl]methanamine (5o)**. Yield 185 mg (85%). Pale-yellow solid. Mp 138–139°C (139–140°C[8a]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.83–2.98 (2H, m, $NC\underline{H}_2CHNH$); 3.61 (1H, d, *J* = 13.5) and 3.69 (1H, d, *J* = 13.5, $PhC\underline{H}_2$); 5.04 (1H, dd, *J* = 6.3, *J* = 3.9, NCH); 6.16 (1H, dd, *J* = 3.3, *J* = 1.2, H Ar); 6.44 (1H, t, *J* = 3.3, H Ar); 7.09–7.13 (2H, m, H Ar); 7.19 (2H, d, *J* = 9.0, H Ar); 7.23–7.25 (1H, m, H Ar); 7.27–7.32 (2H, m, H Ar); 7.36 (2H, d, *J* = 9.0, H Ar); 7.98 (1H, dd, *J* = 3.0, *J* = 1.5, H Ar); 8.12 (1H, s, H Ar).

The Supplementary information file containing NMR spectra of all new compounds is available at http://link.springer.com/journal/10593.

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