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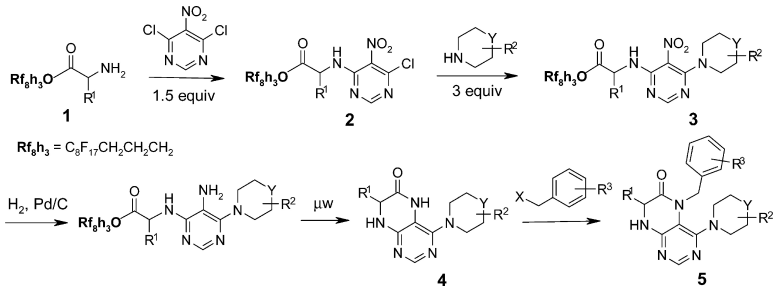

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Solution-Phase Parallel Synthesis of an N-Alkylated Dihydropteridinone Library from Fluorous Amino Acids

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Parallel synthesis of an N-alkylated dihydropteridinone library has been accomplished in five steps starting from two displacement reactions of 4,6-dichloro-5-nitropyrimidine, first with fluorous amino acids, then with secondary amines. The hydrogenation of the nitro group followed by microwave-assisted cyclization gave the dihydropteridinones. Further diversification was achieved by the reaction of dihydropteridinones with benzyl halides to afford mono-N-alkylated products. All the reaction intermediates and final products were purified by SPE or precipitation without the need to perform chromatography.

Introduction

Light fluorous synthesis is a new solution-phase method that combines the fluorous tagging strategy with unique fluorous separation techniques.[1] Perfluoroalkyl groups, such as C_8F_{17}, are usually employed as "phase tags" to enable tagged compounds to be separated from untagged compounds by fluorous solid-phase extraction (F-SPE).[2] Reactions can be conducted in a homogeneous environment using common organic solvents. Reaction mixtures can be easily analyzed by conventional methods, such as TLC, NMR, and LC/MS without cleaving the fluorous tag. Intermediates can be purified by fluorous separation methods as well as by chromatography, crystallization, and distillation.

As a part of our continuing effort on the development of fluorous technology for solution-phase synthesis,[3] we recently explored the parallel synthesis of a dihydropteridinone library. Dihydropteridinone is a privileged heterocyclic ring system[4] because many of its derivatives possess useful biological activities.[5] Our goal is to develop an efficient synthetic route utilizing fluorous tags and F-SPE techniques to facilitate reaction and separation processes. This project was inspired by a work from the Cox group (Scheme 1).[6] In their solid-phase synthesis of dihydropteridinones, 4,6-dichloro-5-nitropyrimidine was first reacted with Wang resin-attached amino acids, followed by reaction with amino acid methyl esters.[7] The reduction of the nitro group with $SnCl_2$ followed by the spontaneous cyclization led to the formation of dihydropteridinones. Two possible cyclization products could be generated by the competitive cyclizations. The product with the polymer linker was released by the treatment of TFA.

In the fluorous synthesis, we made the following changes or modifications (Scheme 2): (1) fluorous amino acids were used for the first displacement reaction; (2) secondary amines were used for the second displacement reaction to eliminate the competitive cyclization at the late step; (3) hydrogenation with a Pd/C catalyst was used for nitro group reduction because it is easy to separate the catalyst from the reaction mixture, and this kind of heterogeneous reaction is difficult to perform in the solid-phase synthesis; (4) microwave irradiation was used to promote the cyclization for the formation of the dihydropteridinone ring;[8] and (5) the dihydropteridinones were further decorated by selective N-benzylation to afford a final product with three points of diversity.

Results and Discussion

Fluorous amino acids are readily prepared from the corresponding *N*-Boc-amino acids **6**. As shown in Scheme 3, four Boc-protected amino acids were reacted with 3-(perfluorooctyl)propanol using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI−HCl) and 1-hydroxybenzotriazole (HOBT) as the coupling agents and *N*,*N*-diisopropylethylamine (DIEA) as a base. Each product was purified by washing with aq $NaHCO_3$ to remove the excess Boc-amino acid followed by washing with 1 N HCl to remove basic side products. The Boc group was removed by treatment with trifluoroacetic acid (TFA) to afford the TFA salt of the amino acid **1**{*1*−*4*}. The TFA salts were used in the next step without further purification.

We recently reported the reductive amination of fluorous amino acids in the synthesis of hydantoin analogues.[3d] In this work, fluorous amino acids were used for displacement reactions. Two displacement reactions of 4,6-dichloro-5-nitropyrimidine were conducted in one pot. Solutions of four different fluorous amino esters **1**{*1*−*4*} in dimethylformamide (DMF), each divided into five portions, was added to 20 different vials, each containing 1.5 equiv of 4,6-dichloro-5-nitropyrimidine. The exothermic reactions initiated by addition of DIEA were finished within 10 min. LC/MS analysis of reaction mixtures showed no indication of formation of disubstituted byproducts. Five different amines **7**{*1*−*5*} (3.0 equiv) were added for a second displacement reaction. The resulting 20 reaction mixtures were directly charged onto Fluoro*Flash* SPE cartridges.[9] The cartridges

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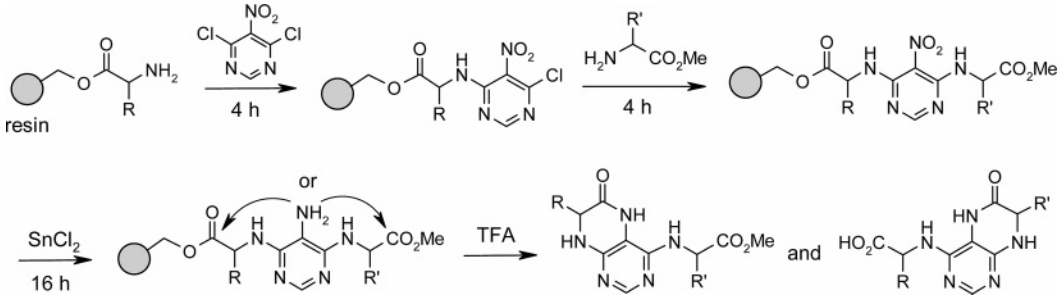
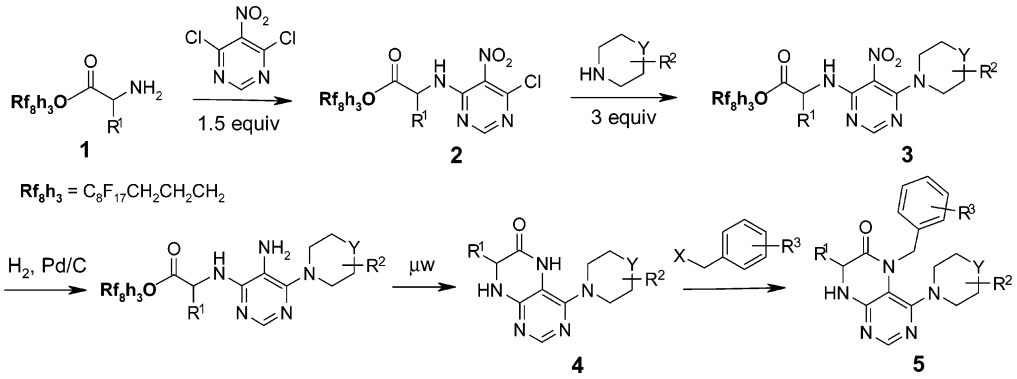
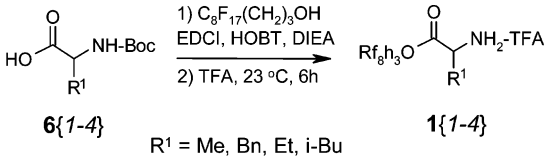
Scheme 1. Solid-Phase Synthesis of Dihydropteridinones



Scheme 2. Fluorous Synthesis of Dihydropteridinones



Scheme 3. Preparation of Four Fluorous Tagged Amino Acids **1**{*1*−*4*}



were first eluted with 80:20 MeOH−H_2O (120 mL) to remove nonfluorous components. The desired product was collected in the second fraction eluted with acetone (120 mL). The LC/MS analysis of the products showed moderate purities (average ∼60%). The impurity has a short retention time on the reverse C18 HPLC column and found to poison the palladium catalyst in the next step. This polar impurity was removed by SPE with normal silica gel. Purities and yields of compounds **3**{*1*−*4*,*1*−*5*} are shown in Table 1.

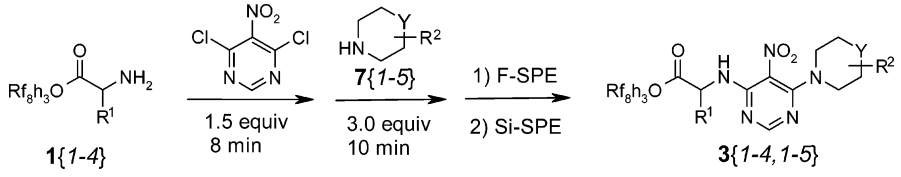
Twenty intermediates **3**{*1*−*4*,*1*−*5*} were subjected to hydrogenation with Pd/C (3 mol % loading) at 1 atm of H_2 for 12 h (Scheme 5). The catalyst was easily removed from the products by passing through a pad of Celite. We found that only a small amount of hydrogenation product underwent spontaneous cyclization, which was in contrast to the Sn(II) reduction reported by the Cox group in their solid-phase synthesis.[6] Probably Sn(II) or Sn(IV) in the reaction mixture acted as a Lewis acid to promote the cyclization. We tried

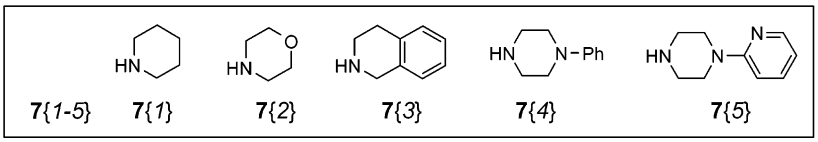
Table 1. Yields and Purities of Intermediate **3**{*1*−*4*,*1*−*5*}

compound	yield (%)	purity (%)
3{*1*,*1*}	80	96
3{*1*,*2*}	60	96
3{*1*,*3*}	88	95
3{*1*,*4*}	59	98
3{*1*,*5*}	31	96
3{*2*,*1*}	89	98
3{*2*,*2*}	71	95
3{*2*,*3*}	70	98
3{*2*,*4*}	59	96
3{*2*,*5*}	49	nd[a]
3{*3*,*1*}	70	94
3{*3*,*2*}	67	92
3{*3*,*3*}	70	90
3{*3*,*4*}	59	95
3{*3*,*5*}	53	nd
3{*4*,*1*}	73	95
3{*4*,*2*}	62	95
3{*4*,*3*}	61	nd
3{*4*,*4*}	53	95
3{*4*,*5*}	60	nd

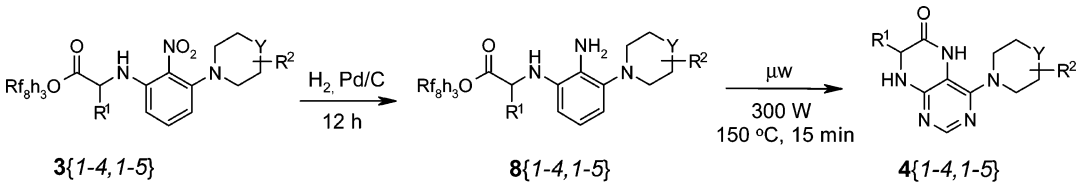
[a] nd = not determined.

Scheme 4. Formation of **3**{*1*−*4*,*1*−*5*} by Double Displacement of 4,6-Dichloro-5-nitropyrimidine





Scheme 5. Formation of **4**{*1−4,1−5*} by Hydrogenation and Cyclization of **3**{*1−4,1−5*}



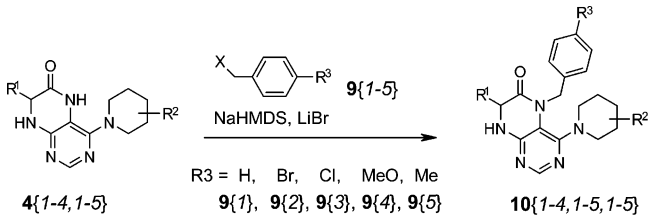
3{*1-4,1-5*} **8**{*1-4,1-5*} **4**{*1-4,1-5*}

Table 2. Amounts, Yields, and Purities of Dihydropteridinone **4**{*1−4,1−5*}

compound	amount (g)	yield (%)[a]	purity (%)
4{*1,1*}	0.33	36	98
4{*1,2*}	0.31	34	100
4{*1,3*}	0.45	41	98
4{*1,4*}	0.39	32	94
4{*1,5*}	0.31	26	93
4{*2,1*}	0.47	39	88
4{*2,2*}	0.53	44	93
4{*2,3*}	0.56	41	86
4{*2,4*}	0.58	39	98
4{*2,5*}	0.41	28	95
4{*3,1*}	0.34	35	96
4{*3,2*}	0.38	39	100
4{*3,3*}	0.37	32	92
4{*3,4*}	0.35	28	97
4{*3,5*}	0.37	30	94
4{*4,1*}	0.33	31	97
4{*4,2*}	0.39	37	100
4{*4,3*}	0.41	33	100
4{*4,4*}	0.41	30	97
4{*4,5*}	0.49	36	98

[a] Yields are calculated based on **1**.

Scheme 6. N-Benzylation of **4**{*1−4,1−5*}



4{*1-4,1-5*} **9**{*1*}, **9**{*2*}, **9**{*3*}, **9**{*4*}, **9**{*5*} **10**{*1-4,1-5,1-5*}

the reduction of **3** with $SnCl_2$; however, the reaction was low-yielding and produced many unidentified byproducts.

To promote the cyclization, the reduced products **8**{*1−4,1−5*} were heated under microwaves (300 W, 15 min at 150 °C) to give **4**{*1−4,1−5*}. Since the cyclized products had low solubility in many organic solvents at room temperature, they precipitated out from the reaction mixture and were collected by filtration. The amounts, yields, and purities of 20 cyclized products **4**{*1−4,1−5*} are shown in Table 2.

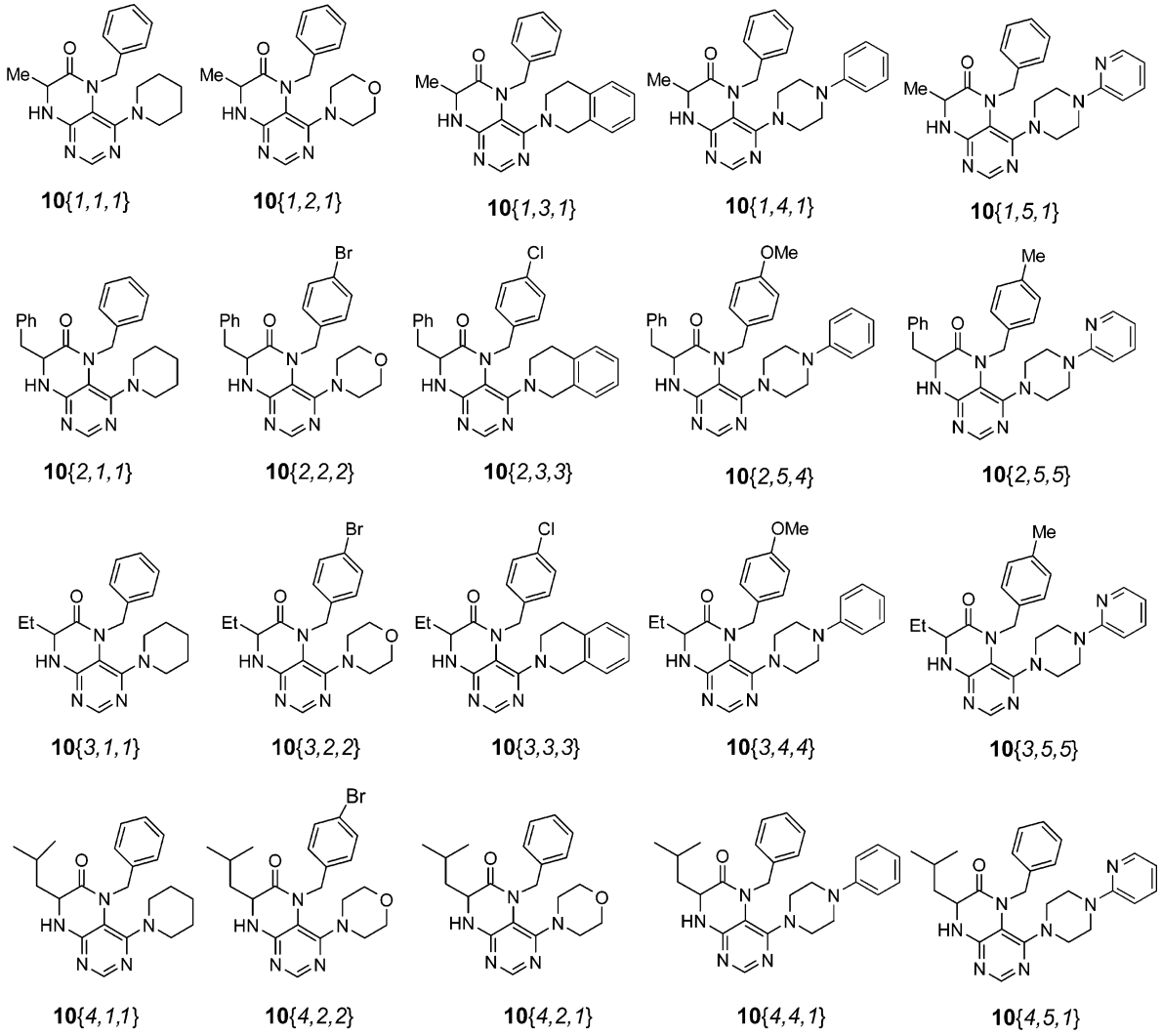
The final step of the library synthesis was the N-alkylation of dihydropteridinone. We initially attempted N-acylation with different acid chlorides, such as benzoyl chloride and cyclohexylcarbonyl chloride; however, the regioselectivity between the two nitrogens in compound **4** was poor. Two different monoacylated products (presumably regioisomers) together with the double acylated product were observed in the reaction mixture by LC/MS analysis. The N-alkylation reaction with 1.0 equiv of a benzyl halide and 1.0 equiv of a base gave a monoalkylated product in high selectivity. A small amount of LiBr was used to minimize the formation of the *O*-alkylation byproducts[3a] (Scheme 6). NaHMDS in THF was used as the base for the reaction of dihydropteridinones **4**{*1−4,1−5*} with five benzyl halides **9**{*1−5*}. The alkylation reactions were finished in 10 min. After aqueous workup, the products were purified by Si−SPE to remove the starting material if there was any. Purities and yields of **10**{*1−4,1−5,1−5*} are shown in Table 3. Among the 89 products, 71 gave purities >80%. The major impurity found was the double alkylated product as assayed by LC/MS analysis. The representative structures of synthesized final products are listed in Scheme 7.

Table 3. Yields and Purities of Final Products **10**{*1−4,1−5,1−5*}

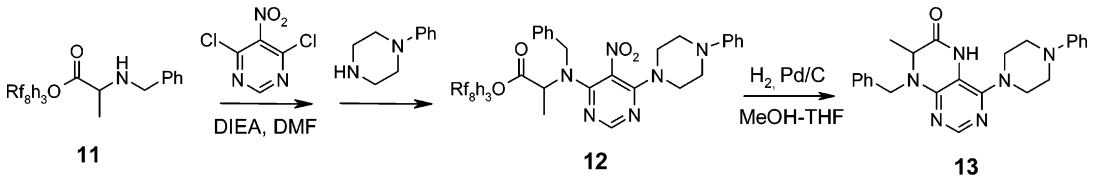
compound	yield (%)	purity (%)	compound	yield (%)	purity (%)
10{*1,2,1*}	66	79	**10**{*2,2,1*}	93	81
10{*1,2,2*}	53	77	**10**{*2,2,2*}	95	81
10{*1,2,3*}	56	64	**10**{*2,2,3*}	84	76
10{*1,2,4*}	49	71	**10**{*2,2,4*}	71	73
10{*1,2,5*}	63	71	**10**{*2,2,5*}	91	72
10{*1,3,1*}	77	89	**10**{*2,3,1*}	80	85
10{*1,3,2*}	83	85	**10**{*2,3,2*}	87	70
10{*1,3,3*}	74	88	**10**{*2,3,3*}	77	46
10{*1,3,4*}	83	89	**10**{*2,3,4*}	94	68
10{*1,3,5*}	73	80	**10**{*2,3,5*}	88	16
10{*1,4,1*}	59	97	**10**{*2,4,1*}	>99	93
10{*1,4,2*}	57	96	**10**{*2,4,2*}	77	88
10{*1,4,3*}	72	86	**10**{*2,4,3*}	93	90
10{*1,4,4*}	72	85	**10**{*2,4,4*}	>99	93
10{*1,4,5*}	74	81	**10**{*2,4,5*}	95	84
10{*1,5,1*}	59	97	**10**{*2,5,1*}	89	88
10{*1,5,2*}	37	85	**10**{*2,5,2*}	99	86
10{*1,5,3*}	64	89	**10**{*2,5,3*}	>99	85
10{*1,5,4*}	74	87	**10**{*2,5,4*}	94	90
10{*1,5,5*}	26	78	**10**{*2,5,5*}	94	84
10{*2,1,1*}	73	77	**10**{*3,1,1*}	80	95
10{*2,1,2*}	71	77	**10**{*3,1,2*}	92	92
10{*2,1,3*}	32	72	**10**{*3,1,3*}	94	92
10{*2,1,4*}	82	82	**10**{*3,1,4*}	92	95
10{*2,1,5*}	89	81	**10**{*3,1,5*}	85	93
10{*3,2,1*}	83	92	**10**{*4,1,1*}	89	98
10{*3,2,2*}	82	81	**10**{*4,1,2*}	93	93
10{*3,2,3*}	89	83	**10**{*4,1,3*}	94	94
10{*3,2,4*}	68	92	**10**{*4,1,4*}	98	96
10{*3,2,5*}	94	80	**10**{*4,1,5*}	92	87
10{*3,3,1*}	87	85	**10**{*4,2,1*}	>99	94
10{*3,3,2*}	84	83	**10**{*4,2,2*}	>99	94
10{*3,3,3*}	92	83	**10**{*4,2,3*}	97	94
10{*3,3,4*}	93	86	**10**{*4,2,4*}	85	86
10{*3,3,5*}	88	63	**10**{*4,2,5*}	83	90
10{*3,4,1*}	86	95	**10**{*4,4,1*}	92	93
10{*3,4,2*}	95	92	**10**{*4,4,2*}	>99	86
10{*3,4,3*}	91	90	**10**{*4,4,3*}	96	89
10{*3,4,4*}	>99	93	**10**{*4,4,4*}	>99	93
10{*3,4,5*}	>99	85	**10**{*4,4,5*}	91	82
10{*3,5,1*}	76	87	**10**{*4,5,1*}	>99	94
10{*3,5,2*}	88	83	**10**{*4,5,2*}	>99	94
10{*3,5,3*}	89	86	**10**{*4,5,3*}	>99	93
10{*3,5,4*}	71	87	**10**{*4,5,4*}	>99	96
			10{*4,5,5*}	>99	89

The regiochemistry for the N-akylation of **4** was determined by ^{13}C NMR (HMBC, HMQC) analysis of **10**{*1,4,1*} and

Scheme 7. Representative Structures of N-Alkylated Dihydropteridinones **10**{*1−4,1−5,1−5*}



Scheme 8. Preparation of **13**



confirmed by the analysis of its regioisomer **13**. Compound **13** was prepared from *N*-benzyl-substituted alanine **11** (Scheme 8). Double substitutions of 4,6-dichloro-5-nitropyrimidine with **11** and 4-phenylpiperazine, followed by hydrogenation of **12**, led to formation of cyclized product **13**. The ^{1}H NMR spectrum of **13** was clearly different from that of **10**{*1,4,1*}. Thus, the benzyl group in compound **10** was confirmed to be attached to the amide nitrogen, as shown in Scheme 6.

Conclusions

We have developed a 5-step protocol for solution-phase parallel synthesis of an N-alkylated dihydropteridinone library. The reaction for the disubstituted intermediate **3**{*1−4,1−5*} requires less than 20 min under high concentration conditions. The cyclization reactions for **4**{*1−4,1−5*} were promoted by microwave heating. The dihydropteridinone ring was further decorated by N-alkylation to introduce an additional diversity point.

In this project, we have demonstrated the following advantages of fluorous synthesis: there is no need to perform chromatography for solution-phase library synthesis; literature procedures for solid-phase synthesis can be adapted by fluorous synthesis with minimal development effort; each reaction step can be closely monitored by TLC or LC/MS analysis; reaction mixtures can be purified by fluorous SPE as well as by other methods, such as precipitation; and microwave and fluorous technologies can be coupled to achieve high synthetic efficiency.

Experimental Section

General Methods. All starting materials, solvents, and reagents were commercially available and were used without further purification. Fluoro*Flash* SPE cartridges were obtained from Fluorous Technologies, Inc. SPE purification was conducted in parallel on a 2 × 12 SPE manifold available from Supelco and Fisher. Microwave reactions were con-

ducted sequentially on a CEM Explorer single mode microwave reactor with a 10-mL cap-sealed tube. NMR spectra were obtained on a Bruker AC-270 spectrometer (270 MHz). ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.5 MHz, respectively. Chemical shifts are in parts per million relative to TMS (0 ppm). $CDCl_3$ was used as the solvent unless otherwise specified. LC/MS spectra were obtained on an Agilent 1100 system. Purities were calculated on the basis of UV254 absorption. APCI was used as the ion source for all MS. Liquid chromatography/mass spectra were performed under the following conditions. Method 1. Column: XTerra MS C18 3.5 μm 4.6 × 100 mm. Eluent A, water; B, MeOH. Flow rate: 1 mL/min. Detection: UV (254 nm). 65−100% B in A over 5 min, 100% B for 5 min. Method 2. Column: XTerra MS C18 3.5 μm 4.6 × 100 mm. Flow rate: 0.9 mL/min. Eluent A, water; B, MeOH. Detection: UV (254 nm). 5% B in A for 0.5 min, 5−100% B in A over 6.5 min, 100% B for 3.5 min. Method 3. Column: Luna 3u C18(2) 100A 2.0 × 50 mm. Eluent A, water, TFA 0.025%; B, acetonitrile, TFA 0.02%. Flow rate: 0.9 mL/min. Detection: UV (254 nm). 5% B in A for 0.5 min, 5−100% B in A over 3.5 min, then 100% B for 3.5 min.

Representative Procedure for Fluorous Tagging of Amino Acids. Preparation of 1{*3*}. To a mixture of 3-(perfluorooctyl)propanol (12.0 g, 25.0 mmol), *N*-Boc-2-aminobutyric acid (7.60 g, 37.5 mmol), HOBt (5.4 g, 40 mmol), and *N*,*N*-diisopropylethylamine (13 mL, 74 mmol) in CH_2Cl_2 (110 mL) was added EDCI−HCl (7.2 g, 38 mmol) in one portion at 23 °C. The mixture was stirred for 1 day, and saturated aq $NaHCO_3$ (50 mL) was added. After 20 min, Et_2O (250 mL) was added, and the ether layer was washed with 1 N HCl (3 × 100 mL), H_2O (1 × 100 mL), saturated aqueous $NaHCO_3$ (2 × 100 mL), and brine (1 × 100 mL). The ether layer was dried over $MgSO_4$. After the evaporation of the solvent, the residue was dissolved in DCM (120 mL), and TFA (30 mL) was added at 23 °C. The reaction completed in 6 h (TLC analysis), and the solvent and the excess TFA were removed under reduced pressure to give viscous oil that was used for the next step without any purification.

3-(Perfluorooctyl)propyl 2-Aminopropionate TFA Salt. 1{*1*}. ^{1}H NMR (270 MHz, CD_3OD) δ = 4.33 (2H, t, J = 6.3 Hz), 4.13 (1H, q, J = 7.2 Hz), 2.45−2.21 (2H, m), 2.10−1.95 (2H, m), 1.54 (3H, d, J = 7.2 Hz). LC/MS (method 3): m/z = 550.1 $[M + H]^+$ (t_R = 5.14 min by MSD).

3-(Perfluorooctyl)propyl 2-Amino-3-phenylpropionate TFA Salt 1{*2*}. ^{1}H NMR (270 MHz, CD_3OD) δ = 7.41−7.22 (5H, m), 4.34 (1H, t, J = 7.2 Hz), 4.31−4.13 (2H, m), 3.20 (2H, d, J = 7.3 Hz), 2.23−1.99 (2H, m), 1.95−1.80 (2H, m). LC/MS (method 3): m/z = 626.1 $[M + H]^+$ (t_R = 5.55 min by MSD).

3-(Perfluorooctyl)propyl 2-Aminobutanoate TFA Salt 1{*3*}. ^{1}H NMR (270 MHz, CD_3OD) δ = 4.34 (2H, t, J = 6.3 Hz), 4.04 (1H, t, J = 6.2 Hz), 2.43−2.20 (2H, m), 2.09−1.86 (4H, m), 1.05 (3H, t, J = 7.5 Hz). LC/MS (method 3): m/z = 564.1 $[M + H]^+$ (t_R = 5.30 min by MSD).

3-(Perfluorooctyl)propyl 2-Amino-4-methylpentanoate TFA Salt 1{*4*}. ^{1}H NMR (270 MHz, CD_3OD) δ = 4.34 (2H, t, J = 6.3 Hz), 4.07 (1H, t, J = 6.7 Hz), 2.43−2.20 (2H, m), 2.09−1.95 (2H, m), 1.88−1.60 (3H, m), 1.00 (3H, d, J = 5.9 Hz), 0.99 (3H, d, J = 5.9 Hz). LC/MS (method 3): m/z = 592.1 $[M + H]^+$ (t_R = 5.44 min by MSD).

Representative Procedure for Substitution on 4,6-Dichloro-5-nitropyrimidine. Preparation of 3{*1,2*}. To a vial that contained 4,6-dichloro-5-nitropyrimidine (1.0 g, 5.2 mmol, 1.5 equiv) was added a solution of **1**{*1*} in DMF (0.62 M, 6.0 mL, 3.7 mmol, 1.0 equiv) and then DIEA (2.2 mL, 12.6 mmol, 3.4 equiv). After 8 min, morpholine (1.0 mL, 11 mmol, 3 equiv) was added in one portion. After 1 day, the mixture was loaded on top of a Fluro*Flash* silica gel cartridge (30 g) which had been preconditioned with MeOH−H_2O (80:20). The cartridge was eluted with MeOH−H_2O (120 mL), then acetone (120 mL). The acetone fraction was concentrated and dissolved in EtOAc (5 mL). It was eluted through a silica gel cartridge (30 g) with hexanes−EtOAc (4:1). The solvent was evaporated under a reduced pressure to give **3**{*1,2*} as a yellow viscous oil (1.67 g, 2.21 mmol, 60% yield).

3-(Perfluorooctyl)propyl 2-{6-(Morpholin-4-yl)-5-nitoropyrimidin-4-ylamino)propionate 3{*1,2*}. Yield: 1.67 g (60%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.48 (1H, d, J = 6.5 Hz), 8.00 (1H, s), 4.81 (1H, pentet, J = 7.0 Hz), 4.33−4.21 (2H, m), 3.76 (4 H, t, J = 4.8 Hz), 3.70−3.60 (2 H, m), 3.57−3.45 (2H, m), 2.35−1.93 (4H, m), 1.57 (3H, d, J = 7.2 Hz). LC/MS (method 1): m/z = 758.1 $[M + H]^+$ (96%, t_R = 7.40 min).

3-(Perfluorooctyl)propyl 2-{6-(Morpholin-4-yl)-5-nitoropyrimidin-4-ylamino)-3-phenylpropionate 3{*2,2*}. Yield: 2.21 g (71%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.51 (1H, d, J = 6.7 Hz), 8.00 (1H, s), 7.38−7.28 (3 H, m), 7.26−7.18 (2H, m), 5.04 (1H, q, J = 6.7 Hz), 4.30−4.08 (2H, m), 3.75 (4H, t, J = 4.8 Hz), 3.70−3.58 (2H, m), 3.56−3.42 (2H, m), 3.21 (2H, d, J = 6.7 Hz), 2.16−1.82 (4H, m). LC/MS (method 1): m/z = 834.2 $[M + H]^+$ (95%, t_R = 7.78 min).

3-(Perfluorooctyl)propyl 2-{6-(Morpholin-4-yl)-5-nitoropyrimidin-4-ylamino)butanoate 3{*3,2*}. Yield: 1.92 g (67%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.53 (1H, d, J = 6.8 Hz), 8.01 (1H, s), 4.77 (1H, q, J = 5.7 Hz), 4.38−4.20 (2H, m), 3.77 (4H, t, J = 4.8 Hz), 3,72−3.61 (2H, m), 3.57−3.45 (2H, m), 2.32−1.83 (6H, m), 1.04 (3H, t, J = 7.5 Hz). LC/MS (method 1): m/z = 772.1 $[M + H]^+$ (92%, t_R = 7.61 min).

3-(Perfluorooctyl)propyl 4-Methyl-2-{6-(morpholin-4-yl)-5-nitoropyrimidin-4-ylamino)pentanoate 3{*4,2*}. Yield: 1.82 g (62%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.39 (1H, d, J = 6.9 Hz), 8.00 (1H, s), 4.80 (1H, q, J = 6.9 Hz), 4.36−4.17 (2H, m), 3.77 (4H, t, J = 4.8 Hz), 3.76−3.62 (2H, m), 3.55−3.42 (2H, m), 2.30−1.93 (4H, m), 1.83−1.68 (3H, m), 1.01 (3H, d, J = 6.1 Hz), 0.96 (3H, d, J = 6.1 Hz). LC/MS (method 1): m/z = 800.2 $[M + H]^+$ (95%, t_R = 7.86 min).

Representative Hydrogenation−Cyclization Procedure. Preparation of 4{*4,5*}. To a flask that contained **3**{*4,5*} (1.94 g, 2.22 mmol) and Pd/C (5 wt %, 50% wet, 0.48 g, 3% loading) was added THF−MeOH (2:1, 20 mL). The mixture was stirred vigorously under an atmosphere of hydrogen (1 atm) for 1 day. The mixture was filtered through a pad of Celite, and the Celite was rinsed with EtOAc (70 mL). The filtrate was concentrated to ∼5 mL, and it was irradiated

by microwave at 300 W, 150 °C for 15 min. After cooling to room temperature, hexanes (5 mL) was added. The precipitate was collected by filtration, and it was washed with hexanes (10 mL) to give **4**{*4,5*} (0.49 g, 1.34 mmol, 36% yield based on the amount of **1**{*1*} as light brown powder).

7-Methyl-4-piperidin-1-yl-7,8-dihydro-5*H*-pteridin-6-one 4{*1,1*}. Yield: 0.33 g (36%). ^{1}H NMR (270 MHz, DMSO-d_6) δ = 9.51 (1H, s), 7.87 (1H, s), 7.37 (1H, s), 3.89 (1H, q, J = 6.6 Hz), 3.18 (4H, brs), 1.56 (6H, brs), 1.25 (3H, d, J = 6.6 Hz). LC/MS (method 1): m/z = 248.2 [M + H]$^+$ (98%, t_R = 1.62 min).

7-Methyl-4-morpholin-4-yl-7,8-dihydro-5*H*-pteridin-6-one 4{*1,2*}. Yield: 0.31 g (34%). ^{1}H NMR (270 MHz, DMSO-d_6) δ = 9.77 (1H, s), 7.90 (1H, s), 7.48 (1H, s), 3.92 (1H, q, J = 7.0 Hz), 3.78−3.62 (4H, m), 3.28−3.08 (4H, m), 1.26 (3H, d, J = 6.7 Hz). LC/MS (method 1): m/z = 250.1 [M + H]$^+$ (100%, t_R = 1.24 min).

7-Methyl-4-(4-phenyl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 4{*1,4*}. Yield: 0.39 g (32%). ^{1}H NMR (270 MHz, DMSO-d_6) δ = 9.75 (1H, s), 7.91 (1H, s), 7.48 (1H, s), 7.21 (2H, t, J = 8.3 Hz), 6.95 (2H, d, J = 8.2 Hz), 6.77 (1H, t, J = 7.5 Hz), 3.94 (1H, q, J = 6.2 Hz), 3.45−3.15 (8H, m), 1.27 (3H, d, J = 6.7 Hz). LC/MS (method 1): m/z = 325.2 [M + H]$^+$ (94%, t_R = 1.89 min).

7-Methyl-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 4{*1,5*}. Yield: 0.31 g (26%). ^{1}H NMR (270 MHz, DMSO-d_6) δ = 9.76 (1H, s), 8.11 (1H, dd, J = 4.8, 1.5 Hz), 7.91 (1H, s), 7.60−7.45 (2H, m), 6.84 (1H, d, J = 8.6 Hz), 6.63 (1H, dd, J = 6.9, 4.9 Hz), 3.94 (1H, q, J = 6.8 Hz), 3.71−3.52 (4H, m), 3.35−3.20 (4H, m), 1.28 (3H, d, J = 6.7 Hz). LC/MS (method 1): m/z = 326.2 [M + H]$^+$ (93%, t_R = 1.57 min).

Representative Procedure for N-Alkylation Reactions. Preparation of 10{*1,4,1*}. To a vial that contained 7-methyl-4-(4-phenyl-piperazin-1-yl)-7,8-dihydro-5H-pteridin-6-one **4**{*1,4*} (49.6 mg, 0.15 mmol) and LiBr (one small scoop) in DMF (anhydrous, 1 mL) was added NaHMDS (1.0 M in THF, 0.15 mL) at 23 °C. The mixture was stirred for 10 min, and then a solution of benzyl bromide (0.15 M, 1.0 mL, 0.15 mmol) was added in one portion. After 10 min, H_2O (5 mL) and EtOAc (5 mL) were added, and the two layers were separated. The aqueous layer was extracted with EtOAc (5 mL). The EtOAc layers were combined and were dried over $MgSO_4$. After the removal of the solvent, the residue was loaded on top of a silica gel SPE cartridge (5 g), and the product was eluted with hexanes−EtOAc (3:1 to 1:1).

5-Benzyl-7-methyl-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*1,4,1*}. Yield: 36.8 mg (59%) ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.00 (1H, s), 7.32 (2H, t, J = 8.3 Hz), 7.24−7.13 (3H, m), 7.08−6.98 (4H, m), 6.93 (1H, t, J = 7.3 Hz), 5.73 (1H, brs), 5.32 (1H, d, J = 14.5 Hz), 5.06 (1H, d, J = 14.5 Hz), 3.96 (1H, q, J = 6.7 Hz), 3.83−3.12 (8H, m), 1.49 (3H, d, J = 6.7 Hz). LC/MS (method 2): m/z = 415.2 [M + H]$^+$ (97%, t_R = 8.47 min).

5-(4-Bromobenzyl)-7-methyl-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*1,4,2*}. Yield: 42.4 mg (57%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.01 (1H, s), 7.38−7.27 (4H, m), 7.03−6.86 (5H, m), 5.85 (1H, brs), 5.26 (1H, d, J = 14.5 Hz), 4.99 (1H, d, J = 14.5 Hz), 3.95 (1H, q, J = 6.6 Hz), 3.82−3.10 (8H, m), 1.48 (3H, d, J = 6.7 Hz). LC/MS (method 2): m/z = 493.1 [M + H]$^+$ (96%, t_R = 9.37 min).

5-(4-Chlorobenzyl)-7-methyl-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*1,4,3*}. Yield 48.9 mg (72%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.01 (1H, s), 7.32 (2H, t, J = 7.5 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.04−6.88 (5H, m), 5.84 (1H, brs), 5.28 (1H, d, J = 14.5 Hz), 5.01 (1H, d, J = 14.4 Hz), 3.94 (1H, q, J = 6.7 Hz), 3.81−3.10 (8H, m), 1.49 (3H, d, J = 6.7 Hz). LC/MS (method 2): m/z = 449.2 [M + H]$^+$ (86%, t_R = 9.21 min).

5-(4-Methoxybenzyl)-7-methyl-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*1,4,4*}. Yield: 48.3 mg (72%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.99 (1H, s), 7.31 (2H, t, J = 8.5 Hz), 7.08−6.90 (5H, m), 6.70 (2H, d, J = 8.7 Hz), 5.68 (1H, brs), 5.24 (1H, d, J = 14.2 Hz), 4.98 (1H, d, J = 14.2 Hz), 3.93 (1H, q, J = 6.8 Hz), 3.72 (3H, s), 3.85−3.10 (8H, m), 1.47 (3H, d, J = 6.8 Hz). LC/MS (method 2): m/z = 445.2 [M + H]$^+$ (85%, t_R = 8.47 min).

5-(4-Methylbenzyl)-7-methyl-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*1,4,5*}. Yield: 48.0 mg (74%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.00 (1H, s), 7.32 (2H, t, J = 7.3 Hz), 7.05−6.87 (7H, m), 5.73 (1H, brs), 5.28 (1H, d, J = 14.4 Hz), 5.01 (1H, d, J = 14.3 Hz), 3.94 (1H, q, J = 6.7 Hz), 3.82−3.12 (8H, m), 2.24 (3H, s), 1.48 (3H, d, J = 6.7 Hz). LC/MS (method 2): m/z = 429.2 [M + H]$^+$ (81%, t_R = 9.10 min).

7-Benzyl-5-(benzyl)-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*2,4,1*}. Yield: 74.8 mg (>99%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.98 (1H, s), 7.39−7.28 (5H, m), 7.23−7.12 (5H, m), 7.09−6.99 (4H, m), 6.94 (1H, t, J = 7.3 Hz), 5.20 (2H, broad d), 4.18−4.08 (1H, m), 3.81−3.12 (9H, m), 2.87 (1H, dd, J = 13.9, 10.5 Hz). LC/MS (method 2): m/z = 415.2 [M + H]$^+$ (97%, t_R = 7.40 min). LC/MS (method 2): m/z = 491.2 [M + H]$^+$ (93%, t_R = 9.53 min).

7-Benzyl-5-(4-bromobenzyl)-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*2,4,2*}. Yield: 66.2 mg (77%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.00 (1H, s), 7.38−7.25 (7H, m), 7.21−7.12 (2H, m), 7.05−6.88 (5H, m), 5.16 (2H, s), 4.18−4.05 (1H, m), 3.80−3.10 (9H, m), 2.88 (1H, dd, J = 3.8, 10.4 Hz). LC/MS (method 2): m/z = 569.2 [M + H]$^+$ (88%, t_R = 10.12 min).

7-Benzyl-5-(4-chlorobenzyl)-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*2,4,3*}. Yield: 73.7 mg (93%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.00 (1H, s), 7.38−7.28 (5H, m), 7.21−7.12 (4H, m), 7.04−6.91 (5H, m), 5.18 (2H, s), 4.17−4.08 (1H, m), 3.80−3.10 (9H, m), 2.88 (1H, dd, J = 4.1, 10.4 Hz). LC/MS (method 2): m/z = 525.2 [M + H]$^+$ (90%, t_R = 10.00 min).

7-Benzyl-5-(4-methoxybenzyl)-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*2,4,4*}. Yield: 78.8 mg (>99%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.98 (1H, s), 7.37−7.25 (5H, m), 7.20−7.13 (2H, m), 7.04−6.89 (5H, m), 6.72 (2H, d, J = 8.6 Hz), 5.15 (2H, s), 4.15−4.05 (1H, m), 3.73 (3H, s), 3.70−3.11 (9H, m), 2.85 (1H, dd, J = 13.9, 10.5 Hz). LC/MS (method 2): m/z = 521.3 [M + H]$^+$ (93%, t_R = 9.55 min).

7-Benzyl-5-(4-methylbenzyl)-4-(4-pyridin-2-yl-piperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*2,4,5*}. Yield: 72.1 mg (95%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.99 (1H, s), 7.37−7.24 (6H, m), 7.20−7.13 (2H, m), 7.06−6.89 (6H, m), 5.18 (2H, s), 4.18−4.08 (1H, m), 3.82−3.12 (9H, m), 2.89 (1H, dd, J = 10.5, 3.3 Hz), 2.25 (3H, s). LC/MS (method 2): m/z = 505.3 $[M + H]^+$ (84%, t_R = 9.94 min).

5-Benzyl-7-ethyl-4-(morpholin-4-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*3,2,1*}. Yield: 44.2 mg (83%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.98 (1H, s), 7.23−7.13 (3H, m), 7.07−6.96 (2H, m), 5.80 (1H, m), 5.21 (1H, d, J = 14.5 Hz), 5.10 (1H, d, J = 14.4 Hz), 4.02−3.75 (5H, m), 3.60−3.07 (4H, m), 1.97−1.62 (2H, m), 1.01 (3H, t, J = 7.4 Hz). LC/MS (method 2): m/z = 354.2 $[M + H]^+$ (92%, t_R = 5.01 min).

5-(4-Bromobenzyl)-7-ethyl-4-morpholin-4-yl-7,8-dihydro-5*H*-pteridin-6-one 10{*3,2,2*}. Yield: 53.1 mg (82%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.98 (1H, s), 7.30 (2H, d, J = 8.4 Hz), 6.90 (2H, d, J = 8.3 Hz), 5.97 (1H, brs), 5.15 (1H, d, J = 14.4 Hz), 5.03 (1H, d, J = 14.4 Hz), 4.05−3.72 (5H, m), 3.60−3.09 (4H, m), 1.95−1.64 (2H, m), 1.01 (3H, t, J = 7.4 Hz). LC/MS (method 2): m/z = 432.1 $[M + H]^+$ (81%, t_R = 6.69 min).

5-(4-Chlorobenzyl)-7-ethyl-4-morpholin-4-yl-7,8-dihydro-5*H*-pteridin-6-one 10{*3,2,3*}. Yield: 52.0 mg (89%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.98 (1H, s), 7.15 (2H, d, J = 8.3 Hz), 6.96 (2H, d, J = 8.4 Hz), 5.86 (1H, brs), 5.17 (1H, d, J = 14.3 Hz), 5.05 (1H, d, J = 14.5 Hz), 4.05−3.70 (5H, m), 3.60−3.05 (4H, m), 1.96−1.60 (2H, m), 1.01 (3H, t, J = 7.4 Hz). LC/MS (method 2): m/z = 388.2 $[M + H]^+$ (83%, t_R = 6.58 min).

5-(4-Methoxybenzyl)-7-ethyl-4-morpholin-4-yl-7,8-dihydro-5*H*-pteridin-6-one 10{*3,2,4*}. Yield: 39.2 mg (68%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.97 (1H, s), 6.96 (2H, d, J = 8.6 Hz), 6.70 (2H, d, J = 8.6 Hz), 5.74 (1H, brs), 5.14 (1H, d, J = 14.2 Hz), 5.02 (1H, d, J = 14.2 Hz), 4.05−3.76 (5H, m), 3.72 (3H, s), 3.67−3.05 (4H, m), 1.95−1.60 (2H, m), 1.01 (3H, t, J = 7.5 Hz). LC/MS (method 2): m/z = 384.2 $[M + H]^+$ (92%, t_R = 5.06 min).

5-(4-Methylbenzyl)-7-ethyl-4-morpholin-4-yl-7,8-dihydro-5*H*-pteridin-6-one 10{*3,2,5*}. Yield: 52.2 mg (94%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.97 (1H, s), 6.98 (2H, d, J = 8.1 Hz), 6.91 (2H, d, J = 8.2 Hz), 5.81 (1H, s), 5.17 (1H, d, J = 14.3 Hz), 5.05 (1H, d, J = 14.3 Hz), 4.05−3.72 (5H, m), 3.63−3.05 (4H, m), 2.24 (3H, s), 1.98−1.60 (2H, m), 1.01 (3H, t, J = 7.4 Hz). LC/MS (method 2): m/z = 368.2 $[M + H]^+$ (80%, t_R = 6.30 min).

5-Benzyl-7-isobutyl-4-(piperidin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*4,1,1*}. Yield: 50.8 mg (89%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.96 (1H, s), 7.24−7.12 (3H, m), 7.07−6.97 (2H, m), 5.75−5.52 (1H, br doublet), 5.23 (1H, d, J = 14.4 Hz), 5.04 (1H, d, J = 14.4 Hz), 4.02−3.92 (1H, m), 3.65−3.43 (2H, m), 3.28−2.98 (2H, m), 1.90−1.45 (9H, m), 0.96 (3H, d, J = 6.3 Hz), 0.92 (3H, d, J = 6.3 Hz). LC/MS (method 2): m/z = 380.2 $[M + H]^+$ (98%, t_R = 8.89 min).

5-(4-Bromobenzyl)-7-isobutyl-4-(piperidin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*4,1,2*}. Yield: 63.8 mg (93%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.97 (1H, s), 7.29 (2H, d, J = 8.4 Hz), 6.89 (2H, d, J = 8.4 Hz), 5.69 (1H, brs), 5.17 (1H, d, J = 14.4 Hz), 4.99 (1H, d, J = 14.4 Hz), 4.01−3.89 (1H, m), 3.65−3.40 (2H, m), 3.26−2.97 (2H, m), 1.90−1.43 (9H, m), 0.95 (3H, d, J = 6.3 Hz), 0.92 (3H, d, J = 6.2 Hz). LC/MS (method 2): m/z = 458.1 $[M + H]^+$ (93%, t_R = 9.60 min).

5-(4-Chlorobenzyl)-7-isobutyl-4-(piperidin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*4,1,3*}. Yield: 58.3 mg (94%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.97 (1H, s), 7.14 (2H, d, J = 8.4 Hz), 6.95 (2H, d, J = 8.6 Hz), 5.76 (1H, brs), 5.18 (1H, d, J = 14.4 Hz), 5.00 (1H, d, J = 14.4 Hz), 4.02−3.90 (1H, m), 3.63−3.40 (2H, m), 3.28−3.12 (1H, m), 3.10−2.97 (1H, m), 1.90−1.43 (9H, m), 0.95 (3H, d, J = 7.0 Hz), 0.92 (3H, d, J = 6.9 Hz). LC/MS (method 2): m/z = 414.2 $[M + H]^+$ (94%, t_R = 9.46 min).

5-(4-Methoxybenzyl)-7-isobutyl-4-(piperidin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*4,1,4*}. Yield: 60.4 mg (98%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.96 (1H, s), 6.96 (2H, d, J = 8.6 Hz), 6.69 (2H, d, J = 8.6 Hz), 5.57 (1H, brs), 5.16 (1H, d, J = 14.2 Hz), 4.97 (1H, d, J = 14.2 Hz), 3.99−3.89 (1H, m), 8.72 (3H, s), 3.67−3.42 (2H, m), 3.29−3.14 (1H, m), 3.11−2.96 (1H, m), 1.90−1.42 (9H, m), 0.95 (3H, d, J = 6.2 Hz), 0.92 (3H, d, J = 6.2 Hz). LC/MS (method 2): m/z = 410.2 $[M + H]^+$ (96%, t_R = 8.94 min).

5-(4-Methylbenzyl)-7-isobutyl-4-(piperidin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 10{*4,1,5*}. Yield: 54.7 mg (92%). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.96 (1H, s), 6.97 (2H, d, J = 8.2 Hz), 6.91 (2H, d, J = 8.2 Hz), 5.65 (1H, s), 5.19 (1H, d, J = 14.3 Hz), 5.00 (1H, d, J = 14.3 Hz), 3.99−3.90 (1H, m), 3.67−3.42 (2H, m), 3.27−3.13 (1H, m), 3.09−2.95 (1H, m), 2.24 (3H, s), 1.90−1.43 (9H, m), 0.95 (3H, d, J = 6.5 Hz), 0.92 (3H, d, J = 6.2 Hz). LC/MS (method 2): m/z = 394.2 $[M + H]^+$ (87%, t_R = 9.40 min).

8-Benzyl-7-methyl-4-(4-phenylpiperazin-1-yl)-7,8-dihydro-5*H*-pteridin-6-one 13. ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.25 (1H, s), 7.88 (1H, brs), 7.40−7.23 (7H, m), 6.97 (2H, d, J = 8.1 Hz), 6.91 (1H, t, J = 7.24 Hz), 5.37 (1H, d, J = 15.2 Hz), 4.36 (1H, d, J = 15.2 Hz), 4.08 (1H, q, J = 6.9 Hz), 3.58−3.19 (8H, m), 1.30 (3H, d, J = 6.9 Hz). LC/MS (method 3): m/z = 415.2 $[M + H]^+$ (95%, t_R = 4.87 min).

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Supporting Information Available. Spectra of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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