Chonggang Duan,[a] Jiong Jia,[b] Rongxiu Zhu,[b] and Jianwu Wang[b]*

[a]Key Laboratory of Chemical Drugs of Shandong Province, Shandong Institute of Pharmaceutical Industry, Jinan 250101, People's Republic of China
[b]College of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, People's Republic of China
*E-mail: jwwang@sdu.edu.cn
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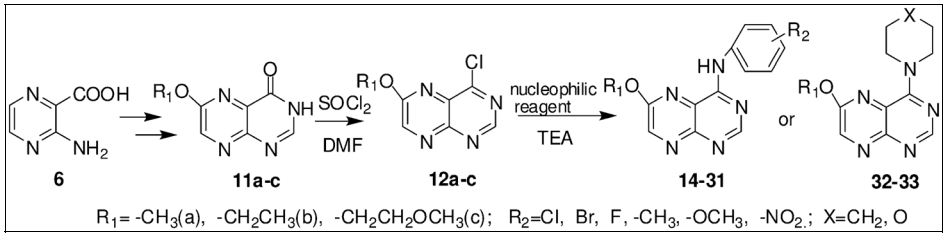

A novel seven-step methodology for the synthesis of *N*-substituted-6-alkoxypteridin-4-amine has been developed with the total yields of 35.4–41%. Twenty new compounds were synthesized by heterocyclization of easily prepared 3-amino-6-bromopyrazine-2-carboxamide, subsequent alkoxylation, chlorination, and nucleophilic substitution. Their structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, ESI-MS, and elemental analysis. The structure of *N*-(3-chloro-4-fluorophenyl)-6-ethoxypteridin-4-amine was further determined by X-ray crystallographic analysis. It was found that different chlorinating reagents gave different products. The possible chlorination mechanism was discussed.

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INTRODUCTION

The protein kinases (PKs) regulate many cellular functions, such as cell growth, proliferation, mitosis, and death [1]. PKs, therefore, have become primary targets for drug discovery for the treatment of tumour and many other diseases [2–6]. In recent years, great efforts have been devoted to the discovery of therapeutically useful inhibitors of PKs, and a variety of templates which provide selective inhibition both within and across different PK families have been identified [7,8]. Among these templates, 4-anilinoquinazolines and related 4-anilinopyrido [*d*]-pyrimidines have served as the core template for a variety of ATP-competitive epidermal growth factor receptor (EGFr) tyrosine kinase inhibitors [9]. The leading example is the clinically approved anticancer agent Iressa (ZD1839) **1** (Fig. 1) [10,11]. Additionally, purine derivatives have been reported as kinase inhibitors for mainly cyclin-dependent kinases [12], quinoxalines as potent kinase inhibitors of platelet derived growth factor receptor tyrosine kinase [13,14], and pteridine-like molecules **2** (Fig. 1) from Abbott compound library as an adenosine kinase inhibitor [15,16].

To search for novel lead PKs inhibitors, based on the structure and activity relationship of the EGFr inhibitors [17–26], we designed and synthesized a series of *N*-substituted-6-alkoxypteridine-4-amine compounds **14–33** (Fig. 1, Table 1).

Although 6(7)-alkyl or aryl substituted pteridines can be conveniently obtained by Isay and Taylor method [27], there has been no report on the synthesis of 6(7)-alkoxyl substituted pteridines. Previously, we have tried to obtain 6(7)-alkoxyl substituted pteridines by cyclization of 4-[(un)substituted anilino]-5,6-diaminopyrimidine **3** with oxalic acid [28]. However, we didn't get 4-arylamiopteridine-6,7-dione **5**, but got the unexpected 4-amino-8-arylpteridine-6,7-dione **4** due to the regioselectivity of the cyclization, as shown in Scheme 1.

In this article, we developed a novel method to get the desired compounds **14–33,** and their structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, ESI-MS, and elemental analysis.

RESULTS AND DISCUSSION

The synthesis of pteridine-liked compounds are described in Scheme 2. The intermediates **7–10** can be obtained by the reported methods [29–31]. The key intermediates **12a–c** were prepared by the alkoxylation of **10**, followed by chlorination of the resulting 6-alkoxy-4-pteridinone **11a–c** with thionyl chloride under catalytic amount of DMF. Finally, the desired compounds **14–31** were obtained by the reactions of **12a–c** with equimolar aniline or substituted aniline in isopropanol in 79.4–86.2% yields, and **32**, **33** were prepared by reactions of **12a** with equimolar piperidine and morpholine.

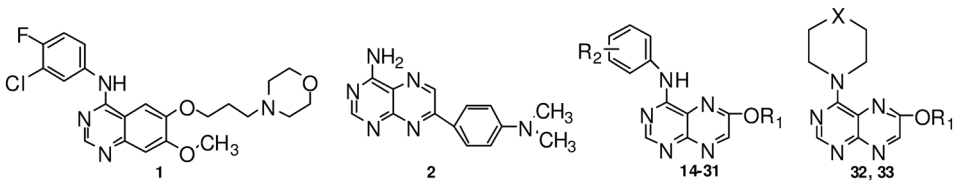


Figure 1. Comparison of reported kinase inhibitors and designed compounds.

The influence of amino group on the reactivity. In 3-amino-6-bromopyrazine-2-carboxamide **9**, the 6-bromo is inert to sodium alkoxylate because of the electronic effects of 3-amino group. Therefore, it is better to cyclize **9** to form **10** first, and the subsequent nucleophilic reaction can take place smoothly.

The chlorination of 6-alkoxyl-4 (*3H*)-pteridinone 11a-c. To obtain the 6-alkoxyl-4-chloropteridine **12a–c**, we used different chlorinating reagents, and the results are shown in Table 2.

From Table 2, it can be seen that the requisite 4-chloropteridines were obtained in poor yields when **11a–c** were treated with $POCl_3$ alone. Catalytic amount of DMA could reduce the yields of 4-chloropteridines due to the formation of impurities **13a–c** (Scheme 3). When equivalent amount of DMA was added to the system, no desired products were obtained but only the by-products **13a–c**. While $SOCl_2$/DMF could give the corresponding products in excellent yields, hardly influenced by the 6-substituent group.

Based on the above results, we concluded that DMA is not a catalyst but a reactant in these reactions. The proposed mechanism of DMA involved chlorination was shown in Scheme 4. The generated HCl results in the demethylation effect but has no influence on the other groups ($R_1 \neq CH_3$).

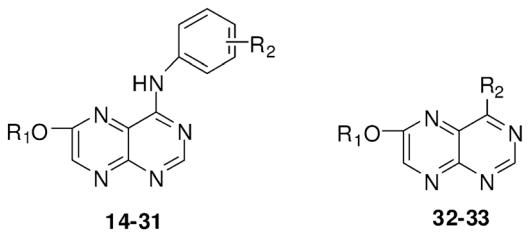
The chlorination reactions can be carried out in good yields by using thionyl chloride and catalytic amount of DMF, and the products were pure enough to be used directly in the next reaction. The possible reaction mechanism is shown in Scheme 5.

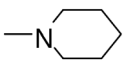
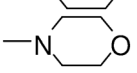
The single crystal structure of compound 26. The single crystal structure of compound **26** was shown in Figure 2. The formula of **26** is $C_{14}H_{11}ClFN_5O$, Mr = 319.73, Monoclinic; P2(1)/c; a = 12.677(3) Å; b = 16.172(4) Å; c = 6.8673(15) Å; α = 90.00°; β = 92.009(4)°; γ= 90.00°; V = 1407.0(5) Å^3; Z = 4; D_c = 1.509 g cm^{-3}; μ = 0.292 mm^{-1}; F(000) = 656; T = 298(2) K; yellow block; 0.28 mm × 0.23 mm × 0.06 mm.

In summary, we have developed an original route for the synthesis of *N*-substituted-6-alkoxypteridin-4-amine. The seven-step procedure, using very inexpensive starting materials and involving 6-alkoxy-4-chloropteridine

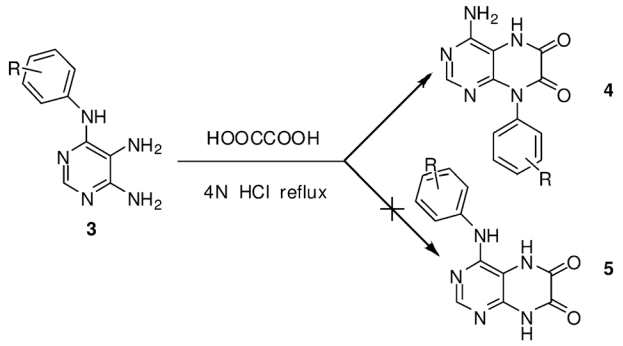
Table 1

Structures of compounds **14**–**33**.



No.	R_1	R_2	No.	R_1	R_2
14	CH_3-	4-OCH_3	**24**	CH_3CH_2-	3-Cl
15	CH_3-	4-CH_3	**25**	CH_3CH_2-	3-Br
16	CH_3-	H	**26**	CH_3CH_2-	3-Cl-4-F
17	CH_3-	4-F	**27**	$CH_3OCH_2CH_2-$	3-Cl
18	CH_3-	4-Cl	**28**	$CH_3OCH_2CH_2-$	4-Cl
19	CH_3-	3-Cl-4-F	**29**	$CH_3OCH_2CH_2-$	3-Br
20	CH_3-	3-Cl	**30**	$CH_3OCH_2CH_2-$	4-F
21	CH_3-	3-Br	**31**	$CH_3OCH_2CH_2-$	3-Cl-4-F
22	CH_3CH_2-	4-NO_2	**32**	CH_3-	
23	CH_3CH_2-	4-Cl	**33**	CH_3-	

Scheme 1. The regioselectivity of cyclization of compound **3.**



as the key intermediates, is very straightforward and gives the overall yields of 35.4–41% under mild reaction conditions. $SOCl_2$ and catalytic amount of DMF were used as the chlorinating reagents to get the 6-alkoxy-4-chloropteridine conveniently, and its possible mechanism was discussed. Efforts to explore the biological activities of the compounds are ongoing in our group.

EXPERIMENTAL

All starting materials were obtained commercially, and all solvents were dried using standard laboratory procedures. Melting points were determined using a WRS-1B digital melting point apparatus and were reported uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AV 300 spectrometer. ESI-MS were recorded on an ABI API 4000 spectrometers. Elemental analyses were recorded on Elementar Vario EL-III elemental analysis apparatus. Analytical thin-layer chromatography was performed on silica gel 60 F-254 plates for routine monitoring of reaction mixtures.

Compounds **7–10** were prepared according to literatures [29–31].

General procedure for the synthesis of 11a–b. ***6-Methoxypteridin-4(3H)-one (11a) [30].*** To a 250 mL flask with a mechanical stirrer, a thermometer and a reflux condenser attached to a $CaCl_2$ dry tube, was added 100 mL methanol.

Scheme 2. Synthesis of compounds **14–33.**

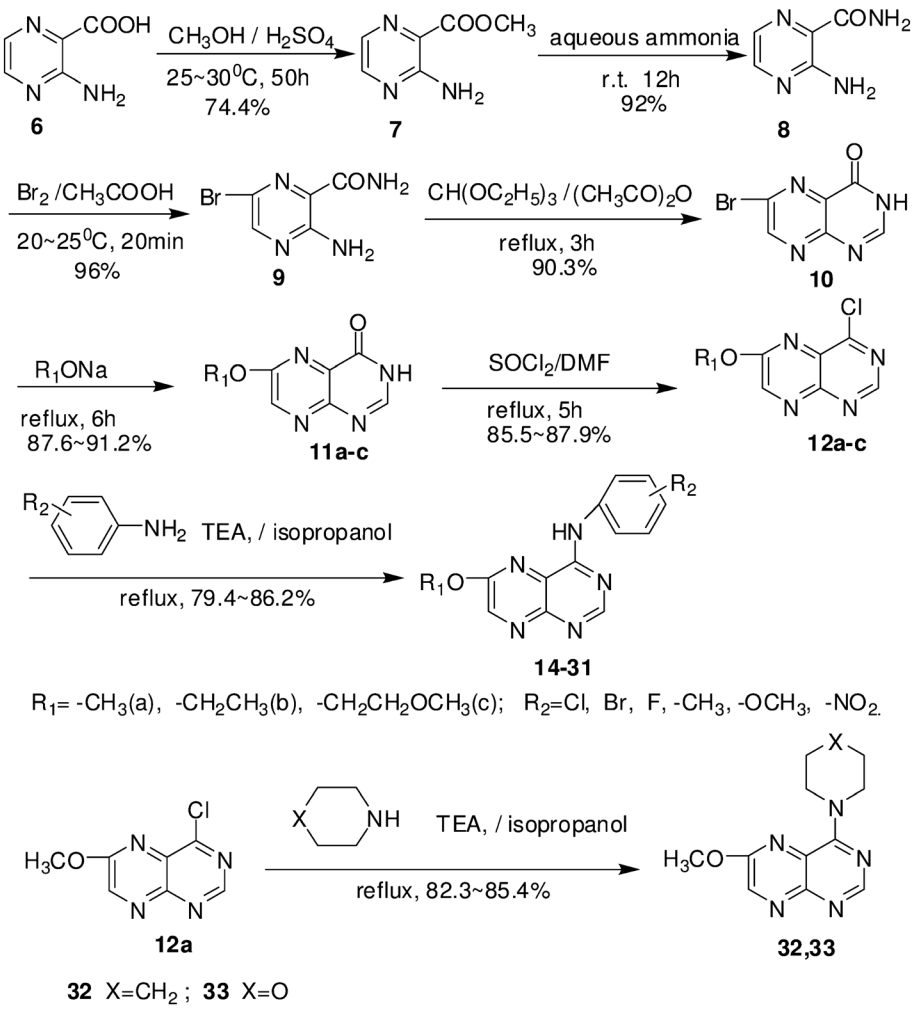
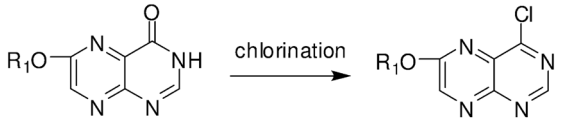


Table 2

Chlorination of 6-alkoxylpteridin-4(*3H*)-one with different reagents.



Entry	R_1	Reagent	Temperature (°C)	Time (h)	Yield (%)
1	CH_3-	$POCl_3$	100	4	53.5
2	CH_3CH_2-	$POCl_3$	82	6	55.8
3	$CH_3OCH_2CH_2-$	$POCl_3$	82	6	57.4
4	CH_3-	$POCl_3$/DMA[a]	82	6	26.4
5	CH_3CH_2-	$POCl_3$/DMA[a]	82	6	20.7
6	$CH_3OCH_2CH_2-$	$POCl_3$/DMA[a]	90	6	22.6
7	CH_3-	$POCl_3$/DMA[b]	100	3	_
8	CH_3CH_2-	$POCl_3$/DMA[b]	82	5	_
9	$CH_3OCH_2CH_2-$	$POCl_3$/DMA[b]	90	6	_
10	CH_3-	$SOCl_2$/DMF[c]	82	5	87.9
11	CH_3CH_2-	$SOCl_2$/DMF[c]	82	5	86.5
12	$CH_3OCH_2CH_2-$	$SOCl_2$/DMF[c]	82	6	85.8

[a]DMA(*N*,*N*-dimethylaniline) is catalytic amount.
[b]DMA: 6-alkoxypteridin-4(*3H*)-one = 1:1.
[c]DMF(*N*,*N*-Dimethylformamide) is catalytic amount.

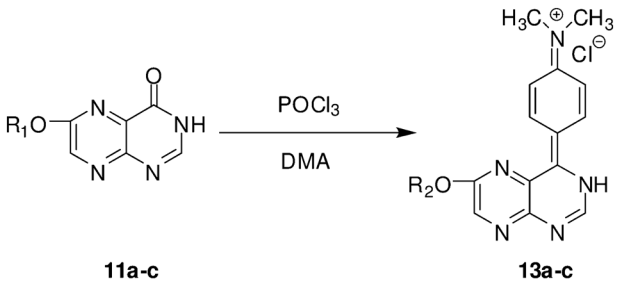
Sodium (1.2 g, 0.052 mol) was carefully dissolved in the methanol to get the sodium methoxide solution. Then 6-bromopteridin-4(*3H*)-one **10** (4.54 g, 0.02 mol) was charged. The mixture was refluxed for 6 h. When the starting material disappeared, the mixture was cooled to room temperature, poured into 150 mL water, and adjusted the pH to 3–4. The white precipitate was filtered, washed with water, and recrystalized with isopropanol and water to give 3.1 g white **11a**. yield: 91.2%; m.p. 278–281°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.69 (s, 1H, ArH), 8.24 (s, 1H, ArH), 4.02 (s, 3H, OCH_3); ^{13}C-NMR (300MHz, DMSO-d_6) δ: 160.6, 158.4, 151.3, 146.6, 143.5, 130.4, 54.7; ESI-MS *m*/*z*: 179.07 $[M+H]^+$. Anal. calcd for $C_7H_6N_4O_2$: C, 47.19; H, 3.39; N, 31.45. found: C, 47.23; H, 3.35; N, 31.39.

6-Ethoxypteridin-4(3H)-one (11b). **W**hite powder, yield 89.7%; m.p. 260–261°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.66 (s, 1H, ArH), 8.22 (s, 1H, ArH), 4.46 (q, J = 7.2 Hz, 2H, CH_2CH_3), 1.40 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) δ: 160.6, 158.0, 151.2, 146.5, 143.5, 130.4, 63.3, 14.6; ESI-MS *m*/*z*: 193.08 $[M+H]^+$. Anal. calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. found C, 49.96; H, 4.22; N, 29.09.

6-(2-Methoxyethoxy)pteridin-4(3H)-one (11c). Ethylene glycol monomethyl ether (3.5 g, 0.046 mol) was mixtured with 100 mL dry tetrahydrofuran in a 250 mL flask equipped with a magnetic stir bar, a thermometer and a refluxing condensor. Sodium hydride (60%) (1.8 g, 0.046 mol) was added and stired for 30 mins at room temperature to get the sodium methoxyethoxlate. **10** (4.54 g, 0.02 mol) was then charged and the mixture was refluxed for 6 h. The solvent was distilled to dry under reduced pressure, the residue was dissolved in 10 mL water. The pH was adjusted to 3–4 with 4N hydrochloride acid and the precipatated white solid was filtered, washed with water and dried to give 3.89 g **11c**, yield: 87.6%. m.p. 236.5–237°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.71 (s, 1H, ArH), 8.24 (s, 1H, ArH), 4.55–4.52 (m, 2H, OCH_2CH_2O), 3.76–3.73 (m, 2H, OCH_2CH_2O), 3.33 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) δ: 160.5, 157.9, 151.3, 146.6, 143.5, 130.3, 70.2, 66.4, 58.6; ESI-MS *m*/*z*: 222.12 $[M+H]^+$. Anal. calcd for $C_9H_{10}N_4O_2$: C, 48.65; H, 4.54; N, 25.21. found C, 48.59; H, 4.58; N, 25.24.

General procedure for the synthesis of 12a–c. ***4-Chloro-6-methoxypteridine (12a).*** Compound **11a** (3.0 g, 16.8 mmol), 20 mL thionyl chloride and 2 drops of *N*,*N*-dimethyl formamide was charged into a 50 mL single necked round-bottom flask with a magnetic stir bar, a thermometer and a refluxing condensor. The mixture was refluxed with stirring for 5 h, then distilled to dry under reduced pressure and the residue was dissolved in 30 mL ethyl acetate. The mixture was washed with water, saturated sodium bicarbonate, and water, dried with anhydrous magnesium sulphate and distilled to dry to obtain 2.9 g **12a** in 87.9% yield. Yellow powder. m.p. 140.2–141.5°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.71 (s, 1H, ArH), 8.44 (s, 1H, ArH), 4.04 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) δ: 160.2, 158.6, 149.8, 147.1, 143.5, 130.3, 54.8; ESI-MS *m*/*z*: 197.2 $[M(^{35}Cl)+H]^+$, 199.1 $[M(^{37}Cl)+H]^+$.Anal. calcd for

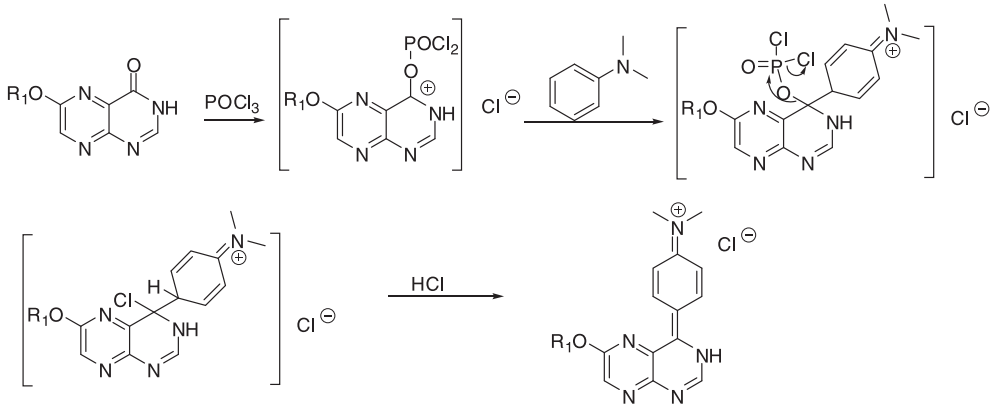
Scheme 3. The chlorination of **11a-c** by $POCl_3$ and DMA.



11a-c **13a-c**

R_1=CH_3, R_2=H; R_1≠CH_3, R_2=R_1

Scheme 4. The proposed mechanism of chlorination of **11a-c** by $POCl_3$ and DMA.



$C_7H_5ClN_4O$: C, 42.77; H, 2.56; N, 28.50. found C, 42.83; H, 2.51; N, 28.47.

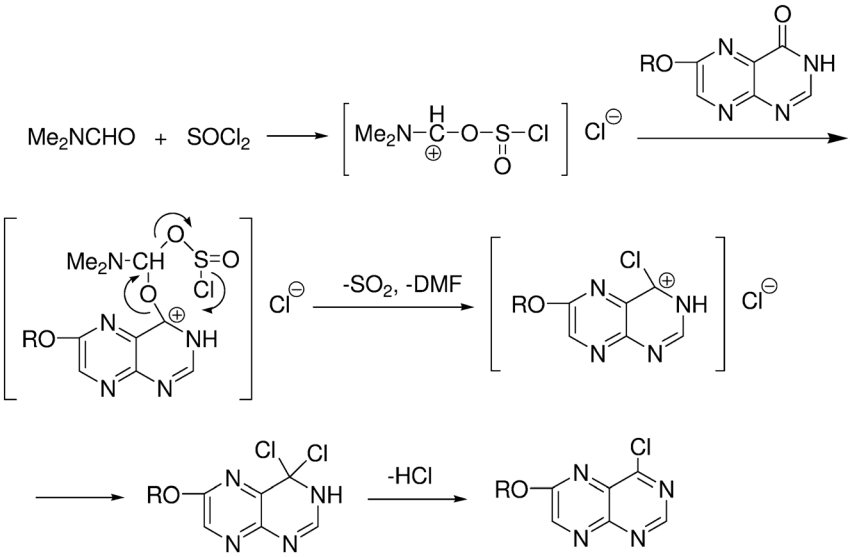
4-Chloro-6-ethoxypteridine (12b). Yellowish powder, yield: 86.5%. m.p. 156–157°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 9.16 (s, 1H, ArH), 9.03 (s, 1H, ArH), 4.60 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 1.47 (t, J = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) δ: 160.4, 158.7, 150.2, 147.2, 143.5, 129.9, 64.4, 14.6; ESI-MS *m/z*: 211.1 $[M(^{35}Cl)+H]^+$, 213.1 $[M(^{37}Cl)+H]^+$. Anal. calcd for $C_8H_7ClN_4O$: C, 45.62; H, 3.35; N, 26.60. found C, 45.57; H, 3.38; N, 26.64.

4-Chloro-6-(2-methoxyethoxy)pteridine (12c). Yellowish powder, yield: 85.8%. m.p. 97.5–98°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.73 (s, 1H, ArH), 8.65 (s, 1H, ArH), 4.55 (q, 2H, OCH_2CH_2O), 3.75 (t, J = 4.5 Hz, 2H, OCH_2CH_2O), 3.34 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) δ: 159.0, 157.7, 149.5, 148.2, 143.2, 128.8, 69.6, 66.1, 58.0; ESI-MS *m/z*: 241.1 $[M(^{35}Cl)+H]^+$, 243.1 $[M(^{37}Cl)+H]^+$.Anal. calcd for $C_9H_9ClN_4O_2$: C, 44.92; H, 3.77; N, 23.28. found C, 44.87; H, 3.83; N, 23.31.

General procedure for the synthesis of compounds 13a–c.

N-(4-(6-Hydroxypteridin-4(3H)-ylidene)cyclohexa-2,5-dienylidene)-N-methyl methanaminium chloride (13a). **11a** (2.0 g, 0.011 mol) and 20 mL phosphorus oxychloride were charged into a 100 mL four-necked round-bottom flask. *N*,*N*-dimethylaniline (1.34 g, 0.012 mol) was added dropwise with stirring and the mixture was heated to 100°C for 3 h. The exceeding $POCl_3$ was removed by distillation under reduced pressure, the residue was dissolved in 30 mL ethyl acetate and then 20 mL cool water was added while stirring. The organic layer was seperated and the aqueous layer was extracted with ethyl acetate (20 mL × 2). The combined ethyl acetate was dried with anhydrous magnesium sulphate and decoloured with active carbon. The filtrate was distilled to dry to get the title compound 2.55 g in 76.2% yield. Brown powder. ^{1}H-NMR (300MHz, DMSO-d_6) δ: 10.44 (s, 1H, OH), 8.75 (d, J = 1.8 Hz 1H, ArH), 8.00 (s, 1H, ArH), 7.07 (d, J = 8.7 Hz, 2H, ArH), 6.69 (d, J = 8.7 Hz, 2H, ArH), 5.11 (d, J = 2.1 Hz, 1H, NH), 2.86 (s, 6H, $N(CH_3)_2$); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 163.4, 153.8, 152.5, 151.2, 150.6, 140.4,

Scheme 5. The proposed mechanism of chlorination by $SOCl_2$/DMF.



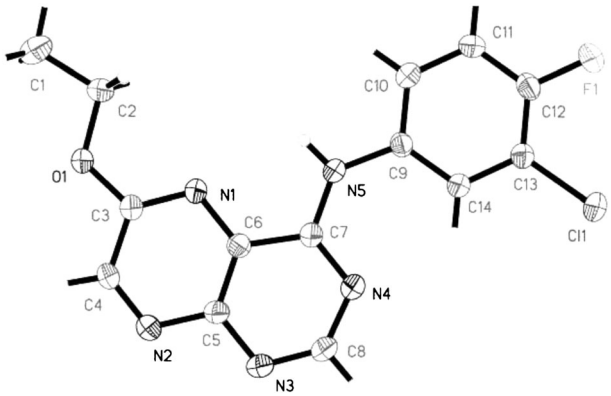


Figure 2. The single crystal structure of compound **26**.

128.2, 127.7, 118.3, 112.5, 58.8; ESI-MS *m/z*: 304.3 $[M(^{35}Cl)+H]^+$, 306.4 $[M(^{37}Cl)+H]^+$.

N-(4-(6-ethoxypteridin-4(3H)-ylidene)cyclohexa-2,5-dienylidene)-N-methyl methanaminium chloride (13b). Brown powder, yield: 72.5%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.93 (s, 1H, ArH), 7.10 (d, *J* = 8.7 Hz, 2H, ArH), 6.66 (d, *J* = 8.7 Hz, 2H, ArH), 6.40 (s, 1H, ArH), 5.27(s, 1H, NH), 4.37(q, 2H, OCH_2CH_3), 2.95 (s, 6H, $N(CH_3)_2$), 1.27(t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 161.8, 154.1, 153.7, 151.5, 151.2, 141.3, 128.0, 127.3, 120.2, 112.9, 63.9, 57.3, 14.4; ESI-MS *m/z*: 332.6 $[M(^{35}Cl)+H]^+$, 334.1 $[M(^{37}Cl)+H]^+$.

N-(4-(6- methoxyethoxy pteridin-4(3H)-ylidene)cyclohexa-2,5-dienylidene)-N-methyl methanaminium chloride (13c). Brown powder, yield: 70.8%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.02 (s, 1H, ArH), 7.24 (d, *J* = 8.7 Hz 2H, ArH), 6.70 (d, *J* = 8.7 Hz, 2H, ArH), 6.54 (s, 1H, ArH), 5.31(s, 1H, NH), 4.69(t, *J* = 7.2 Hz, 2H, OCH_2CH_2O), 3.82(t, *J* = 7.2 Hz, 2H, OCH_2CH_2O), 3.46(s, 3H, OCH_3), 2.92 (s, 6H, $N(CH_3)_2$); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 163.4, 153.6, 152.8, 151.9, 151.3, 140.7, 128.2, 127.5, 116.6, 112.8, 71.3, 65.3, 58.2, 40.8; ESI-MS *m/z*: 362.5 $[M(^{35}Cl)+H]^+$, 364.3 $[M(^{37}Cl)+H]^+$.

General procedure for the synthesis of compounds 14–33.

6-Methoxy-N-(4-methoxyphenyl)pteridin-4-amine (14). **A** 50 mL flask was charged with 6-methoxy-4-chloropteridine **12a** (0.5 g, 2.54 mmol), 4-methoxyaniline (0.37 g, 3.0 mmol), triethylamine (0.30 g, 3.0 mmol) and 25 mL isopropanol. The mixture was refluxed for 8 h with stirring. When the starting material disappeared, the mixture was cooled to room temperature and poured into 50 mL water, then extracted with ethyl acetate (50 mL × 3). The extracted solution was dried with anhydrous magnesium sulphate and distilled to dry under reduced pressure. The residue was dissolved in small amount of chloroform and chromatographied on a silica gel column (ethyl acetate: petroleum ether = 1:2) to give 0.58 g **14** as a yellowish powder, yield: 81.6%. m.p. 161.5–162.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.76 (s, 1H, ArH), 8.69 (s, 1H, ArH), 8.38 (s, 1H, NH), 7.71–7.67 (t, *J* = 9.0 Hz, 2H, ArH), 6.97–6.94 (d, *J* = 9.0 Hz, 2H, ArH), 4.14 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.5, 157.4, 156.7, 156.0, 149.8, 145.2, 130.7, 122.8, 121.6, 114.3, 55.5, 54.6; ESI-MS *m/z*: 283.2 $[M+H]^+$. Anal. calcd for $C_{14}H_{13}N_5O_2$: C, 59.36; H, 4.63; N, 24.72. found: C, 59.41; H, 4.58; N, 24.70.

6-Methoxy-N-p-tolylpteridin-4-amine (15). Yellow powder, yield: 83.2%. m.p. 180–181°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.85 (s, 1H, ArH), 8.67 (s, 1H, ArH), 8.36 (s, 1H, NH), 7.78 (d, *J* = 8.4 Hz, 2H, ArH), 7.24 (d, *J* = 8.4 Hz, 2H, ArH), 4.20 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) δ: 158.3, 157.9, 155.1, 149.01, 145.9, 136.0, 134.1, 129.5, 122.9, 122.1, 55.5, 21.0; ESI-MS *m/z*: 269.3 $[M+H]^+$. Anal. calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. found: C, 62.85; H, 4.94; N, 26.27.

6-Methoxy-N-phenylpteridin-4-amine (16). Yellow powder, yield: 79.5%. m.p. 148.5–150.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.82 (s, 1H, ArH), 8.71 (s, 1H, ArH), 8.49 (s, 1H, NH), 7.86 (t, *J* = 7.8 Hz, 2H, ArH), 7.42 (t, *J* = 7.8 Hz, 2H, ArH), 7.17 (t, *J* = 8.4 Hz, 1H, ArH), 4.15 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.5, 157.3, 155.9, 149.9, 145.5, 137.9, 129.2, 124.5, 121.6, 120.7, 54.6; ESI-MS *m/z*: 254.2 $[M+H]^+$. Anal. calcd for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. found: C, 61.57; H, 4.42; N, 27.61.

N-(4-Fluorophenyl)-6-methoxypteridin-4-amine (17). Yellow powder, yield: 81.7%. m.p. 176–177°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.79 (s, 1H, ArH), 8.72 (s, 1H, ArH), 8.42 (s, 1H, NH), 7.82-7.77 (m, 2H, ArH), 7.14–7.09 (m, 2H, ArH), 4.15 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.9, 157.4, 155.9, 150.0, 145.6, 133.9, 122.7, 121.6, 116.0, 115.7, 54.6; ESI-MS *m/z*: 272.4 $[M+H]^+$. Anal. calcd for $C_{14}H_{14}N_6O$: C, 57.56; H, 3.72; N, 25.82. found: C, 57.49; H, 3.85; N, 25.90.

N-(4-Chlorophenyl)-6-methoxypteridin-4-amine (18). Yellow powder, yield: 84.6%. m.p. 163–165°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.82 (s, 1H, ArH), 8.73 (s, 1H, ArH), 8.48 (s, 1H, NH), 7.86–7.82 (m, 2H, ArH), 7.40–7.37 (m, 2H, ArH), 4.17 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.6, 157.1, 155.7, 149.9, 145.7, 136.5, 129.4, 129.2, 121.8, 121.5, 54.6; ESI-MS *m/z*: 288.2 $[M(^{35}Cl)+H]^+$, 290.4 $[M(^{37}Cl)+H]^+$. Anal. calcd for $C_{13}H_{10}ClN_5O$: C, 54.27; H, 3.50; N, 24.34. found: C, 54.35; H, 3.53; N, 24.28.

N-(3-Chloro-4-fluorophenyl)-6-methoxypteridin-4-amine (19). Yellow powder, yield: 86.2%. m.p. 170.5–172.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.84 (s, 1H, ArH), 8.75 (s, 1H, ArH), 8.43 (s, 1H, NH), 8.10–8.07 (m, 2H, ArH), 7.71–7.66 (m, 1H, ArH), 7.27–7.16 (m, 1H, ArH), 4.17 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.6, 157.1, 155.7, 150.0, 145.9, 134.6, 130.9, 122.7, 121.5, 120.3, 116.9, 54.7; ESI-MS *m/z*: 306.1 $[M(^{35}Cl)+H]^+$, 308.1 $[M(^{37}Cl)+H]^+$. Anal. calcd for $C_{13}H_9ClFN_5O$: C, 51.08; H, 2.97; N, 22.91. found: C, 50.98; H, 3.04; N, 22.85.

N-(3-Chlorophenyl)-6-methoxypteridin-4-amine (20). Yellow powder, yield: 83.6%. m.p. 151–153°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.85 (s, 1H, ArH), 8.74 (s, 1H, ArH), 8.48 (s, 1H, NH), 8.03 (m, 1H, ArH), 7.72–7.69 (m, 1H, ArH), 7.36–7.27 (m, 1H, ArH), 7.14–7.11 (m, 1H, ArH), 4.17 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.6, 157.0, 155.7, 150.0, 145.8, 139.1, 134.8, 130.1, 124.2, 121.5, 120.4, 118.4, 54.7; ESI-MS *m/z*: 288.1 $[M(^{35}Cl)+H]^+$, 290.2 $[M(^{37}Cl)+H]^+$. Anal. calcd for $C_{13}H_{10}ClN_5O$: C, 54.27; H, 3.50; N, 24.34. found: C, 54.32; H, 3.47; N, 24.29.

N-(3-Bromophenyl)-6-methoxypteridin-4-amine (21). Yellow powder, yield: 85.1%. m.p. 160.5–161.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.85 (s, 1H, ArH), 8.73 (s, 1H, ArH), 8.48 (s, 1H, NH), 8.15 (s, 1H, ArH), 7.80–7.76 (m, 1H, ArH), 7.28–7.26 (m, 2H, ArH), 4.17 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.6, 157.0, 155.7, 149.9, 145.8, 139.2, 130.4, 127.1, 123.2, 122.7, 121.5, 118.9, 54.7; ESI-MS *m/z*: 332.0 $[M(^{79}Br)+H]^+$,

334.1 [M(^{81}Br)+H]$^+$. Anal. calcd for $C_{13}H_{10}BrN_5O$: C, 47.01; H, 3.03; N, 21.08. found: C, 46.95; H, 3.10; N, 20.99.

N-(4-Nitrophenyl)-6-ethoxypteridin-4-amine (22). Yellow powder, yield: 79.4%. m.p. 146–146.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.82 (s, 1H, ArH), 8.71 (s, 1H, ArH), 8.52 (s, 1H, NH), 7.85–7.81 (m, 2H, ArH), 7.44–7.66 (m, 2H, ArH), 4.57 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 1.56 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.4, 157.1, 155.8, 149.8, 145.9, 141.7, 127.7, 126.9, 121.8, 121.6, 63.7, 14.2; ESI-MS *m/z*: 313.4 [M+H]$^+$. Anal. calcd for $C_{14}H_{12}N_6O_3$: C, 53.85; H, 3.87; N, 26.91. found: C, 53.78; H, 3.94; N, 26.83.

N-(4-Chlorophenyl)-6-ethoxypteridin-4-amine (23). Yellow powder, yield: 84.3%. m.p. 172–174°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.81 (s, 1H, ArH), 8.71 (s, 1H, ArH), 8.45 (s, 1H, NH), 7.85–7.80 (m, 2H, ArH), 7.40–7.35 (m, 2H, ArH), 4.56 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 1.55 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.2, 157.1, 155.6, 149.8, 145.9, 136.5, 129.3, 129.1, 121.8, 121.5, 63.6, 14.2; ESI-MS *m/z*: 302.8 [M(^{35}Cl)+H]$^+$, 304.6 [M(^{37}Cl)+H]$^+$. Anal. calcd for $C_{14}H_{12}ClN_5O$: C, 55.73; H, 4.01; N, 23.21. found: C, 55.68; H, 4.07; N, 23.26.

N-(3-Chlorophenyl)-6-ethoxypteridin-4-amine (24). Yellow powder, yield: 82.6%. m.p. 161–163°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.85 (s, 1H, ArH), 8.72 (s, 1H, ArH), 8.47 (s, 1H, NH), 8.03–8.017 (m, 1H, ArH), 7.72–7.69 (m, 1H, ArH), 7.36–7.27 (m, 1H, ArH), 7.14–7.11 (m, 1H, ArH), 4.57 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 1.55 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.3, 157.0, 155.6, 149.8, 146.0, 139.1, 134.8, 130.1, 124.2, 121.5, 120.3, 118.3, 63.7, 14.1; ESI-MS *m/z*: 302.6 [M(^{35}Cl)+H]$^+$, 304.7 [M(^{37}Cl)+H]$^+$. Anal. calcd for $C_{14}H_{12}ClN_5O$: C, 55.73; H, 4.01; N, 23.21. found: C, 55.72; H, 3.97; N, 23.17.

N-(3-Bromophenyl)-6-ethoxypteridin-4-amine (25). Yellow powder, yield: 85.2%. m.p. 154–156°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.84 (s, 1H, ArH), 8.71 (s, 1H, ArH), 8.45 (s, 1H, NH), 8.14 (s, 1H, ArH), 7.80–7.76 (m, 1H, ArH), 7.28–7.26 (m, 2H, ArH), 4.57 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 1.55 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.3, 157.0, 155.5, 149.8, 146.0, 139.3, 130.4, 127.0, 123.1, 122.7, 121.5, 118.8, 63.7, 14.2; ESI-MS *m/z*: 346.4 [M(^{79}Br)+H]$^+$, 348.3 [M(^{81}Br)+H]$^+$. Anal. calcd for $C_{14}H_{12}BrN_5O$: C, 48.57; H, 3.49; N, 20.23. found: C, 48.59; H, 3.45; N, 20.19.

N-(3-Chloro-4-fluorophenyl)-6-ethoxypteridin-4-amine (26). Yellow powder, yield: 83.8%. m.p. 192.5–194.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.83 (s, 1H, ArH), 8.72 (s, 1H, ArH), 8.41 (s, 1H, NH), 8.09–8.06 (m, 1H, ArH), 7.71–7.67 (m, 1H, ArH), 7.22–7.16 (m, 1H, ArH), 4.57 (q, *J* = 6.9 Hz, 2H, OCH_2CH_3), 1.55 (t, *J* = 6.9 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.3, 157.0, 155.5, 149.8, 146.1, 134.6, 122.8, 121.4, 120.3, 120.2, 116.9, 116.6, 63.7, 14.2; ESI-MS *m/z*: 320.0 [M(^{35}Cl)+H]$^+$, 322.1 [M(^{37}Cl)+H]$^+$. Anal. calcd for $C_{14}H_{11}ClFN_5O$: C, 52.59; H, 3.47; N, 21.90. found: C, 52.53; H, 3.51; N, 21.88.

N-(3-Chlorophenyl)-6-(2-methoxyethoxy)pteridin-4-amine (27). Yellow powder, yield: 86.1%.m.p. 131–131.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.85 (s, 1H, ArH), 8.79 (s, 1H, ArH), 8.46 (s, 1H, NH), 8.03–8.02 (m, 1H, ArH), 7.72–7.68 (m, 1H, ArH), 7.36–7.28 (m, 1H, ArH), 7.14–7.11 (m, 1H, ArH), 4.67 (t, *J* = 6.8 Hz, 2H, OCH_2CH_2), 3.88 (t, *J* = 6.8 Hz, 2H, CH_2CH_2O), 3.50 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.0, 157.0, 155.8, 150.0, 145.9, 139.1, 134.8, 130.1, 124.2, 121.3, 120.4, 118.4, 70.2, 66.8, 59.3; ESI-MS *m/z*: 332.4 [M(^{35}Cl)+H]$^+$, 334.3 [M(^{37}Cl)+H]$^+$. Anal. calcd for $C_{15}H_{14}ClN_5O_2$: C, 54.30; H, 4.25; N, 21.11. found: C, 54.27; H, 4.28; N, 21.06.

N-(4-Chlorophenyl)-6-(2-methoxyethoxy)pteridin-4-amine (28). Yellow powder, yield: 81.7%. m.p. 145–146°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.82 (s, 1H, ArH), 8.78 (s, 1H, ArH), 8.45 (s, 1H, NH), 7.83–7.79 (m, 2H, ArH), 7.40–7.36 (m, 2H, ArH), 4.66 (t, *J* = 7.2 Hz, 2H, OCH_2CH_2), 3.87 (t, *J* = 7.2 Hz, 2H, CH_2CH_2O), 3.49 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.1, 157.0, 155.8, 150.0, 145.8, 136.5, 129.3, 129.1, 121.8, 121.4, 70.2, 66.7, 59.3; ESI-MS *m/z*: 332.3 [M(^{35}Cl)+H]$^+$, 334.1 [M(^{37}Cl)+H]$^+$. Anal. calcd for $C_{15}H_{14}ClN_5O_2$: C, 54.30; H, 4.25; N, 21.11. found: C, 54.34; H, 4.22; N, 21.16.

N-(3-Bromophenyl)-6-(2-methoxyethoxy)pteridin-4-amine (29). Yellow powder, yield: 83.6%. m.p. 136.5–137.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.85 (s, 1H, ArH), 8.79 (s, 1H, ArH), 8.45 (s, 1H, NH), 8.14 (s, 1H, ArH), 7.80-7.76 (m, 1H, ArH), 7.28–7.26 (m, 2H, ArH), 4.66 (t, *J* = 6.9 Hz, 2H, OCH_2CH_2), 3.88 (t, *J* = 6.9 Hz, 2H, CH_2CH_2O), 3.50 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.0, 157.0, 155.8, 150.0, 145.9, 139.2, 130.4, 127.1, 123.2, 122.7, 121.3, 118.9, 70.2, 66.8, 59.3; ESI-MS *m/z*: 376.4 [M(^{79}Br)+H]$^+$, 378.1 [M(^{81}Br)+H]$^+$. Anal. calcd for $C_{15}H_{14}BrN_5O_2$: C, 47.89; H, 3.75; N, 18.62. found: C, 47.81; H, 3.83; N, 18.67.

N-(4-Fluorophenyl)-6-(2-methoxyethoxy)pteridin-4-amine (30). Yellow powder, yield: 82.9%. m.p. 120–121°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.80 (s, 1H, ArH), 8.78 (s, 1H, ArH), 8.42 (s, 1H, NH), 7.83–7.78 (m, 2H, ArH), 7.16–7.10 (m, 2H, ArH), 4.66 (t, *J* = 4.8 Hz, 2H, OCH_2CH_2), 3.87 (t, *J* = 4.8 Hz, 2H, CH_2CH_2O), 3.50 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.9, 157.0, 155.9, 150.0, 145.7, 133.8, 122.7, 121.3, 116.9, 116.6, 70.2, 66.8, 59.3; ESI-MS *m/z*: 316.2 [M+H]$^+$. Anal. calcd for $C_{15}H_{14}FN_5O_2$: C, 57.14; H, 4.48; N, 22.21. found: C, 57.21; H, 4.42; N, 22.17.

N-(3-Chloro-4-fluorophenyl)-6-(2-methoxyethoxy)pteridin-4-amine (31). Yellow powder, yield: 84.4%. m.p. 138–140.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.85 (s, 1H, ArH), 8.80 (s, 1H, ArH), 8.40 (s, 1H, NH), 8.09-8.06 (m, 1H, ArH), 7.72-7.66 (m, 1H, ArH), 7.23–7.17 (m, 1H), 4.67 (t, *J* = 7.2 Hz, 2H, OCH_2CH_2), 3.87 (t, *J* = 7.2 Hz, 2H, CH_2CH_2O), 3.50 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 157.1, 157.0, 155.8, 153.1, 150.1, 146.0, 134.6, 122.7, 121.3, 120.3, 116.9, 116.6, 70.2, 66.8, 59.3; ESI-MS *m/z*: 350.1 [M(^{35}Cl)+H]$^+$, 352.1 [M(^{37}Cl)+H]$^+$. Anal. calcd for $C_{15}H_{13}ClFN_5O_2$: C, 51.51; H, 3.75; N, 20.02. found: C, 51.47; H, 3.80; N, 19.96.

6-Methoxy-4-(piperidin-1-yl)pteridine (32). Tan powder, yield: 82.3%. m.p. 103–106°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.74 (s, 1H, ArH), 8.52 (s, 1H, ArH), 4.24 (t, *J* = 4.8 Hz, 4H, NCH_2), 3.98 (s, 3H, OCH_3), 1.71 (t, *J* = 4.8 Hz, 6H, CH_2); ^{13}C-NMR (300 MHz, DMSO-d_6) δ: 159.3, 155.1, 154.9, 151.7, 144.2, 123.4, 54.6, 49.0, 26.5, 24.6 ; ESI-MS *m/z*: 246.2 [M+H]$^+$. Anal. calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. found: C, 58.72; H, 6.19; N, 28.61.

6-Methoxy-4-morpholinopteridine (33). Yellowish powder, yield: 85.4%. m.p. 179–181°C. ^{1}H-NMR(300 MHz, DMSO-d_6) δ:8.79 (s, 1H, ArH), 8.60 (s, 1H, ArH), 4.32 (t, *J* = 4.8 Hz, 4H, OCH_2), 3.98 (s, 3H, OCH_3), 3.79 (t, *J* = 4.8 Hz, 4H, NCH_2); ^{13}C-NMR (300 MHz, DMSO-d_6) δ: 159.4, 155.3, 154.5, 151.3, 144.8, 123.4, 66.8, 54.9, 48.3; ESI-MS *m/z*: 248.4 [M+H]$^+$. Anal. calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30, N; 28.32. found: C, 53.38; H, 5.36; N, 28.35.

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