Pteridin-4(3*H*)-ones and related compounds: synthesis *via* intermolecular aza-Wittig reaction–heterocyclization and crystal structure

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2,3-Disubstituted pteridin-4(3*H*)-one derivatives have been synthesized by the intermolecular aza-Wittig reaction–heterocyclization methodology. The structures of 3-allyl-2-anilinopteridin-4(3*H*)-one and 2-anilino-3-isopropylpteridin-4(3*H*)-one were determined by X-ray crystallographic analysis. Furthermore, imidazo[2,1-*b*]pteridine derivatives were synthesized by heterocyclization including iodoamination.

Folic acid, methotrexate, L-biopterin[1] and leucettidine[2] *etc.* are known as natural products having a pteridine skeleton which play an essential role in several biological processes and methotrexate has a long and distinguished history as an antineoplastic and immunosuppressive drug. Although several methods for the synthesis of these important pteridine ring skeletons have been reported,[3,4] new technologies that advance the field are still in demand. Recently, Wamhoff and Kroth reported a synthesis of pteridin-4(3*H*)-one derivatives from 3-aroylaminopyrazine-2-carboxylates, or 2-arylpyrazino[2,3-*d*]-[3,1]oxazin-4-ones.[5] Also, we have reported two different synthetic routes to pteridin-4-(3*H*)-one derivatives from the corresponding *N*-(pyrazin-2-yl)iminophosphorane derivatives *via* intermolecular aza-Wittig reaction, with isocyanates followed by addition of alcohols or amines for the desired heterocyclization,[6,7] and with acid chlorides followed by internal heterocyclization.[8] In the former methodology, two kinds of pteridin-4(3*H*)-one derivatives were inevitably obtained by addition of the primary amine to the corresponding carbodiimide intermediates because of formation of the guanidine intermediate, which has two nucleophilic nitrogen atoms. Therefore, we investigated the alternative, more regioselective, synthesis of pteridin-4(3*H*)-one derivatives *via* the intermolecular aza-Wittig reaction–heterocyclization. The aza-Wittig reaction has been shown to be one of the most useful methodologies[9–12] for the formation of C=N bonds (imine, amidine and guanidine, *etc.*) and heterocumulene bonds (carbodiimide, *etc.*), and for synthesis of nitrogen heterocyclic compounds. We, as well as other workers, have recently demonstrated that the intramolecular aza-Wittig reaction is a powerful tool for the synthesis of five to eight membered heterocycles[10,13,14] including natural products such as DC-81,[15,16] (−)-vasicinone,[17] (−)-benzomalvin A[18] and (+)-fumiquinazoline G[19] *etc.* Furthermore, we demonstrated that the intramolecular aza-Wittig reaction could be utilized for preparation of 6-(trifluoromethyl)-4,5-dihydro-2(3*H*)-pyridone, a starting material for indolizidine derivatives having a trifluoromethyl group.[20] On the other hand, the intermolecular aza-Wittig reaction followed by electrocyclization, cycloaddition or heterocyclization, *i.e.*, the tandem aza-Wittig methodology has been utilized for synthesis of many important heterocyclic compounds including natural products by Molina,[21] Wamhoff,[22] Quintela,[23] Saito,[24] Noguchi[25] and Weinreb.[26] Furthermore, *N*-vinyliminophosphoranes have been studied by Nitta[27] and Palacios.[28] We have been interested in the preparation and the reactivity of *N*-heteroaryliminophosphoranes and the corresponding carbodiimides because these species seem to have been less studied, notwithstanding their promising role as building blocks for synthesis of heterocyclic compounds. For example, we have reported a facile synthesis of pteridin-4(3*H*)-ones *via* the intermolecular aza-Wittig reaction and heterocyclization,[6–8] and pyrazino[2,3-*e*][1,4]diazepin-5-ones *via* the intramolecular aza-Wittig reaction.[29]

Results and discussion

At first, secondary amide derivatives **3** were synthesized as follows (Table 1). When the commercially available and liquid primary amines were employed, methyl 3-aminopyrazine-2-carboxylate **1** was converted into secondary amides **3a**–**d** in quantitative yield by ester–amide exchange, using DBU as base (Method A). By this method, secondary amide **3e** containing a *tert*-butyl group was not synthesized due to steric effects. In addition, methyl anthranilate and methyl 2-aminonicotinate could not be converted into the corresponding secondary amide derivatives by the above ester–amide exchange reaction. When the other primary amines were used, the corresponding secondary amides **3e**–**h** were obtained by utilizing 3-aminopyrazine-2-carboxylic acid **2** and condensation reagents (DMC or DEPC) in moderate yields (method B). 1-Methylprop-2-enylamine and 1-methylbut-3-enylamine were prepared from but-3-en-2-ol and pent-4-en-2-ol, respectively, by Gabriel's method. The secondary amides **3** obtained were converted into iminophosphoranes **4** in high yields by treatment with triphenylphosphine–hexachloroethane–triethylamine (Table 1).

As the next step, we examined the reaction of **4** with aryl isocyanates to afford pteridin-4(3*H*)-ones **5** *via* the intermolecular aza-Wittig reaction and heterocyclization. The iminophosphorane **4b** reacted with phenyl isocyanate in dry dichloromethane at room temperature to give triphenylphosphine *P*-oxide and a heterocyclic compound. However, the reaction was very slow and was not completed even after 24 h.

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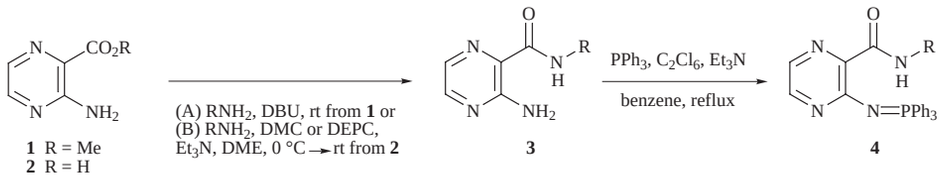
Table 1



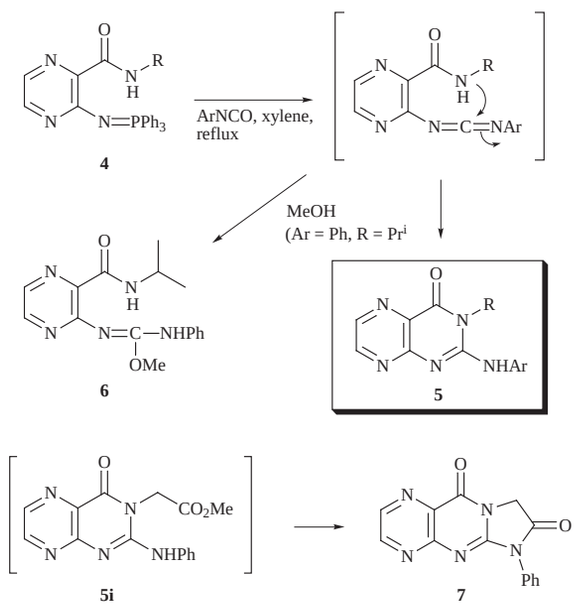
Entry	R	Compd. **3**	Method[b]	Yield (%)[c] of **3**	Compd. **4**	Yield (%)[c] of **4**
1	Allyl	**3a**	A	100	**4a**	100
2	Pr	**3b**	A	100	**4b**	83
3	Pr^i	**3c**	A	90	**4c**	93
4	Bu^s	**3d**	A	100	**4d**	72
5	Bu^t	**3e**	B	68	**4e**	96
6	CH_2CO_2Me	**3f**	B	80	**4f**	100
7	1-Methylprop-2-enyl	**3g**	B	60	**4g**	76
8	1-Methylbut-3-enyl	**3h**	B	32	**4h**	99

[a] DMC = 2-chloro-1,3-dimethylimidazolinium dichloride. DEPC = diethylphosphonyl cyanide. [b] Method A was ester–amide exchange. Method B was condensation. [c] Isolated yield.

After 96 h, although traces of the iminophosphorane **4b** remained (TLC monitored), the heterocyclic compound was isolated by silica gel column chromatography. According to Molina's report,[30] the corresponding 4*H*-[1,3]oxazino[4,5-*b*]-pyrazin-4-imine derivative could be obtained by the method for synthesis of quinazolin-4(3*H*)-ones. Nevertheless, only pteridin-4(3*H*)-one derivative **5d** was produced (46% yield). In this reaction, we found that the corresponding 4*H*-[1,3]-oxazino[4,5-*b*]pyrazine-4-imine derivative could not be synthesized. Furthermore, we studied the optimum conditions for synthesis of pteridin-4(3*H*)-ones. When the intermolecular aza-Wittig reaction and heterocyclization were conducted at 80 °C in benzene for 2 h (iminophosphorane **4b** was all consumed, by TLC monitoring), pteridin-4(3*H*)-one **5d** was formed in 41% yield. In addition, at 120 °C in dry toluene for 2 h, **5d** was obtained in 48% yield and at 140 °C in dry xylene for 2 h, in 67% yield. Next, we investigated synthesis of pteridin-4(3*H*)-ones **5** with various functionalities under the same conditions (Scheme 1 and Table 2). The iminophosphorane **4a** having an *N*-allyl secondary amide group reacted with phenyl, 4-chlorophenyl and 4-methoxyphenyl isocyanates to give the corresponding pteridin-4(3*H*)-one **5a**–**c** in 71, 65 and 58% yield, respectively (Entries 1–3 in Table 2). Although the order of reactivity of aryl isocyanate was 4-chlorophenyl isocyanate > phenyl isocyanate > 4-methoxyphenyl isocyanate, these results did not show a substituent effect on the yield.

Moreover, the molecular structure of **5a** was supported by X-ray crystallographic analysis. As summarized in Fig. 1 and Tables 3 and 4 (bond lengths and torsion angles, respectively), the pteridine skeleton was confirmed. Some of the bond lengths in **5a**, such as N3–C5 [1.392(2) Å] and N4–C5 [1.317(2) Å] are slightly longer (at least 0.016 Å), while N4–C6 [1.356(2) Å] and N5–C5 [1.347(2) Å] are a little shorter (at least 0.02 Å), than those of the 2-acetylaminopteridin-4(3*H*)-one derivative[31] reflecting an effect of the anilino group at 2-position in **5a**. The torsion angles of **5a** indicated that the pteridin-4(3*H*)-one skeleton was approximately planar, and the allyl function and pteridine ring were almost perpendicular [C4–N3–C7–C8: −101.9(2)°]. Also, the phenyl ring and pteridine ring were at an angle of about 45° [C5–N5–C10–C15: 49.6(3)°, Fig. 1 and Table 4].[32]

In entry 5 of Table 2, iminophosphorane **4c** with an isopropyl group was converted into the corresponding pteridin-4(3*H*)-one **5e**. In this reaction, isourea derivative **6** was obtained as a by-product (22% yield) when methanol was added after the initial reaction. Formation of **6** suggested that the intermediate in this reaction was the corresponding carbodiimide and cyclization of the carbodiimide containing the isopropyl group was very slow. Furthermore, it was clear that **6** was not cyclized by the mechanism in our previous report on the synthesis of pteridin-4(3*H*)-one derivatives.[6,7] The NMR spectra of **5e** in $CDCl_3$ and *o*-$C_6D_4Cl_2$ showed the presence of two isomers in 1 : 1 ratio and in 1 : 3 ratio, respectively. However, those of **5e** in [$^2H_6$]-DMSO and CD_3OD showed only a single isomer. Furthermore, on variable temperature studies of **5e** in $CDCl_3$ (20–55 °C) and *o*-$C_6D_4Cl_2$ (20–100 °C), signal coalescence was not observed. Thus, in $CDCl_3$ and *o*-$C_6D_4Cl_2$, the tautomeric interconversion was slow on the ^1H NMR timescale. The signals of protons of



Scheme 1

Table 2

Entry	R	Ar	Compd.	Yield (%)[a]
1	Allyl	Ph	**5a**	71
2	Allyl	4-Cl-C_6H_4	**5b**	65
3	Allyl	4-MeO-C_6H_4	**5c**	58
4	Pr	Ph	**5d**	67
5	Pr^i	Ph	**5e**	53
6	Pr^i	4-Cl-C_6H_4	**5f**	43 + 26[b]
7	Bu^s	Ph	**5g**	36
8	Bu^t	Ph	**5h**	0[c]
9	CH_2CO_2Me	Ph	**7**	37
10	1-Methylprop-2-enyl	Ph	**5j**	81
11	1-Methylbut-3-enyl	Ph	**5k**	25

[a] Isolated yield. [b] **10** was also obtained. [c] The desired compound was not obtained.

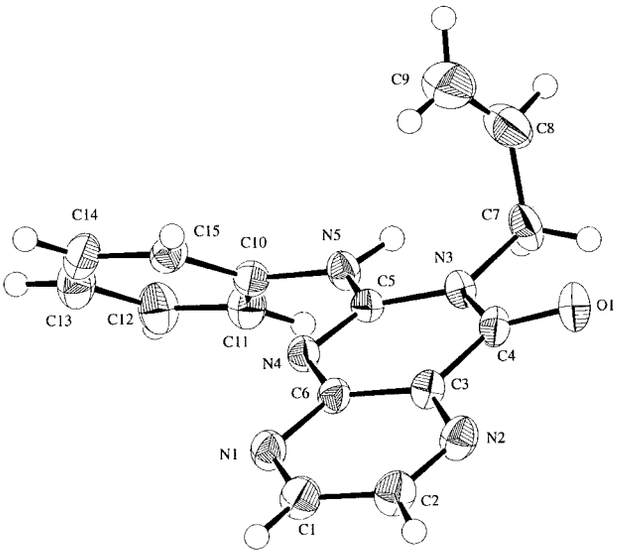


Fig. 1 ORTEP drawing of 3-allyl-2-anilinopteridin-4(3*H*)-one **5a**

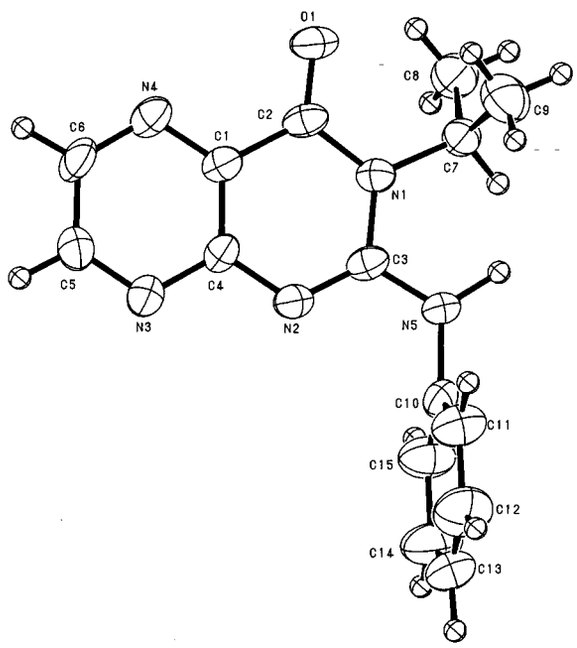


Fig. 2 ORTEP drawing of 2-anilino-3-isopropylpteridin-4(3*H*)-one **5e–1**

both tautomeric forms were observed separately and the tautomeric composition was determined according to their relative intensities (*cf.* prototropy transfer of the guanidine function). But in the case of [$^2H_6$]-DMSO and CD_3OD, a single signal pattern was observed because of the rapid tautomeric interconversion on the ^1H NMR timescale or absence of tautomer (see Experimental). This behavior was not observed in the compounds with allyl and 1-methylprop-2-enyl groups (Entries 1–3 and 10 in Table 2) but recognized in the substrates with propyl, isopropyl, *sec*-butyl and 1-methylbut-3-enyl groups at the 3-position (Entries 4–7 and 11 in Table 2). As a result, pteridin-4(3*H*)-one derivatives **5a**–**c** and **5j** having a prop-2-enyl group at the 3-position showed a single isomer in both $CDCl_3$ and [$^2H_6$]-DMSO. The reason for this is not clear but Molina reported similar behavior in 13-methoxymethyl-13*H*-diquino[4,3-*b*:3′,4′-*d*]pyrrole derivatives.[33] Thus, the molecular structure of **5e** was studied by X-ray crystallographic analysis (Fig. 2). The packing drawing of **5e** is shown in Fig. 3. This is a rare example that has three kinds of structures (**5e-1**, **5e-2** and **5e-3**) in a lattice. The difference between these structures in the lattice was the conformation of isopropyl and anilino functions, which were sterically congested (for details, see the deposited material at the CCDC).[32] As summarized in Tables 5 and 6 (bond lengths and torsion angles of **5e-1**, respectively), the pteridine skeleton was thus confirmed. The bond lengths of **5e-1** (Table 5) such as N1–C3 (1.407(5) Å) and N2–C3 (1.310(6) Å) are slightly longer, while N2–C4 (1.350(5) Å) and N5–C3 (1.346(5) Å) are a little shorter than those of 2-acetylaminopteridin-4(3*H*)-one derivative[31] as found for **5a**. Torsion angles of **5e-1** indicated that the pteridin-4(3*H*)-one skeletons were approximately planar and the two methyl groups of the isopropyl function were almost bisected by the pteridine ring [*cf.* C2–N1–C7–C9: 78.4(5)° in Fig. 2]. The phenyl ring and pteridine ring are perpendicular to each other [C3–N5–C10–C11: −100.3(6)° in Fig. 2 and Table 6].

Table 3 Selected bond lengths (Å) of **5a**[a]

O1–C4	1.288(2)	N4–C6	1.356(2)
N1–C1	1.326(2)	N5–C5	1.347(2)
N1–C6	1.363(2)	N5–C10	1.427(2)
N2–C2	1.321(3)	C1–C2	1.393(3)
N2–C3	1.340(2)	C3–C4	1.462(2)
N3–C4	1.395(2)	C3–C6	1.400(2)
N3–C5	1.392(2)	C7–C8	1.461(3)
N3–C7	1.474(2)	C8–C9	1.273(4)[b]
N4–C5	1.317(2)		

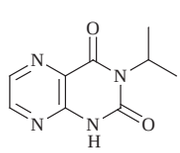
[a] Estimated standard deviations in the least significant figure are given in parentheses. [b] This short bond length as the C=C double bond may be due to large temperature factors of the related atoms.

Table 4 Selected torsion angles (°) of **5a**[a]

(1)–(2)–(3)–(4)		(1)–(2)–(3)–(4)	
O1–C4–N3–C5	−175.4(2)	N4–C5–N3–C4	2.9(2)
O1–C4–N3–C7	1.5(2)	N4–C5–N3–C7	−173.9(2)
O1–C4–C3–N2	−8.4(3)	N4–C5–N5–C10	2.5(2)
N1–C1–C2–N2	2.7(3)	N5–C5–N3–C4	−176.3(1)
N1–C6–N4–C5	−176.1(1)	N5–C5–N3–C7	7.0(2)
N1–C6–C3–N2	3.4(3)	N5–C5–N4–C6	173.0(1)
N2–C3–C4–N3	171.4(1)	C3–C4–N3–C7	−178.3(1)
N2–C3–C6–N4	−174.0(2)	C4–N3–C7–C8	−101.9(2)
N3–C5–N4–C6	−6.1(2)	C5–N3–C7–C8	75.0(2)
N3–C5–N5–C10	−178.3(1)	C5–N5–C10–C11	−133.7(2)
N3–C7–C8–C9	7.0(4)	C5–N5–C10–C15	49.6(3)

[a] The sign is positive if when looking from atom (2) to atom (3) a clockwise motion of atom (1) would superimpose it on atom (4) and estimated standard deviations in the least significant figure are given in parentheses.

Furthermore, when 4-chlorophenyl isocyanate was used, not only the corresponding pteridin-4(3*H*)-one **5f** (43% yield) but also the hydrolyzed compound, 3-isopropylpteridin-2,4-(1*H*,3*H*)-dione **10** (26% yield) were obtained (Entry 6 in Table 2). When the iminophosphorane with a *tert*-butyl group **4e** was used, the corresponding pteridin-4(3*H*)-one **5h** was not obtained at all because of steric hindrance (Entry 8, Table 2). In the case of **4f** derived from glycine methyl ester hydrochloride and 3-aminopyrazine-2-carboxylic acid **1**, **5i** may be produced initially and then this cyclized, *in situ*, to imidazo[2,1-*b*]pteridine derivative **7** (Entry 9, Table 2 and Scheme 1) as observed, and the corresponding urea derivative **8** was formed as a by-product. Moreover, pteridin-2,4(1*H*,3*H*)-dione derivative **9** was often produced in this reaction.



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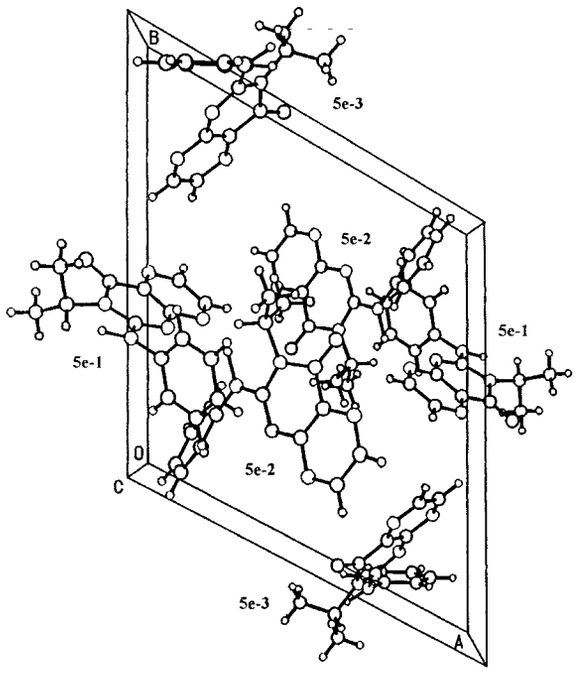


Fig. 3 Packing drawing of 2-anilino-3-isopropylpteridin-4(3*H*)-one **5e**

Table 5 Selected bond lengths (Å) of **5e**–**1** [a]

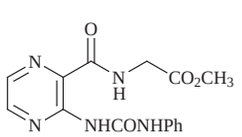
O1–C2	1.218(5)	N4–C1	1.331(5)
N1–C2	1.403(5)	N4–C6	1.319(6)
N1–C3	1.407(5)	N5–C3	1.346(5)
N1–C7	1.505(6)	N5–C10	1.443(6)
N2–C3	1.310(6)	C1–C2	1.464(6)
N2–C4	1.350(5)	C1–C4	1.399(6)
N3–C4	1.359(6)	C5–C6	1.397(7)
N3–C5	1.314(6)	C7–C8	1.514(6)

[a] Estimated standard deviations in the least significant figure are given in parentheses.

Table 6 Selected torsion angles (°) of **5e**–**1** [a]

(1)–(2)–(3)–(4)		(1)–(2)–(3)–(4)	
O1–C2–N1–C3	167.8(4)	N3–C4–C1–N4	0.3(7)
O1–C2–N1–C7	−7.7(6)	N3–C5–C6–N4	1.3(9)
O1–C2–C1–N4	4.9(7)	N5–C3–N1–C2	−166.6(4)
O1–C2–C1–C4	−175.2(4)	N5–C3–N1–C7	8.8(6)
N1–C2–C1–N4	−172.5(4)	N5–C3–N2–C4	177.9(4)
N1–C3–N2–C4	−1.4(7)	C1–C2–N1–C7	169.7(4)
N1–C3–N5–C10	178.6(4)	C2–N1–C7–C8	−49.5(6)
N2–C3–N1–C2	12.7(7)	C2–N1–C7–C9	78.4(5)
N2–C3–N1–C7	−171.9(4)	C3–N1–C7–C8	135.1(4)
N2–C3–N5–C10	−0.7(7)	C3–N1–C7–C9	−97.1(5)
N2–C4–C1–N4	−176.9(4)	C3–N5–C10–C11	−100.3(6)
N3–C4–N2–C3	176.2(4)	C3–N5–C10–C15	83.7(6)

[a] The sign is positive if when looking from atom (2) to atom (3) a clockwise motion of atom (1) would superimpose it on atom (4) and estimated standard deviations in the least significant figure are given in parentheses.



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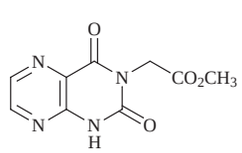

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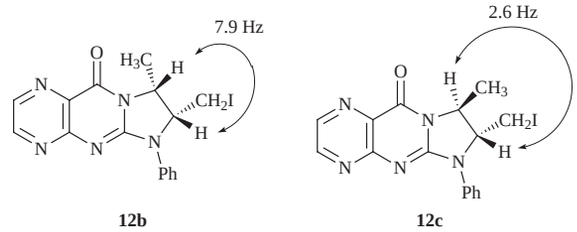
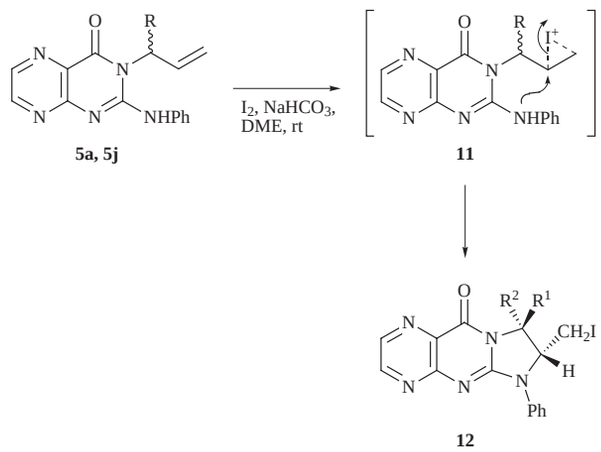
Finally, imidazo[2,1-*b*]pteridine derivatives **12** as a linear 6,6,5 cyclic system were synthesized by iodoamination.[34] Pteridin-4(3*H*)-one derivatives **5a** and **5j** having a prop-2-enyl function at the 3-position were converted into the corresponding imidazo[2,1-*b*]pteridine derivatives **12a**–**c** by iodine and



12b **12c**

Fig. 4

sodium hydrogen carbonate in DME at room temperature for 1 h in moderate yields *via* iodonium cation intermediate **11** (Scheme 2). Diastereomers **12b** and **12c** were obtained in a 1 : 1



5a, 5j **11** **12**

Entry	R	Compd.	Yield (%) [a]
1	H	**12a**	54
2	Me	**12b** + **12c** [b]	25 + 25

[a] Isolated yield. [b] **12b** was R^1 = H, R^2 = Me. **12c** was R^1 = Me, R^2 = H.

Scheme 2

ratio and could be separated by silica gel column chromatography. **12b** was assigned as a *syn* isomer with respect to the iodomethyl and methyl functions because the coupling constant was 7.9 Hz, and **12c** as an *anti* isomer because the coupling constant was 2.6 Hz (Fig. 4).

In summary, we have demonstrated that 2,3-disubstituted pteridin-4(3*H*)-one derivatives and imidazo[2,1-*b*]pteridine derivatives were synthesized by the intermolecular aza-Wittig reaction–heterocyclization methodology. The structures of 3-allyl-2-anilinopteridin-4(3*H*)-one **5a** and 2-anilino-3-isopropylpteridin-4(3*H*)-one **5e** were determined by X-ray crystallographic analyses. The iminophosphoranes **4** were thus concluded to be useful intermediates for the synthesis of 2,3-disubstituted pteridin-4(3*H*)-one derivatives by the intermolecular aza-Wittig reaction with aryl isocyanates and heterocyclization. The further application of aza-Wittig methodology to the synthesis of various fused pyrimidine derivatives is in progress in our laboratories.

Experimental

General

Thin layer chromatography (TLC) was performed on E. Merck Kieselgel 60 F_{254} pre-coated silica plates (0.15 mm layer thickness). Melting points were determined with a Yanagimoto micro-melting-point hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a Varian GEMINI-200 or 500 spectrometer at 200 or 500 and 50 or 125 MHz, respectively, for samples in $CDCl_3$, [$^2H_6$]-DMSO, *o*-$C_6D_4Cl_2$ and CD_3OD solution with Me_4Si as internal stand-

ard. Chemical shifts are reported in ppm (δ). Coupling constants, J_H and J_C, are given in Hz. IR spectra were recorded on a JASCO FTIR 5300 spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a JEOL JMS-AX 505 HA (EI and/or CI, 70 eV). Microanalyses were performed with a Perkin-Elmer 2400S elemental analyzer. Flash chromatography were performed with a silica gel column (Fuji Davison BW-300) eluted with mixed solvents [hexane (H), ethyl acetate (A)].

Reagents and solvents. Benzene, toluene and xylene were stored over Na. Isocyanates were dried over CaH_2, distilled, and stored over 3 Å molecular sieves. All reactions were carried out under nitrogen. 3-Aminopyrazine-2-carboxylic acid **2** and DMC were supplied by Nippon Soda Co., Ltd. and Shiratori Pharmaceutical Co., Ltd., respectively. Methyl 3-aminopyrazine-2-carboxylate **1** and DEPC were purchased from Sigam-Aldrich Japan K. K. and Tokyo Kasei Co., Ltd., respectively. This reagent was used without further purification.

N-Allyl-3-aminopyrazine-2-carboxamide 3a (Method A): general procedure

Methyl 3-aminopyrazine-2-carboxylate **1** (277 mg, 1.81 mmol) was dissolved in allylamine (10.0 cm^3) and to this solution was added DBU (0.27 cm^3, 1.81 mmol). The resultant solution was stirred at room temperature for 4 h. The mixture was diluted with water (50 cm^3) and extracted with chloroform (50 $cm^3 \times 3$). The combined organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product, which was purified on a silica gel column using A and H (1 : 2, v/v) as eluent to give secondary amide derivative **3a** (323 mg, 1.81 mmol, 100%). Other secondary amine derivatives **3b**–**d** were also obtained by similar methods (Entries 1–4 in Table 1). The data for secondary amide derivatives **3a**–**d** have already been reported.[8]

N-Methoxycarbonylmethyl-3-aminopyrazine-2-carboxamide 3f (Method B): general procedure

To a mixture of 3-aminopyrazine-2-carboxylic acid **2** (571 mg, 4.10 mmol) and glycine methyl ester hydrochloride (618 mg, 4.94 mmol) in dry 1,2-dimethoxyethane (DME) (30.0 cm^3) was added dropwise DEPC (93%, 0.80 cm^3, 4.94 mmol) and triethylamine (1.36 cm^3, 9.76 mmol) respectively at 0 °C. The resultant solution was stirred at 0 °C for 1 h and at 40 °C for 1 h under nitrogen. The mixture was diluted with ethyl acetate (500 cm^3) and washed with water (50 cm^3), saturated aqueous sodium hydrogen carbonate (50 cm^3), water (50 cm^3) and saturated sodium chloride (50 cm^3) successively. The combined organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product, which was purified by recrystallization from A and H to give secondary amide derivative **3f** (pale yellow needles, 689 mg, 3.28 mmol, 80%). The other secondary amide derivatives **3e**, **3g** and **3h** were also obtained by similar methods (see, Entries 5–8 in Table 1). The data for secondary amide derivatives **3e**, **3f** and **3h** have been already reported.[8]

***N*-(1-Methylprop-2-enyl)-3-aminopyrazine-2-carboxamide 3g.** Pale yellow solid (208 mg, 1.09 mmol, 60%), mp 35–37 °C (Found: M^+, 192.1009. $C_9H_{12}N_4O$ requires M, 192.1011); R_F 0.52 (A : H 1 : 1); ν_{max}(KBr)/cm^{-1} 3387, 1659, 1603, 1516, 1437, 1190, 936, 814 and 669; δ_H($CDCl_3$, 200 MHz) 8.15 (1H, d, J 2.4, H-5), 7.95–7.80 (1H, br, CONH), 7.80 (1H, d, J 2.4, H-6), 7.2–6.0 (2H, br, NH_2), 5.93 (1H, ddd, J 17.3, 10.3, 5.2, CHC*H*=CH_2, 5.23 (1H, ddd, J 17.4, 1.7, 1.1, CH=CH_2), 5.14 (1H, ddd, J 10.4, 1.5, 1.1, CH=CH_2), 4.69 [1H, qdr, J 6.8, 5.2, 1.6, NHC*H*(CH_3)-CH=CH_2] and 1.36 (3H, d, J 6.8, CHCH_3); δ_C($CDCl_3$, 50 MHz) 165.74 (CONH), 155.57 (C-3), 147.03 (C-5), 139.77 (CH*C*H=CH_2), 131.97 (C-6), 127.01 (C-2), 114.66 (CH=*C*H_2), 46.85 [NH*C*H(CH_3)CH=CH_2] and 20.54 (CH*C*H_3); MS (EI) *m*/*z* 192 (45%, M^+), 177 (36), 165 (11), 122 (47), 95 (20), 94 (52), 70 (100), 68 (9) and 67 (13); MS (CI) *m*/*z* 193 (MH).

N-Methoxycarbonylmethyl 3-(triphenylphosphoranylideneamino)pyrazine-2-carboxamide 4f: general procedure

To a stirred mixture of the corresponding 3-aminopyrazine-2-carboxamide **3f** (432 mg, 2.06 mmol), hexachloroethane (486 mg, 2.05 mmol) and triphenylphosphine (539 mg, 2.05 mmol) in dry benzene (20.0 cm^3) was added dropwise triethylamine (0.58 cm^3, 4.11 mmol). The resultant solution was heated at reflux for 2 h. After cooling, the mixture was filtered under pressure in order to remove the precipitates and the filtrate was evaporated under reduced pressure to give a solid residue, which was purified on a silica gel column using A and H (1 : 1→2 : 1→A only, v/v) as an eluent to afford the iminophosphorane **4f** (964 mg, 2.05 mmol, 100%). The other iminophosphorane derivatives **4a**–**e**, **4g** and **4h** were also obtained by similar methods (Table 2). The data for **4a**–**f** and **4h** have already been reported.[8]

***N*-(1-Methylprop-2-enyl)-3-(triphenylphosphoranylidene)-aminopyrazine-2-carboxamide 4g.** Pale yellow solid (356 mg, 0.79 mmol, 76%), mp 182–185 °C (Found: M^+, 452.1763. $C_{27}H_{25}N_4OP$ requires M, 452.1765); R_F 0.10 (tailing, A); ν_{max}(neat)/cm^{-1} 3169, 2969, 1659, 1547, 1510, 1447, 1171, 1115, 993, 748, 721 and 693; δ_H($CDCl_3$, 200 MHz) 11.15 (1H, d, J 7.8, CON*H*CH), 8.00 (1H, d, J 2.2, H-5), 7.81–7.69 (1H + 6H, m, H-6 + C_6H_5), 7.63–7.42 (9H, m, C_6H_5), 5.98 (1H, ddd, J 17.5, 10.3, 4.8, CHC*H*=CH_2), 5.23 (1H, dq, J 17.2, 1.5, CH=CH_2), 5.04 (1H, dq, J 10.4, 1.5, CH=CH_2), 5.04–4.92 [1H, m, NHC*H*(CH_3)CH=CH_2] and 1.32 (3H, d, J 6.8, CHCH_3); δ_C($CDCl_3$, 50 MHz) 164.78 (CONH), 158.36 (d, J 7.8, C-3), 142.90 (C-5), 140.71 (CH*C*H=CH_2), 137.45 (d, J 19.2, C-2), 133.86 (C-6), 133.39 (d, J 9.9, C′-3), 132.66 (d, J 2.9, C′-4), 128.61 (d, J 101.2, C′-1), 128.03 (d, J 12.2, C′-2), 113.84 (CH=*C*H_2), 46.63 [NH*C*H(CH_3)CH=CH_2] and 20.51 (CH*C*H_3) MS (EI) *m*/*z* 453 (13%, $M^+ + 1$), 452 (45, M^+), 397 (6), 383 (7), 355 (26), 354 (100), 262 (13), 183 (17) and 108 (6); MS (CI) *m*/*z* 453 (MH).

Synthesis of 3-allyl-2-anilinopteridin-4(3*H*)-one 5a: general procedure

To a solution of the iminophosphorane **4a** (210 mg, 0.48 mmol) in dry xylene (10 cm^3) was added dropwise phenyl isocyanate (200 mg, 1.68 mmol, 3.5 equiv.) with exclusion of moisture. The mixture was stirred at reflux for 2 h and was then evaporated under reduced pressure and the solid residue was purified on a silica gel column using H : A (1 : 1→1 : 2→only A, v/v) as eluents to give 3-allyl-2-anilinopteridin-4(3*H*)-one **5a** (95.5 mg, 0.34 mmol, 71%). The other pteridin-4-(3*H*)-one derivatives **5b**–**g**, **5j**, **5k**, **7** and **8** were also obtained by similar methods (Table 3). The physical data for pteridin-4(3*H*)-one derivatives **5a**–**c** have already been reported.[7]

3-Anilino-2-propylpteridin-4(3*H*)-one 5d. Yellow cubic crystals (54.7 mg, 0.19 mmol, 67%), mp 141–143 °C (Found: M^+, 281.1279. $C_{15}H_{15}N_5O$ requires M, 281.1277); R_F 0.28 (A); ν_{max}(KBr)/cm^{-1} 2965, 1692, 1607, 1561, 1528, 1472, 1451, 1416, 1221, 1057 and 754; δ_H([$^2H_6$]-DMSO, 200 MHz) 9.12 (1H, br s, NH), 8.69 (1H, d, J 2.2, H-7), 8.47 (1H, d, J 2.0, H-6), 7.59–7.55 (2H, m, C_6H_5), 7.46–7.38 (2H, m, C_6H_5), 7.26–7.18 (1H, m, C_6H_5), 4.20 (2H, t, J 7.7, N$CH_2$$CH_2$), 1.72 (2H, sextet, J 7.5, CH_2C$H_2$$CH_3$) and 0.96 (3H, t, J 7.4, CH_2CH_3); δ_C([$^2H_6$]-DMSO, 50 MHz) 161.25 (C-4), 154.99 (C-2 or C-8a), 151.02 C-2 or C-8a), 150.40 (C-7), 140.72 (C-6), 138.59 (C′-1), 129.36 (C-4a), 128.79 (C′-3), 125.41 (C′-2), 125.34 (C′-4), 42.91 (N$CH_2$$CH_2$), 20.49 ($CH_2CH_2$$CH_3$) and 11.00 ($CH_2CH_3$); MS (EI) *m*/*z* 282 (11%, $M^+ + 1$), 281 (56, M^+), 280 (11), 240 (19), 239 (17), 238 (100), 224 (15), 195 (8), 170 (4), 164 (9), 145 (4), 118 (5) and 77 (10); MS (CI) *m*/*z* 282 (MH).

3-Anilino-2-isopropylpteridin-4(3*H*)-one 5e

Pale yellow solid (72.0 mg, 0.26 mmol, 53%), mp 200–205 °C (Found: M^+, 281.1287. $C_{15}H_{15}N_5O$ requires M, 281.1277); R_F 0.40 (A); ν_{max}(KBr)–cm^{-1} 3231, 1696, 1605, 1559, 1524, 1449,

1420, 1360, 1277, 1221, 1186, 1067, 876, 826, 739, 693 and 646; δ_H($CDCl_3$, 500 MHz) 8.73 (0.5H, d, *J* 2.5, H-7), 8.55 (0.5H, d, *J* 2.0, H-7), 8.43 (0.5H, d, *J* 2.5, H-6), 8.32 (0.5H, d, *J* 2.5, H-6), 7.680 (0.5H, br, s, NH), 7.675 (1H, d, *J* 7.5, C_6H_5), 7.43 (1H, t, *J* 7.5, C_6H_5), 7.42 (1H, t, *J* 7.0, C_6H_5), 7.22 (0.5H, t, *J* 7.5, C_6H_5), 7.16 (0.5H, t, *J* 7.5, C_6H_5), 6.94 (1H, d, *J* 7.5, C_6H_5), 6.81 (0.5H, br s, NH), 5.73 [0.5H, br, NC*H*(CH_3)$_2$], 5.57 [0.5H, septet, *J* 7.0, NC*H*(CH_3)$_2$], 1.74 [3H, d, *J* 7.5, CH(C*H*$_3$)$_2$] and 1.65 [3H, d, *J* 6.5, CH(C*H*$_3$)$_2$]; δ_H([$^2H_6$]-DMSO, 200 MHz) 9.15 (1H, br s, NH), 8.67 (1H, d, *J* 2.2, H-7), 8.45 (1H, d, *J* 2.0, H-6), 7.55–7.51 (2H, m, C_6H_5), 7.42–7.34 (2H, m, C_6H_5), 7.22–7.13 (1H, m, C_6H_5), 4.91 [1H, septet, *J* 6.5, NC*H*(CH_3)$_2$] and 1.61 [6H, d, *J* 6.6, CH(C*H*$_3$)$_2$]; δ_H(CD_3OD, 200 MHz) 8.68 (1H, d, *J* 2.0, H-7), 8.49 (1H, d, *J* 2.0, H-6), 7.60–7.56 (2H, m, C_6H_5), 7.47–7.40 (2H, m, C_6H_5), 7.29–7.22 (1H, m, C_6H_5), around 5 [1H, NC*H*(CH_3)$_2$] and 1.77 [6H, d, *J* 7.0, CH(C*H*$_3$)$_2$], the peaks of N*H* were diminished and C*H*(CH_3)$_2$ was concealed by CH_3OH; δ_H(*o*-$C_6D_4Cl_2$, 500 MHz) 8.49 (0.25H, s, H-7), 8.31 (0.25H, s, H-6), 8.10 (0.75H, d, *J* 2.5, H-7), 7.87 (0.75H, d, *J* 2.0, H-6), 7.63–7.58 (0.75H, m, C_6H_5), 7.40 (0.75H, br s, N*H*), 7.25 (1.75H, t, *J* 7.8, C_6H_5), 7.16 (1H, t, *J* 8.0, C_6H_5), 7.01–6.96 (1.5H, m, C_6H_5, 6.87 (0.25H, br s, N*H*) 5.62 [0.75H, septet, *J* 6.8, NC*H*(CH_3)$_2$], 5.33 [0.25H, br, NC*H*(CH_3)$_2$], 1.62 [4.5H, d, *J* 7.0, CHC(C*H*$_3$)$_2$], 1.49 [1.5H, d, *J* 7.0, CH(C*H*$_3$)$_2$]; δ_C($CDCl_3$, 125 MHz) 161.94 (C-4), 159.89 (C-4), 154.64 (C-2 or C-8a), 150.30 (C-7), 149.95 (C-2 or C-8a), 147.46 (C-7), 147.36 (C-2 or C-8a), 146.14 (C-2 or C-8a), 141.50 (C-6), 140.40 (C-6), 137.11 (C′-1), 130.53 (C′-3), 130.38 (C-4a), 129;58 (C′-3), 128.29 (C-4a), 125.65 (C′-4), 124.36 (C′-4), 122.56 (C′-2), 121.91 (C′-2), 47.96 [N*C*H(CH_3)$_2$] (included isomer), 20.73 [CH(*C*H$_3$)$_2$] and 19.16 [CH(*C*H$_3$)$_2$] [a quaternary carbon (C′-1) could not be found]; δ_C([$^2H_6$]-DMSO, 50 MHz) 161.74 (C-4), 154.53 (C-2 or C-8a), 151.15 (C-2 or C-8a), 150.17 (C-7), 140.65 (C-6), 139.32 (C′-1), 130.28 (C-4a), 128.75 (C′-3), 125.04 (C′-2), 124.91 (C′-4), 49.34 [N*C*H(CH_3)$_2$] and 19.36 [CH-(*C*H$_3$)$_2$]; δ_C(CD_3OD, 50 MHz) 164.08 (C-4), 156.07 (C-2 or C-8a), 153.53 (C-2 or C-8a), 151.25 (C-7), 141.73 (C-6), 139.71 (C′-1), 131.76 (C-4a), 129.99 (C′-3), 126.81 (C′-2), 126.58 (C′-4), 51.59 [N*C*H(CH_3)$_2$] and 19.58 [CH(*C*H$_2$)$_2$]; λ_{max}/log ε 231/4.03, 224/4.02, 284/4.05 and 352/3.65; MS (EI) *m*/*z* 282 (9%, M^+ + 1), 281 (54, M^+), 240 (9), 239 (16), 238 (100), 118 (5), 94 (5) and 77 (8); MS (CI) *m*/*z* 282 (MH).

***N*-Isopropyl-3-(2-methyl-1-phenyl-3-isoureido)pyrazine-2-carboxamide 6.** Oil (46.9 mg, 0.15 mmol, 22%) (Found: M^+, 313.1534. $C_{16}H_{19}N_5O_2$ requires *M*, 313.1539); R_F 0.14 (A:H 2:1), ν_{max}(neat)/cm^{-1} 3256, 3052, 2971, 1632, 1599, 1586, 1532, 1414, 1229, 1161, 1063, 754 and 693; δ_H($CDCl_3$, 200 MHz) 12.21 (1H, br s, NHC$_6$H$_5$), 9.91 (1H, d, *J* 7.4, CON*H*CH), 8.27 (1H, d, *J* 2.4, H-5 or H-6), 8.27 (1H, d, *J* 2.6, H-5 or H-6), 7.43–7.16 (5H, m, C_6H_5), 4.46 [1H, d septet, *J* 8.0, 6.6, NH*H*-(CH_3)$_2$], 4.06 (3H, s, OCH_3) and 1.30 [6H, d, *J* 6.6, CH(C*H*$_3$)$_2$]; δ_C($CDCl_3$, 50 MHz) 163.37 (CONH), 157.02 [C-3 or N=*C*(OCH$_3$)N], 154.03 [C-3 or N=*C*(OCH$_3$)N], 140.88 (C-5), 137.36 (C-6), 137.02 (C′-1), 129.52 (C′-3), 125.63 (C′-4), 123.19 (C′-2), 55.19 (OCH_3), 41.48 [NH*C*H(CH_3)$_2$] and 23.20 [CH-[*C*H$_3$)$_2$] [one quaternary carbon (C-2) may be concealed by the peak of 129.52]; MS (EI) *m*/*z* 314 (10%, M^+ + 1), 313 (52, M^+), 238 (7), 228 (15), 227 (100), 223 (8), 221 (6), 195 (15), 179 (8), 134 (6), 119 (210) and 77 (6); MS (CI) *m*/*z* 314 (MH).

2-(4-Chlorophenyl)amino-3-isopropylpteridin-4(3*H*)-one 5f

Yellow solid (74.0 mg, 0.23 mmol, 43%), mp 96–99 °C (Found: M^+, 315.0885. $C_{15}H_{14}ClN_5O$ requires *M*, 315.0886); R_F 0.42 (A:H 3:1); ν_{max}(KBr)/cm^{-1} 3416, 1699, 1642, 1601, 1561, 1526, 1493, 1420, 1323, 1219, 1188, 1090 and 826; δ_H($CDCl_3$, 200 MHz) 8.74 (0.5H, d, *J* 2.0, H-7), 8.55 (0.5H, d, *J* 2.2, H-7), 8.45 (0.5H, d, *J* 2.4, H-6), 8.35 (0.5H, d, *J* 2.2, H-6), 7.62 (1H, d, *J* 8.6, C_6H_4 + 0.5H, br, NH), 7.41–7.34 (2H, m, C_6H_4), 6.98 (1H, d, *J* 8.6, C_6H_4 + 0.5H, br, NH), 5.65 [0.5H, septet, *J* 7.2, NC*H*(CH_3)$_2$], 5.55 [0.5H, septet, *J* 6.8, NC*H*(CH_3)$_2$], 1.72 [3H, d, *J* 7.0, CH(C*H*$_3$)$_2$] and 1.63 [3H, d, *J* 7.0, CH(C*H*$_3$)$_2$]; δ_H([$^2H_6$]-DMSO, 200 MHz) 9.28 (1H, br s, NH), 8.70 (1H, d, *J* 1.4, H-7), 8.49 (1H, d, *J* 1.6, H-6), 7.58 (2H, d, *J* 8.6, C_6H_4), 7.44 (2H, d, *J* 8.8, C_6H_4), 4.92 [1H, septet, *J* 6.4, NC*H*(CH_3)$_2$] and 1.62 [6H, d, *J* 6.8, CH(C*H*$_3$)$_2$]; δ_C($CDCl_3$, 50 MHz) 162.10 (C-4), 160.06 (C-4), 154.70 (C-2 or C-8a), 150.50 (C-7), 150.16 (C-2 or C-8a), 147.92 (C-7), 147.47 (C-2 or C-8a), 144.99 (C-2 or C-8a), 141.84 (C-6), 140.81 (C-6), 135.99 (C′-1), 132.54 (C′-1), 131.01 (C-4a or C′-4), 130.70 (C′-3), 130.05 (C-4a or C′-4), 129.69 (C′-3), 129.18 (C-4a or C′-4), 128.38 (C-4a or C′-4), 124.18 (C′-2), 123.50 (C′-2), 47.99 [N*C*H(CH_3)$_2$], 46.28 [N*C*H(CH_3)$_2$], 20.50 [CH(*C*H$_3$)$_2$] and 18.97 [CH(*C*H$_3$)$_2$]; δ_C([$^2H_6$]-DMSO, 50 MHz) 158.62 (C-4), 151.16 (C-2 or C-8a), 147.70 (C-2 or C-8a), 147.12 (C-7), 137.82 (C-6), 135.63 (C′-1), 127.32 (C-4a or C′-4), 125.66 (C′-3), 123.32 (C′-2), 46.37 [N*C*H(CCH$_3$)$_2$] and 16.33 [CH(*C*H$_3$)$_2$]; one carbon (C-4a or C′-4) could not be found; λ_{max}/log ε 250/4.15, 286/4.12 and 349/3.71; MS (EI) *m*/*z* 317 (22%, M^+ + 2), 316 (11, M^+ + 1), 315 (76, M^+), 275 (6), 274 (37), 273 (18), 272 (100), 238 (23), 164 (6) and 94 (7); MS (CI) *m*/*z* 318 (MH + 2) and 316 (MH).

3-Isopropylpteridine-2,4(1*H*,3*H*)-dione 10. White solid (29.4 mg, 0.14 mmol, 26%), mp 234–236 °C (Found: M^+, 206.0803. $C_9H_{10}N_4O_2$ requires *M*, 206.0803); R_F 0.37 (A:H 3:1), ν_{max}(KBr)/cm^{-1} 3044, 1725, 1657, 1561, 1445, 1408, 1391, 1231, 1078, 936, 870, 812 and 675; δ_H($CDCl_3$, 200 MHz) 9.83–9.78 (1H, br, NH), 8.64 (1H, d, *J* 2.4, H-7), 8.62 (1H, d, *J* 2.4, H-6), 5.33 [1H, septet, *J* 7.0, NC*H*(CH_3)$_2$] and 1.58 [6H, d, *J* 7.0, CH(C*H*$_3$)$_2$]; δ_C($CDCl_3$, 50 MHz) 160.87 (C-4), 150.10 (C-2 or C-8a), 148.23 (C-7), 147.54 (C-2 or C-8a), 141.86 (C-6), 128.34 (C-4a), 47.25 [N*C*H(CH_3)$_2$] and 19.33 [CH(*C*H$_3$)$_2$]; MS (EI) *m*/*z* 207 (10%, M^+ + 1), 206 (100, M^+), 191 (15), 166 (6), 165 (94), 163 (15), 148 (37), 122 (9), 121 (16), 120 (31), 94 (11) and 93 (14); MS (CI) *m*/*z* 207 (MH).

3-Anilino-2-*sec*-butylpteridin-4(3*H*)-one 5g. Yellow oil (25.2 mg, 0.086 mmol, 36%) (Found: M^+, 295.1435. $C_{16}H_{17}N_5O$ requires *M*, 295.1433), R_F 0.28 (A:H 3:1); ν_{max}(neat)/cm^{-1} 3293, 2969, 1692, 1647, 1557, 1528, 1447, 1416, 1217, 1182, 752 and 693; δ_H($CDCl_3$, 200 MHz) 8.74 (0.5H, d, *J* 2.0, H-7), 8.55 (0.5H, d, *J* 2.0, H-7), 8.44 (0.5H, d, *J* 2.4, H-6), 8.33 (0.5H, d, *J* 2.4, H-6), 7.69–7.65 (0.5H, br, NH), 7.67 (1H, d, *J* 7.6, C_6H_5), 7.43 (2H, dd, *J* 7.8, 1.8, C_6H_5), 7.26–7.11 (1H, m, C_6H_5), 6.93 (1H, d, *J* 7.2, C_6H_5), 6.82 (0.5H, br s, NH), 5.65–5.40 [0.5H, br, NC*H*(CH_3)CH_2], 5.37 [0.5H, sextet, *J* 7.2, NC*H*(CH_3)CH_2], 2.40–1.85 (2H, m, CHC*H*$_2$CH$_3$), 1.70 (1.5H, d, *J* 7.2, CHC*H*$_3$), 1.62 (1.5H, d, *J* 7.2, CHC*H*$_3$), 1.03 (1.5H, t, *J* 7.4, CH_2CH_3) and 0.98 (1.5H, d, *J* 7.4, CH_2CH_3); δ_H([$^2H_6$]-DMSO, 200 MHz) 9.11 (1H, br s, NH), 8.67 (1H, d, *J* 2.0, H-7), 8.46 (1H, d, *J* 2.2, H-6), 7.51–7.35 (4H, m, C_6H_5), 7.19 (1H, tt, *J* 7.1, 1.6, C_6H_5), 4.69 [1H, q, *J* 7.1, NC*H*(CH_3)CH_2], 2.23 (1H, d quintet, *J* 13.6, 7.7, CHC*H*$_2$CH$_3$), 1.94 (1H, d quintet, *J* 13.6, 7.1, CHC*H*$_2$CH$_3$), 1.61 (3H, d, *J* 6.6, CHC*H*$_3$) and 0.86 (3H, d, *J* 7.4, CH_2CH_3); δ_C($CDCl_3$, 50 MHz) 162.50 (C-4) (included isomer), 154.95 (C-2 or C-8a), 150.51 (C-7), 150.36 (C-2 or C-8a), 147.68 (C-7), 146.41 (C-2 or C-8a), 141.70 (C-6), 140.59 (C-6), 137.36 (C′-1), 130.67 (C′-2), 130.53 (C-4a), 130.27 (C-4a), 129.71 (C′-2), 125.76 (C′-4), 124.46 (C′-4), 122.68 (C′-3), 121.99 (C′-3), 53.57 [N*C*H(CH_3)CH_2], 51.64 [N*C*H(CH_3)CH_2], 27.92 (CH*C*H$_2$-CH$_3$), 25.74 (CH*C*H$_2$CH$_3$), 18.83 (CH*C*H$_3$), 17.16 (CH*C*H$_3$) and 11.39 (CH_2CH_3) (included isomer); two quaternary carbons (C-2 or C-8a and C′-1) could not be found; δ_C([$^2H_6$]-DMSO, 50 MHz) 161.59 (C-4), 154.50 (C-2 or C-8a), 151.77 (C-2 or C-8a), 150.16 (C-7), 140.63 (C-6), 139.11 (C′-1), 129.93 (C-4a), 128.70 (C′-2), 125.10 (C′-3), 124.93 (C′-4), 54.93 [*C*H(CH_3)CH_2], 25.34 (CH*C*HCH$_3$), 17.43 (CH*C*H$_3$) and 10.94 (CH_2CH_3); λ_{max}/log ε 244/4.03, 286/4.07 and 353/3.66; MS (EI) *m*/*z* 296 (6%, M^+ + 1), 295 (30, M^+), 294 (3), 252 (4), 241 (13), 240 (100), 239 (11), 238 (60), 223 (5), 195 (12), 118 (3), 94 (4) and 77 (5); MS (CI) *m*/*z* 296 (MH).

6-Phenylimidazo[2,1-*b*]pteridine-7,10(6*H*,8*H*)-dione 7. Yellow solid (34.5 mg, 0.12 mmol, 37%), mp 202–206 °C (Found: M^+,

279.0756. $C_{14}H_9N_5O_2$ requires *M*, 279.1756); R_F 0.08 (A:H 1:1); ν_{max}(KBr)/cm^{-1} 3005, 1775, 1705, 1634, 1551, 1501, 1454, 1391, 1202 and 750; δ_H($CDCl_3$, 200 MHz) 8.87 (1H, d, *J* 2.6, H-3), 8.76 (1H, d, *J* 2.0, H-2), 7.63–7.41 (5H, m, C_6H_5) and 4.87 (2H, s, $NCH_2C{=}O$); δ_C($CDCl_3$, 50 MHz) 166.90 (C-7 or C-10), 158.04 (C-7 or C-10), 155.80 (C-4a or C-5a), 152.88 (C-4a or C-5a), 150.42 (C-3), 143.59 (C-2), 132.47 (C′-1), 130.52 (C-10a), 130.06 (C′-3), 130.00 (C′-4), 127.19 (C′-2) and 47.30 (C-8); MS (EI) *m*/*z* 280 (15%, $M^+ + 1$), 279 (100, M^+), 278 (10), 251 (16), 250 (20), 223 (22), 222 (10), 196 (9), 195 (51), 126 (5), 98 (7), 84 (5) and 77 (29); MS (CI) *m*/*z* 280 (MH).

***N*-(Methoxycarbonylmethyl)-2-(*N*′-phenylureido)pyrazine-3-carboxamide 8.** White solid (8.1 mg, 0.025 mmol, 8.5%), mp 210–211 °C (Found: M^+, 329.1120. $C_{15}H_{15}N_5O_4$ requires *M*, 329.1124); R_F 0.46 (A:H 1:1); ν_{max}(KBr)/cm^{-1} 3389, 1748, 1692, 1657, 1568, 1480, 1262, 1213, 1181 and 752; δ_H($CDCl_3$, 200 MHz) 11.14 (1H, s, $NHCONHC_6H_5$), 11.08 (1H, s, $NHCONHC_6H_5$), 8.46 (1H, t, *J* 5.0, $CONHCH_2$), 8.40 (1H, d, *J* 2.4, H-5), 8.19 (1H, d, *J* 2.6, H-6), 7.62–7.56 (2H, m, C_6H_5), 7.39–7.29 (2H, m, C_6H_5), 7.10 (1H, tt, *J* 7.3, 1.4, C_6H_5), 4.25 (2H, d, *J* 5.6, $NHCH_2CO$) and 3.82 (3H, s, OCH_3), δ_C($CDCl_3$, 50 MHz) 170.19 (CO_2), 165.37 (CONH), 151.72 (NHCONH or C-3), 150.01 (NHCONH or C-3), 144.21 (C-5), 138.44 (C′-1), 135.09 (C-6), 129.36 (C-2), 128.87 (C′-3), 124.18 (C′-4), 120.68 (C′-2), 52.79 (OCH_3) and 41.24 ($NHCH_2CO$); MS (EI) *m*/*z* 329 (23%, M^+), 237 (19), 210 (69), 205 (9), 178 (15), 177 (38), 151 (34), 148 (29), 123 (9), 122 (22), 120 (28), 119 (21), 95 (9), 94 (22) and 93 (100); MS (CI) *m*/*z* 330 (MH).

3-Methoxycarbonylmethylpteridine-2,4(1*H*,3*H*)-dione 9. Pale yellow solid (34.2 mg, 0.14 mmol, 17%), mp 233–234 °C (Found: M^+, 236.0548. $C_9H_8N_4O_4$ requires *M*, 236.0546); R_F 0.43 (A); ν_{max}(KBr)/cm^{-1} 3416, 3042, 2922, 1734, 1688, 1562, 1453, 1412, 1231, 1140, 814 and 766; δ_H([$^2H_6$]-DMSO, 200 MHz) 12.50–12.46 (1H, br, NH), 8.74 (1H, d, *J* 2.2, H-7), 8.62 (1H, d, *J* 2.2, H-6), 4.68 (2H, s, NCH_2CO) and 3.70 (3H, s, OCH_3); δ_C([$^2H_6$]-DMSO, 50 MHz) 168.69 (CO_2), 160.41 (C-2, C-4 or C-8a), 149.86 (C-2, C-4 or C-8a), 149.42 (C-7), 148.67 (C-2, C-4 or C-8a), 141.32 (C-6), 126.93 (C-4a), 52.45 (NCH_2CO) and 41.88 (OCH_3); MS (EI) *m*/*z* 237 (10%, M + 1), 236 (81, M), 205 (22), 204 (56), 192 (7), 178 (10), 177 (92), 149 (10), 148 (100), 121 (11), 120 (75) and 93 (11); MS (CI) *m*/*z* 237 (MH).

3-Anilino-2-(1-methylprop-2-enyl)pteridin-4(3*H*)-one 5j. Pale yellow solid (55.6 mg, 0.19 mmol, 81%), mp 138–140 °C (Found: M^+, 293.1279. $C_{16}H_{15}N_5O$ requires *M*, 293.1277); R_F 0.18 (A:H 2:1); ν_{max}(neat)/cm^{-1} 3374, 2986, 2934, 1698, 1557, 1530, 1449, 1254, 750 and 691; δ_H($CDCl_3$, 200 MHz) 8.75 (1H, d, *J* 2.0, H-7), 8.55 (1H, d, *J* 2.2, H-6), 7.65–7.59 (2H, m, C_6H_5), 7.52 (1H, br s, NH), 7.43–7.34 (2H, m, C_6H_5), 7.18 (1H, ddd, *J* 8.6, 6.0, 1.2, C_6H_5), 6.50 [1H, qq, *J* 7.0, 2.8, $NCH(CH_3)CH{=}CH_2$], 6.35 (1H, ddd, *J* 17.4, 10.8, 3.1, $CHCH{=}CH_2$), 5.71 (1H, dd, *J* 10.8, 2.7, $CH{=}CH_2$), 5.68 (1H, dd, *J* 17.4, 2.5, $CH{=}CH_2$) and 1.72 (3H, d, *J* 7.0, $CHCH_3$); δ_C($CDCl_3$, 50 MHz) 161.86 (C-4), 155.14 (C-2 or C-8a), 150.67 (C-7), 149.80 (C-2 or C-8a), 141.68 (C-6), 138.87 ($CHCH{=}CH_2$), 137.50 (C′-1), 130.21 (C-4a), 129.62 (C′-3), 125.44 (C′-4), 121.83 (C′-2), 119.24 ($CH{=}CH_2$), 49.21 [$NCH(CH_3)CH{=}CH_2$] and 14.84 ($CHCH_3$); λ_{max}/log ε 235/4.15, 290/4.38 and 349/3.83; MS (EI) *m*/*z* 294 (14%, $M^+ + 1$), 293 (83, M^+), 292 (35), 278 (37), 264 (11), 250 (27), 240 (8), 239 (19), 238 (100) and 77 (10); MS (CI) *m*/*z* 294 (MH).

2-Anilino-3-(1-methylbut-3-enyl)pteridin-4(3*H*)-one 5k. Yellow oil (33.1 mg, 0.11 mmol, 25%) (Found: M^+, 307.1438. $C_{17}H_{17}N_5O$ requires *M*, 307.1433); R_F 0.47 (A); ν_{max}(neat)/cm^{-1} 3295, 3002, 1692, 1644, 1605, 1557, 1528, 1497, 1447, 1416, 1217 and 750; δ_H([$^2H_6$]-DMSO, 200 MHz) 9.15 (1H, br s, NH), 8.67 (1H, d, *J* 2.2, H-7), 8.45 (1H, d, *J* 2.0, H-6), 7.50–7.35 (4H, m, C_6H_5), 7.19 (1H, tt, *J* 7.0, 1.7, C_6H_5), 5.79 (1H, dddd, *J* 17.0, 10.4, 7.8, 6.5, $CH_2CH{=}CH_2$), 5.01 (1H, dq, *J* 17.2, 1.0, $CH{=}CH_2$), 4.97 (1H, dq, *J* 10.2, 1.0, $CH{=}CH_2$), 4.86 [1H, q, *J* 6.7, $NCH(CH_3)CH_2$], 3.02 (1H, dt, *J* 14.2, 8.2, $CHCH_2CH{=}CH_2$), 2.67 (1H, dt, *J* 13.8, 6.5, $CHCH_2CH{=}CH_2$) and 1.63 (3H, d, *J* 6.6, $CHCH_3$); δ_C([$^2H_6$]-DMSO, 50 MHz) 161.73 (C-4), 154.47 (C-2 or C-8a), 151.68 (C-2 or C-8a), 150.27 (C-7), 140.76 (C-6), 139.24 (C′-1), 135.49 ($CH_2CH{=}CH_2$), 130.02 (C-4a), 128.82 (C′-2 + C′-3), 125.05 (C′-4), 117.96 ($CH{=}CH_2$), 53.01 [$NCH(CH_2)CH_2$], 36.82 ($CHCH_2CH{=}CH_2$) and 17.53 ($CHCH_3$); MS (EI) *m*/*z* 307 (6%, M^+), 306 (4), 241 (12), 240 (100), 239 (7), 238 (33), 233 (9), 216 (12), 195 (17), 94 (3) and 77 (8); MS (CI) *m*/*z* 308 (MH).

X-Ray crystal structure analysis of 5a

Data collection. A yellow prismatic crystal of $C_{15}H_{13}N_5O$ having approximate dimensions of 0.30 × 0.30 × 0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS-IV imaging plate area detector with graphite monochromated Mo-Kα radiation. Indexing was performed from 3 oscillations which were exposed for 4.0 min. The crystal-to-detector distance was 105.00 mm with the detector at the zero swing position. Readout was performed in the 0.100 mm pixel mode.

Cell constants and an orientation matrix for data collection corresponded to a trigonal hexagonal cell (laue class: 3 bar) with dimensions: $a = 25.458(2)$ Å, $c = 11.210(1)$ Å, $V = 6292.3(9)$ Å^3. For $Z = 18$ and $M_r = 279.30$, the calculated density is 1.33 g cm^{-3}. Based on the systematic absences of: *hkil*: $-h + k + l$, $3n$ packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be: $R\bar{3}$ (#148). The data were collected at a temperature of −150 ± 1 °C to a maximum 2θ value of 55.7°. A total of 166.0° oscillation images was collected, each being exposed for 4.0 min. The crystal-to-detector distance was 105.00 mm with the detector at the zero swing position. Readout was performed in the 0.100 mm pixel mode.

Data reduction. A total of 3045 reflections was collected. The linear absorption coefficient, μ, for Mo-Kα radiation is 0.9 cm^{-1}. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 6.630 10 × 10^{-3}).

Structure solution and refinement. The structure was solved by direct methods[35] and expanded using Fourier techniques.[36] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[37] was based on 2568 observed reflections [$I > 30\sigma(I)$] and 191 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.059,$$

$$R_\omega = \sqrt{\Sigma\omega(|F_o| - |F_c|)^2/\Sigma\omega F_o^2} = 0.090.$$

The standard deviation of an observation of unit weight[38] was 1.73. The weighting scheme was based on counting statistics and included a factor ($p = 0.086$) to downweight the intense reflections. Plots of $\Sigma\omega(|F_o| - |F_c|)^2$ *versus* $|F_o|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.81 and −0.35 e Å^{-3}, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[39] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[40] All calculations were performed using the TEXSAN[41] crystallographic software package of the Molecular Structure Corporation.

X-Ray crystal structure analysis of 5e

A white prism crystal of $C_{15}H_{15}N_5O$ having approximate dimensions of 0.180 × 0.560 × 0.820 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5S diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.710 69 Å) and a 2 kW stationary anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 24 carefully centered reflections in range 31.18° < 2θ < 37.78°, corresponded to a triclinic cell with dimensions: a = 15.633 (6) Å, b = 15.958 (7) Å, c = 10.600 (2) Å, V = 2222 (1) Å^3, α = 91.90 (3)°, β = 107.73 (2)°, γ = 115.92 (2)°. For Z = 6 and M_r = 281.32, the calculated density is 1.261 g cm^{-3}. Based on packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be $P\bar{1}$ (#2). The data were collected at a temperature of 20 ± 1 °C using the ω–2θ scan technique to a maximum 2θ value of 55.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.19° with a take-off angle of 6.0°. Scans of (1.63 ± 0.30 tan θ)° were made at a speed of 32.0° min^{-1} (in omega). The weak reflections [I < 10.0σ (I)] were rescanned (maximum of 2 rescans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 40 cm. Of the 10 574 reflections which were collected, 10 200 were unique (R_{int} = 0.074). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection indicating crystal and electronic stability (no decay correction was applied). The linear absorption coefficient for Mo-Kα is 0.8 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods.[44] The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 3905 observed reflections [I > 2.00σ(I)] and 568 variable parameters and converged (largest parameter shift was 0.03 times its esd) with unweighted and weighted agreement factors of: R = 0.067 and R_w = 0.063. The standard deviation of an observation of unit weight was 1.51. The weighting scheme was based on counting statistics and included a factor (p = 0.03, p: p-factor) to downweight the intense reflections. Plots of $\Sigma w(|F_o| - |F_c|)^2$ *versus* $|F_o|$, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.29 and −0.30 e Å^{-3}, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[39] Anomalous dispersion effects were included in F_c;[43] the value for $\Delta f'$ and $\Delta f''$ were those of Cromer.[44] All calculations were performed using the TEXSAN[41] crystallographic software package of Molecular Structure Corporation. Atomic coordinates, bond lengths and bond angles, torsion angles and thermal parameters, *etc.* of both of **5a** and **5e** have been deposited at the Cambridge Crystallographic Data Centre.[32]

Synthesis of imidazo[2,1-*b*]pteridine derivatives 12 by iodoimidazolination: general procedure

To a solution of the 3-allyl-2-anilinopteridin-4(3*H*)-one **5a** (50.3 mg, 0.18 mmol) in THF (5.0 cm^3) was added iodine (91.4 mg, 0.36 mmol, 2.0 equiv.) and sodium hydrogen carbonate (30.3 mg, 0.36 mmol, 2.0 equiv.). The mixture was stirred at room temperature under nitrogen until starting material had disappeared (TLC), for 1 h. The reaction mixture was treated with saturated aqueous sodium sulfite to reduce the excess of iodine after which it was diluted with water and extracted with AcOEt (20 cm^3 × 3). The combined layer extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was purified on a silica gel column (H:A 1:2, v/v, as eluent) to afford 7,8-dihydro-7-iodomethyl-6-phenylimidazo-[2,1-*b*]pteridin-10(6*H*)-one **12a** (39.5 mg, 0.097 mmol, yield 54%). Yellow solid; mp 215–219 °C; R_F 0.18 (A); ν_{max}(KBr)/cm^{-1} 3422, 1696, 1616, 1591, 1553, 1501, 1468, 1443, 1292 and 756; δ_H($CDCl_3$, 200 MHz) 8.69 (1H, d, *J* 2.2, H-3), 8.53 (1H, d, *J* 2.0, H-2), 7.66–7.60 (2H, m, C_6H_5), 7.53–7.45 (2H, m, C_6H_5), 7.39–7.30 (1H, m, C_6H_5), 4.76 (1H, dddd, *J* 9.2, 6.5, 5.4, 2.7, H-7), 4.55 (1H, dd, *J* 12.4, 9.6, NCH_2CH), 4.23 (1H, dd, *J* 12.4, 5.0, NCH_2CH), 3.44 (1H, dd, *J* 11.0, 2.6, CHCH_2I) and 3.33 (1H, dd, *J* 11.0, 6.2, CHCH_2I); δ_C($CDCl_3$, 50 MHz) 159.71 (C-10), 157.38 (C-4a or C-5a), 152.83 (C-4a or C-5a), 149.90 (C-3), 141.23 (C-2), 135.34 (C′-1), 131.09 (C-10a), 130.17 (C′-3), 127.77 (C′-4), 125.19 (C′-2), 57.46 (C-7), 47.42 (C-8) and 7.85 (CHCH_2I); MS (EI) *m*/*z* 278 [14%, M − 127(I)], 277 (100), 276 (26), 249 (6), 248 (37), 128 (21), 127 (7) and 77 (4); MS (CI) 278 (MH − 128); MS (FAB+) *m*/*z* 406 (MH^+). In the HRMS, the M^+ peak of **12a** (405.0087) was hidden by one of the perfluorocarbon peaks ($C_{10}F_{15}$, 404.9760) used as a standard.

(7*R,8*S**)-7,8-Dihydro-7-iodomethyl-8-methyl-6-phenylimidazo[2,1-*b*]pteridin-10(6*H*)-one 12c.** Pale yellow solid (26.4 mg, 0.063 mmol, 25%); mp 242–247 °C (Found: M^+, 419.0242. $C_{16}H_{14}IN_5O$ requires M, 419.0243); R_F 0.19 (A); ν_{max}(neat)/cm^{-1} 2926, 1694, 1618, 1595, 1553, 1537, 1505, 1441, 1292 and 754; δ_H($CDCl_3$, 200 MHz) 8.72 (1H, d, *J* 2.2, H-3), 8.56 (1H, d, *J* 2.2, H-2), 7.72–7.66 (2H, m, C_6H_5), 7.55–7.45 (2H, m, C_6H_5), 7.34 (1H, tt, *J* 5.7, 1.2, C_6H_5), 4.78 (1H, qd, *J* 6.4, 2.6, H-8), 4.27 (1H, dt, *J* 8.0, 2.6, H-7), 3.40 (1H, dd, *J* 10.7, 2.7, CHCH_2I), 3.22 (1H, dd, *J* 10.8, 7.8, CHCH_2I) and 1.76 (3H, d, *J* 6.4, CHCH_3); δ_C($CDCl_3$, 50 MHz) 159.64 (C-10), 157.33 (C-4a or C-5a), 151.76 (C-4a or C-5a), 149.88 (C-3), 141.24 (C-2), 135.79 (C′-1), 131.38 (C-10a), 130.19 (C′-3), 127.53 (C′-4), 124.72 (C′-2), 65.81 (C-7), 55.89, (C-8), 19.41 (CHCH_3) and 6.13 (CHCH_2I); MS (EI) *m*/*z* 419 (69%, M^+), 293 (18), 292 (100), 291 (22), 290 (14), 279 (13), 278 (98), 276 (15), 238 (18) and 77 (23); MS (CI) 420 (MH).

(7*R,8*R**)-7,8-Dihydro-7-iodomethyl-8-methyl-6-phenylimidazo[2,1-*b*]pteridin-10(6*H*)-one 12b.** Pale yellow solid (26.3 mg, 0.063, 25%), mp 110–117 °C (Found: M^+, 419.0242. $C_{16}H_{14}IN_5O$ requires M, 419.0243); R_F 0.17 (A); ν_{max}(neat)/cm^{-1}) 2996, 1698, 1616, 1591, 1551, 1499, 1439, 1298, 1196, 1134 and 754; δ_H($CDCl_3$, 200 MHz) 8.67 (1H, d, *J* 2.2, H-3), 8.53 (1H, d, *J* 2.2, H-2), 7.56–7.46 (2H, m, C_6H_5), 7.43–7.33 (3H, m, C_6H_5), 5.20 (1H, dq, *J* 7.8, 6.5, H-8), 4.82 (1H, ddd, *J* 11.4, 8.0, 3.4, H-7), 3.38 (1H, dd, *J* 10.4, 3.4, CHCH_2I), 3.08 (1H, dd, *J* 11.6, 10.4, CHCH_2I) and 1.69 (3H, d, *J* 6.4, CHCH_3); δ_C($CDCl_3$, 50 MHz) 159.35 (C-10), 157.06 (C-4a or C-5a), 153.89 (C-4a or C-5a), 149.85 (C-3), 141.34 (C-2), 135.80 (C′-1), 131.47 (C-10a), 130.29 (C′-3), 128.45 (C′-4), 126.50 (C′-2), 63.02 (C-7), 53.19 (C-8), 11.22 (CHCH_3) and −3.14 (CHCH_2I); MS (EI) *m*/*z* 419 (37%, M^+), 293 (11), 292 (58), 291 (100), 290 (32), 278 (40), 276 (17), 263 (10), 262 (45), 238 (10), 128 (9) and 77 (13); MS (CI) *m*/*z* 420 (MH).

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