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Synthesis of Methylene-Bridged Analogues of Biologically Active Pteridine Derivatives

Magdalena Ślusarczyk,[a] Wim M. De Borggraeve,*[a] Suzanne Toppet,[a] and Georges J. Hoornaert[a]

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The hepatitis C virus (HCV) is a major cause of liver disease worldwide. The HCV NS5B RNA-dependent RNA polymerase, which is a central enzyme in the replication of the virus, has become a potential target for design and synthesis of small molecule inhibitors useful in the treatment of HCV infection by interfering with viral replication. In this publication we describe the synthesis of cyclic analogues of biologically active pteridine derivatives of type **B**. The key step in the formation of target compounds **1**–**8**, is the condensation reaction of tricyclic diketones **10** and **11** with commercially available 4,5-diamino-6-hydroxypyrimidine (**9**). Subsequent chlorination and amination reactions led to the formation of the target molecules **1**–**8**, which were further biologically evaluated.

Introduction

The hepatitis C virus (HCV) is a major cause of liver disease worldwide – and the main reason for adult liver transplants in developed countries. It is estimated that 3% of the world's population (170 million) suffers from HCV infection which is usually chronic and can lead to fatal conditions such as cirrhosis or hepatocellular carcinoma.[1] HCV is a positive, single-strand RNA virus belonging to the *Flaviviridea* family. According to literature,[2] HCV RNA polymerase (NS5B), a viral enzyme crucial to HCV replication in the host liver, is a potential target in the treatment of HCV infection. Additionally, NS5B is not expressed in uninfected cells making the development of selective and non-toxic inhibitors more favorable.[3] This makes NS5B inhibition an attractive target for the treatment of viral infection. Current therapies based on the combination of pegylated interferons with ribavirin have limited efficacy in a significant proportion of patients and are associated with some side effects. Major side effects of combination therapy include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms.[4] In the light of this knowledge, the development of more efficacious and safer therapeutics for the treatment of chronic HCV infection and associated liver diseases seems to be reasonable and is a major public health objective.

There are few classes of inhibitors useful in the treatment of HCV infection.[5,6] It has been found recently that derivatives of pteridines, compounds of type **A**[4] (Figure 1) exhibit antiviral activity in mammals infected with HCV, in particular by inhibition of HCV replication. Additionally, the compounds of type **A** may diminish the HCV viral load of the patient to undetectable levels. Compounds of type **B**[7] (Figure 1) were reported to possess inhibitory activity against HCV NS5B RNA-dependent RNA polymerase (RdRp).

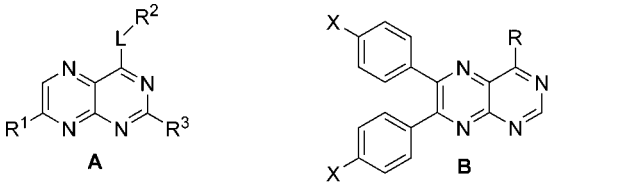


Figure 1. Bioactive pteridines.

In this publication we describe the synthesis of the compounds **1**–**8**, which are cyclic analogues of type **B** compounds. The purpose of this work was to further evaluate their biological properties and the effect of the methylene bridge on the biological activity of the systems. It is known that rigidisation introduced in bioactive compounds can increase inhibitor potency by locking in a bioactive conformation as well as locking out conformations which may be metabolized.[8]

[a] Laboratory for Molecular Design and Synthesis, K.U. Leuven, Celestijnenlaan 200 F, 3001 Leuven, Belgium
Fax: +32-16-327990
E-mail: wim.deborggraeve@chem.kuleuven.be

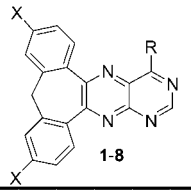
Results and Discussion

The general method we proposed for the preparation of the desired compounds **1**–**8** (Table 1) is briefly depicted in Scheme 1. Condensation reaction of commercially available 4,5-diamino-6-hydroxypyrimidine (**9**) with the tricyclic diketones **10** and **11** could give the compounds **1** and **2**, respectively. Treatment of the alcohols **1** and **2** with $POCl_3$ would lead to the corresponding chlorinated derivatives **3**, **4** which are useful for immediate amination reaction with different amines. According to reported data,[7] pentane-2-amine and 4-methylcyclohexylamine introduced in position 4 of compounds of type **B** increase the activity against HCV NS5B RdRp. Introduction of a fluorine atom at the *para* position of the aryl rings also enhances the potency, while substitutions at the same position with bromine or an electron-donating methoxy group drop the potency drastically. NH and OH at the 4-position and presence of N^1 and N^3 of the pteridine ring seem to be critical for biological activity. On the basis of this knowledge we have designed our target molecules, containing at the *para* position of the aryl moiety: hydrogen (compounds **1**, **3**, **5**, **7** and **7′**) and fluorine (compounds **2**, **4**, **6**, **8** and **8′**), respectively.

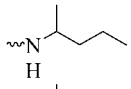
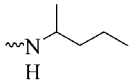
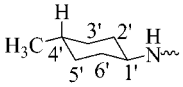
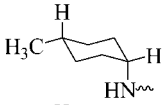
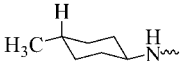
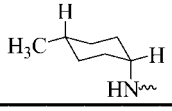
Compound **10** was obtained by oxidation of the monoketone **12** with SeO_2 as described previously.[9] The preparation of the 1,2-diketone **11** starts from the commercially available compound **13** which was cyclized by a Friedel–Crafts acylation strategy to afford **14**[10] (Scheme 2). In order to obtain compound **15**, 6-fluoroindan-1-one (**14**) was treated with the freshly prepared Grignard reagent of 3-bromo-1-fluorobenzene. Further dehydration of 6-fluoro-1-(3-fluorophenyl)indan-1-ol (**15**) using *p*-toluenesulfonic acid in refluxing toluene led to the formation of product **16**.

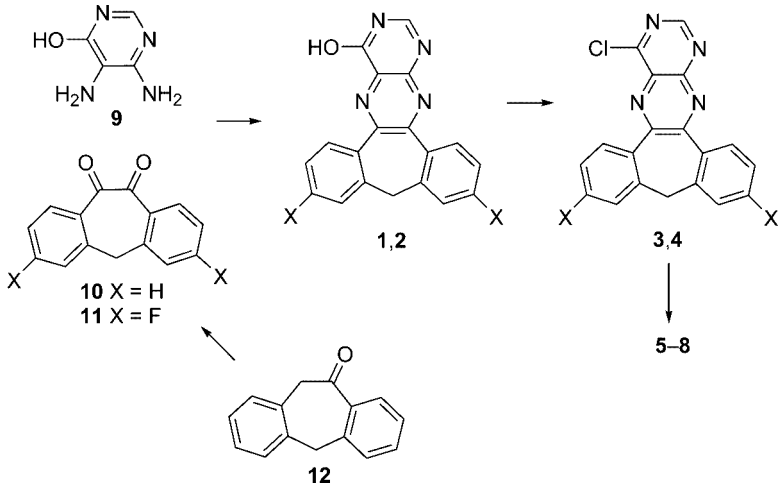
Oxidation of the double bond of compound **16** with CrO_3 gave the [4-fluoro-2-(3-fluorobenzoyl)phenyl]acetic acid (**17**). Esterification of **17** provided the corresponding acetate **18** that upon hydrogenation in the presence of 10% Pd/C under a pressure of 70 psi, at 70 °C in a steel bomb, was converted into the reduced product **19**. Formation of compound **19**, which was used in the next step without purification, was confirmed by mass spectroscopy. It is noteworthy that hydrogenation of the acetate **18** when performed in pure methanol as a solvent gave the alcohol **20**, while hydrogenation performed in the presence of acetic acid gave the desired product **19** with a fully reduced car-

Table 1. Preparation of substituted-pteridine compounds **1**–**8**.

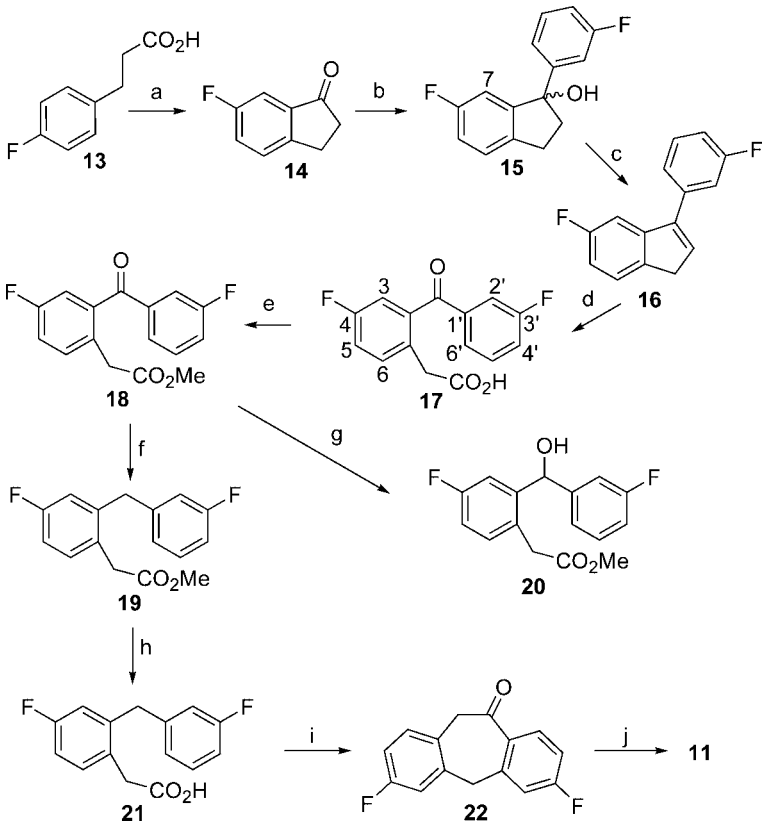


1-8

Entry	X	R	Yield (%)
1	H	OH	85
2	F	OH	90
3	H	Cl	–
4	F	Cl	–
5	H		46
6	F		49
7	H		25
7'	H		24
8	F		29
8'	F		22



Scheme 1. General method for the preparation of the desired compounds **1**–**8**.



Scheme 2. Reagents and conditions: [a] $SOCl_2$, $AlCl_3$, CH_2Cl_2, room temp., 12 h. [b] Mg turnings, dry Et_2O, 3-bromo-1-fluorobenzene, room temp., 5 h. [c] *p*-Toluenesulfonic acid, toluene, reflux, 3 h. [d] CrO_3, AcOH, H_2O, 35 °C, 3 h. [e] MeOH, H_2SO_4, reflux,16 h. [f] H_2-Pd/C, 70 psi, 70 °C, steel bomb, 5 h, AcOH. [g] H_2-Pd/C, 70 psi, 70 °C, steel bomb, 3 h, MeOH. [h] LiOH, THF/MeOH/H_2O, room temp., 15 h. [i] $SOCl_2$, $AlCl_3$, CH_2Cl_2, room temp., 5 h. [j] SeO_2, AcOH, reflux, 30 min.

bonyl group. This indicates the importance of the acidic medium during the reaction, which is believed to go via prior formation of a benzylic alcohol, consecutive protonation and further reduction. Hydrolysis of methyl [4-fluoro-2-(3-fluorobenzyl)phenyl]acetate (**19**) using LiOH in a mixture of THF, MeOH and water afforded compound **21** as a white solid. Appearance of a new signal in ^{1}H NMR and ^{13}C NMR spectra for a CH_2 group at δ = 3.58 ppm and 37.7 ppm, respectively, is indicative for the formation of the desired molecule. In order to obtain the monoketone **22**, the carboxylic acid **21** was activated with $SOCl_2$, and then cyclized using $AlCl_3$ in the Friedel–Crafts acylation reaction. Oxidation of 3,7-difluoro-5,11-dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one (**22**) with SeO_2 afforded desired key intermediate **11** as yellowish needles in very good yield (92%).

In order to prepare the final molecules **5**–**8** (Figure 2) the tricyclic diketones **10** and **11** were submitted to the condensation reaction with 4,5-diamino-6-hydroxypyrimidine (**9**) in refluxing acetic acid and water affording the compounds **1** and **2**, respectively. Further treatment of the alcohols **1** and **2** with $POCl_3$, at 100 °C for 15 h, furnished the corresponding chlorinated compounds **3** and **4**. Subsequent addition of pentane-2-amine and 4-methylcyclohexylamine (1:1 mixture of *cis* and *trans* isomers) to the crude products **3** and **4** dissolved in THF led to the formation of the target products **5**–**8**, respectively. For the synthesis of the cyclohexyl-derived compounds a mixture of *cis*- and *trans*-methylcyclohexylamine was used. Thus we have isolated and individually characterized the *cis* (compounds **7**′, **8**′) and *trans* (compounds **7**, **8**) isomers of 4-methylcyclohexyl-substituted pteridine derivatives. In order to assign the stereochemistry of the cyclohexyl substituents in the compounds **7**, **7**′ and **8**, **8**′ NMR spectroscopic data were analyzed. Because the synthesis was done with a *cis*/*trans* mixture of the 4-methylcyclohexylamine, in one product, the stereochemistry of the cyclohexyl should a priori be *cis* and in the other *trans*. The disposition of the amino substituent (axial or equatorial) on the cyclohexyl ring attached to the 4-position of the pteridine ring, can be deduced from the ^{1}H NMR spectrum. Indicative here is the width of the multiplet (in-

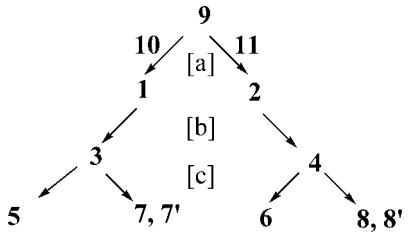


Figure 2. Reagents and conditions: [a] AcOH/H_2O, 100 °C, 30 min. [b] $POCl_3$, 100 °C, 15 h. [c] Amines, THF, reflux, 1 to 12 h.

dicative for the sum of all coupling constants with all other nuclei) for $H^{1'}$ (numbering see Table 1). In compounds **7′** and **8′**, narrow multiplets are observed for the proton $H^{1'}$ (11 Hz) in comparison with the width of the multiplets for $H^{1'}$ in compounds **7** and **8** (29 Hz). Because the width of a multiplet is indicative for the sum of all coupling constants it has to be assumed that $H^{1'}$ in compounds **7′** and **8′** is in an equatorial position (large $^3J_{aa}$ with $H^{2'}$ and $H^{6'}$ are absent in the multiplet). On the contrary, in compounds **7** and **8**, $H^{1'}$ is in an axial disposition (here the large $^3J_{aa}$ with $H^{2'}$ and $H^{6'}$ cause significant broadening of the multiplet).

This automatically implies that in compounds **7′** and **8′**, the amino group is in an axial position. Because it would be very unlikely to have two substituents in an axial position in a cyclohexane we can safely assume that in compounds **7′** and **8′** the methyl group is in the equatorial plane and hence these must be the products with the *cis*-substituted cyclohexylamine. According to the reported data, also in *cis*-4-methyl-1-*N*-phenylcyclohexylamine, the anilino substituent prefers an axial position which is consistent with our observations.

By simple deduction, compounds **7** and **8** must contain the *trans*-substituted cyclohexylamine with both methyl and amino substituent in an equatorial position.

Conclusions

We successfully accomplished the synthesis of the target molecules **1**–**8**, which are considered as cyclic analogues of type **B** compounds. All compounds synthesized were evaluated for inhibitory activity against HCV NS5B RNA-dependent RNA polymerase using a published procedure.[12] Preliminary results show activities which are similar or worse than the ones observed for the unrestrained non-methylene-bridged compounds.[7] Armed with this knowledge we may conclude that making the target molecules more rigid does not drastically improve the biological activity of the synthesized products.

Experimental Section

Commercially available starting materials, reagents and solvents were used as supplied. Reactions were routinely conducted under argon unless otherwise indicated. TLC analyses were performed on Nagel TLC-plates SIL G-25 UV_{254}, spots were visualized under 254-nm UV illumination. Purifications on column chromatography were carried out on 70–230 mesh silica gel (E. M. Merck). HPLC purification of compounds **6**, **7** and **8** was carried out on a normal phase silica column (Bio-Sil 250 × 10 mm) and eluted with CH_2Cl_2/EtOAc (70:30) at a flow rate of 4 mL/min (UV detection at 260 nm). Purification of **17** was performed via chromatotron, Harrison Research. Mass spectra (EI and CI) were run with a Hewlett–Packard MS-Engine 5989A instrument. Exact mass measurements were performed at a resolution of 10000 with a KRATOS MS5OTC instrument. ^1H and ^{13}C were measured with Bruker AMX 300 and 400 at 25 °C, unless otherwise indicated. Infrared spectra were recorded using KBr pellets or thin films between NaCl plates with a Perkin–Elmer 1600 Series Fourier Transform Spectrometer. Melting points were recorded with a digital melting point apparatus Electrothermal 9200.

6-Fluoroindan-1-one (14): 3-(4-Fluorophenyl)propanoic acid **13** (5.00 g, 29.73 mmol) was dissolved in CH_2Cl_2 (100 mL) and thionyl chloride was added (3.30 mL, 44.60 mmol). The reaction mixture was refluxed for 4 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (60 mL), and $AlCl_3$ (4.36 g, 32.70 mmol) was added at 0 °C. The mixture was stirred at room temperature for 12 h. After the reaction mixture was cooled to 0 °C, 1 M HCl was added slowly and the mixture was dissolved in CH_2Cl_2, extracted 3 times with H_2O and brine. Organic layers were combined, dried with $MgSO_4$, evaporated to yield crude oily product which was purified on silica gel with EtOAc/heptane (30:70) as eluent. Pure compound **14** was obtained as yellowish crystals (3.60 g, 83%), with spectroscopic data in agreement with published data.[13] M.p. 54.5–54.7 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.72 (t, J = 5.6 Hz, 2 H, Ar-CH_2CH$_2$CO), 3.11 (t, J = 5.6 Hz, 2 H, Ar-CH$_2$CH_2CO), 7.26–7.32 (m, 2 H, Ar-*H*), 7.45 (dd, $^3J_{HH}$ = 7.8, $^4J_{HF}$ = 4.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.6 (*C*H$_2$CH$_2$CO), 37.3 (CH$_2$*C*H$_2$CO), 109.6 (d, $^2J_{CF}$ = 21.0 Hz, *C*H-Ar-F), 122.5 (d, $^2J_{CF}$ = 25.0 Hz, *C*H-Ar-F), 128.4 (d, $^3J_{CF}$ = 7.3 Hz, *C*H-Ar-F), 139.1 (d, $^3J_{CF}$ = 7.0 Hz, *C*-Ar-F), 150.85 (C-Ar-F), 162.5 (d, $^1J_{CF}$ = 248.0 Hz, *C*-Ar-F), 206.1 (*C*O) ppm. IR: $\tilde{\nu}$ = 1698 (C=O) cm^{-1}. MS (CI) *m*/*z*: [M + H] 151. HRMS: calcd. for C_9H_7FO (M)$^+$: 150.0481; found 150.0483.

6-Fluoro-1-(3-fluorophenyl)indan-1-ol (15): 3-Bromo-1-fluorobenzene (2.72 mL, 24.40 mmol) was added to Mg turnings suspended in dry Et_2O (30 mL) at such a rate to maintain a gentle boiling. After addition the stirring was continued for 1 h, and then 6-fluoroindan-1-one **14** (3.05 g, 20.33 mmol) dissolved in dry Et_2O (40 mL) was added. The reaction mixture was stirred at room temperature for 5 h and then quenched by addition of 10% NH_4Cl and extracted with EtOAc. Column chromatography of the crude mixture with EtOAc/heptane (10:90) as eluent afforded pure compound **15** as a colorless oil (4.30 g, 86%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.23 (s, 1 H, O*H*), 2.43–2.57 (m, 2 H, CH_2CH$_2$COH), 2.86–2.95 (m, 1 H, CH$_2$CH_2COH), 3.05–3.16 (m, 1 H, CH$_2$CH_2COH), 6.74 (dd, ^3J = 8.4, ^4J = 2.2 Hz, 1 H, Ar-H_7), 6.92–7.02 (m, 2 H, Ar-*H*), 7.07–7.14 (m, 2 H, Ar-*H*), 7.23–7.31 (m, 2 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.6 (*C*H$_2$CH$_2$COH), 45.4 (CH$_2$*C*H$_2$COH), 85.5 (*C*-OH), 111.4 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 113.3 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 114.4 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 116.3 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 121.8 (d, $^4J_{CF}$ = 2.6 Hz, *C*H-Ar-F), 126.6 (d, $^3J_{CF}$ = 8.0 Hz, *C*H-Ar-F), 130.2 (d, $^3J_{CF}$ = 7.4 Hz, *C*H-Ar-F), 139.7 (d, $^4J_{CF}$ = 2.3 Hz, *C*-Ar-F), 149.1 (d, $^3J_{CF}$ = 6.6 Hz, *C*-Ar-F), 149.7 (d, $^3J_{CF}$ = 6.8 Hz, *C*-Ar-F), 162.7 (d, $^1J_{CF}$ = 245.0 Hz, *C*-Ar-F), 163.3 (d, $^1J_{CF}$ = 245.0 Hz, *C*-Ar-F) ppm. IR: $\tilde{\nu}$ = 3439 (OH) cm^{-1}. MS (CI) *m*/*z*: [M + H] 246. HRMS: calcd. for $C_{15}H_{12}F_2O$ (M)$^+$: 246.0856; found 246.0847.

5-Fluoro-3-(3-fluorophenyl)-1*H*-indene (16): 6-Fluoro-1-(3-fluorophenyl)indan-1-ol (**15**) (6.60 g, 26.90 mmol) was dissolved in toluene (90 mL), and *p*-toluenesulfonic acid (0.60 g) was added. The resulting reaction mixture was stirred at reflux for 3 h. After cooling, the reaction mixture was diluted with Et_2O (50 mL). The ether solution was washed with 1 N NaOH (20 mL), and brine (20 mL), dried with $MgSO_4$ and evaporated to furnish pure product **16** as a yellowish oil (5.88 g, 96%), which was used for the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.52 (d, J = 2.0 Hz, 2 H, CH_2CH=), 6.73 (t, J = 2.0 Hz, 1 H, CH$_2$C*H*=), 7.02–7.19 (m, 2 H, Ar-*H*), 7.34–7.52 (m, 5 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 38.1 (*C*H$_2$CH), 107.9 (d,

$^2J_{CF}$ = 24.0 Hz, *C*H-Ar-F), 112.3 (d,$^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 114.9 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 115.1 (d,$^2J_{CF}$ = 21.0 Hz, *C*H-Ar-F), 123.7 (*C*H=), 125.3 (d, $^3J_{CF}$ = 9.0 Hz, *C*H-Ar-F), 130.7 (d, $^3J_{CF}$ = 8.8 Hz, *C*H-Ar-F), 134.4 (d,$^4J_{CF}$ = 2.1 Hz, *C*H-Ar-F), 138.2 (d, $^3J_{CF}$ = 7.4 Hz, *C*-Ar-F), 140.4 (*C*=), 144.2 (d, $^4J_{CF}$ = 2.4 Hz, *C*-Ar-F), 145.7 (d, $^3J_{CF}$ = 9.1 Hz, *C*-Ar-F), 162.9 (d, $^1J_{CF}$ = 243.0 Hz, *C*-Ar-F), 163.5 (d, $^1J_{CF}$ = 246.0 Hz, *C*-Ar-F) ppm. MS (CI) *m*/*z*: [M + H] 229. HRMS: calcd. for $C_{15}H_{10}F_2$ $(M)^+$: 228.0751; found 228.0749.

[4-Fluoro-2-(3-fluorobenzoyl)phenyl]acetic Acid (17): CrO_3 (0.50 g, 5.05 mmol) was added with stirring to a solution of the indene **16** (0.35 g, 1.53 mmol) in AcOH (5 mL) and water (5 mL) at 0 °C. The reaction mixture was stirred at 35 °C for 3 h. Acetic acid was evaporated in vacuo, and to that residue water (15 mL) was added followed by extraction with Et_2O (3 × 20 mL). The organic layer was washed with water (2 × 20 mL) and with 1 N NaOH (4 × 10 mL). Then the aqueous fraction was made acidic with conc. HCl. After extraction with EtOAc (3 × 10 mL), the combined organic layers were dried with $MgSO_4$ and the solvents evaporated in vacuo. The residue was purified via chromatotron using CH_2Cl_2/MeOH (99:1) as eluent to afford pure product as white crystals (0.21 g, 51%). M.p. 115–116 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.81 (s, 2 H, CH_2CO_2H), 7.1 (dd, ^3J = 8.3, ^4J = 2.4 Hz, 1 H, Ar-$H^{3\text{ or }2'}$), 7.2 (td, $^3J \approx 8.3$, ^4J = 2.4 Hz, 1 H, Ar-H^5), 7.30–7.36 (m, 2 H, Ar-*H*), 7.40–7.54 (m, 3 H, Ar-*H*), 10.4 (br., CO_2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 38.0 (*C*H_2CO_2H), 116.8 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 117.1 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 118.4 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 120.5 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 126.3 (d, $^4J_{CF}$ = 3.3 Hz, *C*H-Ar-F), 129.3 (d, $^4J_{CF}$ = 3.6 Hz, *C*-Ar-F), 130.2 (d,$^3J_{CF}$ = 8.6 Hz, *C*H-Ar-F), 133.7 (d, $^3J_{CF}$ = 8.6 Hz, *C*H-Ar-F), 138.88 (d, $^3J_{CF}$ = 6.5 Hz, *C*-Ar-F), 138.95 (d, $^3J_{CF}$ = 6.5 Hz, *C*-Ar-F), 160.9 (d, $^1J_{CF}$ = 247.9 Hz, *C*-Ar-F), 162.5 (d, $^1J_{CF}$ = 247.9 Hz, *C*-Ar-F), 176.3 (*C*O), 195.5 (*C*O_2H) ppm. IR: $\tilde{\nu}$ = 1701 (C=O) cm^{-1}. MS (CI) *m*/*z*: [M + H] 277. HRMS: calcd. for $C_{15}H_{10}F_2O_3$ $(M)^+$: 276.0598; found 276.0606.

Methyl [4-Fluoro-2-(3-fluorobenzoyl)phenyl]acetate (18): [4-Fluoro-2-(3-fluorobenzoyl)phenyl]acetic acid (**17**) (1.70 g, 6.15 mmol) dissolved in MeOH (20 mL) was refluxed for 16 h in the presence of 0.6 mL of 95% H_2SO_4. After the reaction was completed, the solvent was evaporated under reduced pressure, and the residue was washed with satd. $NaHCO_3$. After extraction with EtOAc (3 × 30 mL) and evaporation of the combined and dried ($MgSO_4$) organic phases a yellowish oil was obtained and used as such for the next step (1.77 g, 99%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.56 (s, 3 H, OCH_3), 3.85 (s, 2 H, CH_2CO_2Me), 7.09 (dd, ^3J = 8.6, ^4J = 2.3 Hz, 1 H, Ar-*H*), 7.19 (td, $^3J \approx 8.6$, ^4J = 2.3 Hz, 1 H, Ar-*H*), 7.30–7.37 (m, 2 H, Ar-*H*), 7.45–7.59 (m, 3 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 37.7 (*C*H_2CO_2Me), 51.9 (O*C*H_3), 116.7 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 116.8 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 117.9 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 120.3 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 126.2 (d, $^4J_{CF}$ = 3.0 Hz, *C*H-Ar-F), 129.7 (d, $^4J_{CF}$ = 3.0 Hz, *C*-Ar-F), 130.1 (d,$^3J_{CF}$ = 7.8 Hz, *C*H-Ar-F), 133.5 (d, $^3J_{CF}$ = 7.8 Hz, *C*H-Ar-F), 139.1 (d, $^3J_{CF}$ = 6.5 Hz, *C*-Ar-F), 139.3 (d, $^3J_{CF}$ = 6.5 Hz, *C*-Ar-F), 160.9 (d, $^1J_{CF}$ = 249.0 Hz, *C*-Ar-F), 162.5 (d, $^1J_{CF}$ = 249.0 Hz, *C*-Ar-F), 171.3 (*C*O), 195.2 (*C*O_2Me) ppm. MS (CI) *m*/*z*: [M + H] 291. HRMS: calcd. for $C_{16}H_{12}F_2O_3$ $(M)^+$: 290.0755; found 290.0758.

Methyl [4-Fluoro-2-(3-fluorobenzyl)phenyl]acetate (19): A solution of compound **18** (1.60 g, 5.52 mmol) dissolved in AcOH was hydrogenated in the presence of 10% Pd/C (100 mg) under a pressure of 70 psi, at 70 °C for 5 h. The catalyst was filtered off through a pad of Celite. The solvent was evaporated under reduced pressure to yield a yellowish oily product (1.68 g, 98%), which was used for the next step without further purification. MS (CI) *m*/*z*: [M + H] 277.

Methyl {4-Fluoro-2-[(3-fluorophenyl)(hydroxy)methyl]phenyl}acetate (20): A solution of the compound **18** (50.0 mg, 0.17 mmol) dissolved in MeOH was hydrogenated in the presence of 10% Pd/C (ca. 10.0 mg) under a pressure of 70 psi, at 70 °C for 3 h. The catalyst was filtered off through a pad of Celite. Methanol was evaporated under reduced pressure to yield an oily product (48.0 mg, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.62–3.73 (m, 5 H, OCH_3, C$H_2CO_2CH_3$), 6.00 (s, 1 H, C*H*), 6.96–7.08 (m, 4 H, Ar-*H*), 7.19–7.30 (m, 3 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 37.6 (*C*H_2CO_2Me), 52.4 (CO_2CH_3), 72.2 (*C*OH), 113.7 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 114.5 (d, $^2J_{CF}$ = 21.0 Hz, *C*H-Ar-F), 115.0 (d, $^2J_{CF}$ = 21.0 Hz, *C*H-Ar-F), 115.5 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 122.3 (d, $^4J_{CF}$ = 2.7 Hz, *C*H-Ar-F), 127.6 (d, $^4J_{CF}$ = 2.7 Hz, *C*-Ar-F), 130.0 (d, $^3J_{CF}$ = 7.2 Hz, *C*H-Ar-F), 132.8 (d, $^3J_{CF}$ = 8.3 Hz, *C*H-Ar-F), 144.3 (d, $^3J_{CF}$ = 6.8 Hz, *C*-Ar-F), 144.7 (d, $^3J_{CF}$ = 6.8 Hz, *C*-Ar-F), 162.2 (d, $^1J_{CF}$ = 246.0 Hz, *C*-Ar-F), 163.0 (d, $^1J_{CF}$ = 246.0 Hz, *C*-Ar-F), 172.6 (*C*O_2Me). MS (CI) *m*/*z*: [M + H] 293 ppm.

[4-Fluoro-2-(3-fluorobenzyl)phenyl]acetic Acid (21): MeOH (4 mL) and water (4 mL), LiOH (0.29 g, 12.2 mmol) was added to a solution of compound **19** (1.68 g, 6.09 mmol) in THF (16 mL). The reaction mixture was stirred for 15 h at room temperature. The resulting mixture was acidified with 1 N HCl, the solvents were evaporated and the residue was extracted with EtOAc. Organic phases were combined, concentrated in vacuo to afford the desired product **21** as a white solid (1.37 g, 86%). M.p. 96.7–98.2 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.58 (s, 2 H, ArCH_2Ar), 3.99 (s, 2 H, CH_2CO_2H), 6.76–6.96 (m, 5 H, Ar-*H*), 7.19–7.24 (m, 2 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 37.7 (Ar*C*H_2Ar), 38.7 (*C*H_2CO_2H), 113.4 (d, $^2J_{CF}$ = 21.0 Hz, *C*H-Ar-F), 113.9 (d, $^2J_{CF}$ = 21.0 Hz, *C*H-Ar-F), 115.7 (d, $^2J_{CF}$ = 21.4 Hz, *C*H-Ar-F), 117.4 (d, $^2J_{CF}$ = 21.4 Hz, *C*H-Ar-F), 124.4 (d, $^4J_{CF}$ = 3.0 Hz, *C*H-Ar-F), 127.8 (d, $^4J_{CF}$ = 3.0 Hz, *C*-Ar-F), 130.1 (d, $^3J_{CF}$ = 8.3 Hz, *C*H-Ar-F), 132.6 (d, $^3J_{CF}$ = 8.3 Hz, *C*H-Ar-F), 141.0 (d, $^3J_{CF}$ = 7.3 Hz, *C*-Ar-F), 141.6 (d, $^3J_{CF}$ = 7.3 Hz, *C*-Ar-F), 162.2 (d, $^1J_{CF}$ = 247.0 Hz, *C*-Ar-F), 163.0 (d, $^1J_{CF}$ = 247.0 Hz, *C*-Ar-F), 177.3 (*C*O_2H) ppm. IR: $\tilde{\nu}$ = 1694 (C=O) cm^{-1}. MS (CI) *m*/*z*: [M + H] 263. HRMS: calcd. for $C_{15}H_{12}F_2O_2$ $(M)^+$: 262.0805; found 262.0808.

3,7-Difluoro-5,11-dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one (22): Thionyl chloride (0.9 mL, 12.40 mmol) was added to compound **21** (1.30 g, 4.96 mmol) dissolved in CH_2Cl_2 (20 mL). The reaction mixture was refluxed for 3 h. Evaporation of the solvent gave a yellowish solid which was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. $AlCl_3$ (0.73 g, 5.46 mmol) was added to the resulting mixture. The dark brown solution was stirred for 5 h at room temperature. After the reaction was completed, the reaction mixture was cooled to 0 °C and 1 N HCl (10 mL) was added, followed by extraction three times with CH_2Cl_2. Purification on silica gel with EtOAc/heptane (10:90) gave pure **22** as a white solid (0.47 g, 40%). M.p. 100–101.1 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.13 (s, 2 H, CH_2CO), 4.21 (s, 2 H, ArCH_2Ar), 6.89 (td, $^3J_{HF}$ = 8.7, $^4J_{HH}$ = 2.5 Hz, 1 H, Ar-*H*), 6.98–7.05 (m, 3 H, Ar-*H*), 7.24 (dd, $^3J_{HH}$ = 8.7, $^4J_{HF}$ = 5.8 Hz, 1 H, Ar-*H*), 8.14 (dd, $^3J_{HH}$ = 8.7, $^4J_{HF}$ = 5.8 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 41.9 (Ar*C*H_2Ar), 49.9 (*C*H_2CO), 114.1 (d, $^2J_{CF}$ = 21.5 Hz, *C*H-Ar-F), 114.6 (d, $^2J_{CF}$ = 21.5 Hz, *C*H-Ar-F), 115.2 (d, $^2J_{CF}$ = 22.5 Hz, *C*H-Ar-F), 116.4 (d, $^2J_{CF}$ = 21.5 Hz, *C*H-Ar-F), 128.15, 128.19 (*C*-Ar-F), 130.8 (d, $^3J_{CF}$ = 8.4 Hz, *C*H-Ar-F), 133.7 (d, $^3J_{CF}$ = 9.3 Hz, *C*H-Ar-F), 141.0 (d, $^3J_{CF}$ = 8.4 Hz, *C*-Ar-F), 144.7 (d, $^3J_{CF}$ = 8.4 Hz,

C-Ar-F), 161.8 (d, $^1J_{CF}$ = 248.0 Hz, *C*-Ar-F), 165.2 (d, $^1J_{CF}$ = 256.0 Hz, *C*-Ar-F), 192.6 (CO) ppm. IR: $\tilde{\nu}$ = 1678 (C=O) cm^{-1}. MS (CI) *m*/*z*: [M + H] 245. HRMS: calcd. for $C_{15}H_{10}F_2O$ $(M)^+$: 244.0699; found 244.0704.

3,7-Difluoro-5*H*-dibenzo[*a*,*d*]cycloheptene-10,11-dione (11): SeO_2 (0.17 g, 1.58 mmol) was added to a solution of **22** (0.35 g, 1.43 mmol) in AcOH (10 mL). The reaction mixture was refluxed for 30 min, the metal-like selenium powder was filtered off through a pad of Celite and acetic acid was evaporated. The residue was washed with EtOAc, and purified by column chromatography using EtOAc/heptane (20:80) as an eluent. Pure diketone **11** was obtained as yellowish needles (0.34 g, 92%). M.p. 167.8–168.9 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.28 (s, 2 H, ArCH_2Ar), 7.01–7.1 (m, 4 H, Ar-*H*), 7.83–7.89 (m, 2 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 39.9 (Ar*C*H_2Ar), 115.2 (d, $^2J_{CF}$ = 21.5 Hz, 2 C, *C*H-Ar-F), 115.8 (d, $^2J_{CF}$ = 21.5 Hz, 2 C, *C*H-Ar-F), 131.7 (d, $^4J_{CF}$ = 2.6 Hz, 2 C *C*-Ar-F), 134.6 (d, $^3J_{CF}$ = 9.6 Hz, 2 C, *C*H-Ar-F), 142.4 (d, $^3J_{CF}$ = 8.9 Hz, 2 C, *C*-Ar-F), 165.3 (d, $^1J_{CF}$ = 258.0 Hz, 2 C, *C*-Ar-F), 187.2 (2 CO) ppm. IR: $\tilde{\nu}$ = 1661 (C=O) cm^{-1}. MS (CI) *m*/*z*: [M + H] 259. HRMS: calcd. for $C_{15}H_8F_2O_2$ $(M)^+$: 258.0492; found 258.0499.

General Procedure for the Preparation of Compounds 1 and 2: A mixture of the corresponding diketone **10** or **11** and commercially available 4,5-diamino-6-hydroxypyrimidine hemisulfate hydrate **9** in AcOH (40 mL) and water (30 mL) was stirred at 100 °C for 30 min. The yellowish solid which precipitated during the reaction was filtered off, washed 4 times with water and dried.

10*H*-Dibenzo[3,4:6,7]cyclohepta[1,2-*g*]pteridin-4-ol (1): Reaction of diketone **10** (0.21 g, 0.96 mmol) with compound **9** (0.35 g, 0.96 mmol) afforded product **1** (0.25 g, 85%). M.p. above 385 °C decomposition. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.95 (d, *J* = 13.0 Hz, 1 H, ArCH_2Ar), 4.04 (d, *J* = 13.0 Hz, 1 H, ArCH_2Ar), 7.45–7.60 (m, 6 H, Ar-*H*), 7.94 (d, *J* = 7.6 Hz, 1 H, Ar-*H*), 7.99 (d, *J* = 7.6 Hz, 1 H, Ar-*H*), 8.51 (s, 1 H, *H*-pteridine), 12.85 (s, 1 H, O*H*) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 38.6 (Ar-*C*H_2Ar), 126.7, 126.8, 127.3, 127.4, 130.1, 130.7, 130.8, 131.0 (*C*H-Ar), 132.7, 134.7, 134.8, 142.2, 142.7, 143.3 (*C*-Ar), 149.6 (*C*H-pteridine) 150.15, 155.4 (*C*-pteridine), 160.4 (*C*-OH) ppm. IR: $\tilde{\nu}$ = 3336 (OH) cm^{-1}. MS (CI) *m*/*z*: [M + H] 313. HRMS: calcd. for $C_{19}H_{12}N_4O$ $(M)^+$: 312.1011; found 312.1015.

8,12-Difluoro-10*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*g*]pteridin-4-ol (2): Reaction of diketone **11** (0.13 g, 0.51 mmol) with compound **9** (0.18 g, 0.51 mmol) furnished product **2** (0.16 g, 90%). M.p. above 385 °C decomposition. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 3.91 (d, *J* = 13.0 Hz, 1 H, ArCH_2Ar), 4.03 (d, *J* = 13.0 Hz, 1 H, Ar-CH_2Ar), 7.26–7.32 (m, 2 H, Ar-*H*), 7.42 (dd, $^3J_{HF}$ = 7.5, $^4J_{HH}$ = 2.5 Hz, 1 H, Ar-*H*), 7.44 (dd, $^3J_{HF}$ = 7.5, $^4J_{HH}$ = 2.5 Hz, 1 H, Ar-*H*), 7.9 (dd, $^3J_{HH}$ = 8.5, $^4J_{HF}$ = 5.7 Hz, 1 H, Ar-*H*), 7.96 (dd, $^3J_{HH}$ = 8.7, $^4J_{HF}$ = 5.7 Hz, 1 H, Ar-*H*), 8.45 (s, 1 H, *H*-pteridine), 12.9 (s, 1 H, O*H*) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 37.7 (Ar*C*H_2Ar), 113.9 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 114.1 (d, $^2J_{CF}$ = 22.0 Hz, 2 C, *C*H-Ar-F), 114.2 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 131.3 (d, $^4J_{CF}$ = 3.0 Hz, *C*-Ar-F), 131.4 (d, $^4J_{CF}$ = 3.0 Hz, *C*-Ar-F), 132.7 (*C*-Ar), 133.1 (d, $^3J_{CF}$ = 8.9 Hz, *C*H-Ar-F), 133.5 (d, $^3J_{CF}$ = 8.9 Hz, *C*H-Ar-F), 144.0 (d, $^3J_{CF}$ = 8.7 Hz, *C*-Ar-F), 144.5 (d, $^3J_{CF}$ = 8.7 Hz, *C*-Ar-F), 149.0 (*C*-Ar), 149.7 (*C*H-pteridine), 153.3, 154.3 (*C*-pteridine), 160.2 (*C*-OH), 163.3 (d, $^1J_{CF}$ = 249.0 Hz, *C*-Ar-F), 163.7 ($^1J_{CF}$ = 249.0 Hz, *C*-Ar-F) ppm. IR: $\tilde{\nu}$ = 3483 (OH) cm^{-1}. MS (CI) *m*/*z*: [M + H] 349. HRMS: calcd. for $C_{19}H_{10}F_2N_4O$ $(M)^+$: 348.0823; found 348.0828.

General Procedure for the Preparation of 4-Chloro-10*H*-dibenzo-[3,4:6,7]cyclohepta[1,2-*g*]pteridine (3) and 4-Chloro-8,12-difluoro-10*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*g*]pteridine (4): A suspension of compound **1** (70.0 mg, 0.22 mmol) or **2** (60.0 mg, 0.172 mmol) in $POCl_3$ (15 mL) was stirred at 100 °C for 15 h. $POCl_3$ was evaporated to yield a brown oil, which was dissolved in CH_2Cl_2 and poured into the ice/aq. solution of $NaHCO_3$. The resulting residue was extracted 3 times with CH_2Cl_2. Organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure to furnish the products **3** and **4**, respectively, both as a brown oil, which was used immediately for the next step.

General Procedure for the Preparation of Compounds 5 and 6: To the crude compounds **3** (74.0 mg, 0.22 mmol) or **4** (63.0 mg, 0.17 mmol) dissolved in THF (10 mL), pentane-2-amine (0.2 mL) was added. The reaction mixtures were stirred at 70 °C for 1 to 6 h, respectively. Evaporation of the solvent gave residues which were purified to give yellowish solids.

***N*-(1-Methylbutyl)-10*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*g*]pteridin-4-amine (5):** The product **5** (38.5 mg, 46%) was obtained after purification on silica gel with CH_2Cl_2/EtOAc (70:30) as eluent. M.p. 86–88.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01 [t, *J* = 7.1 Hz, 3 H, CH_3(CH$_2$)$_2$CHCH_3], 1.40 [d, *J* = 6.7 Hz, 3 H, CH$_3$(CH$_2$)$_2$CHCH_3], 1.46–1.52 (m, 2 H, CH$_3$CH$_2$CH_2CHCH$_3$), 1.65–1.75 (m, 2 H, CH$_3$CH_2CH$_2$CHCH$_3$), 3.79 (d, *J* = 13.0 Hz, 1 H, ArCH_2Ar), 3.96 (d, *J* = 13.0 Hz, 1 H, ArCH_2Ar), 4.54 (sextet, *J* = 6.7 Hz, 1 H, CH$_3$CH$_2$CH$_2$C*H*CH$_3$), 7.08 (br., 1 H, N*H*), 7.35–7.46 (m, 6 H, Ar-*H*), 7.9 (br., 1 H, Ar-*H*), 8.17 (d, *J* = 7.6 Hz, 1 H, Ar-*H*), 8.83 (s, 1 H, *H*-pteridine) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (*C*H$_3$), 19.3 (*C*H$_2$), 20.6 (*C*H$_3$), 39.0 (*C*H$_2$), 40.1 (Ar*C*H$_2$Ar), 46.8 (*C*HNH), 124.6 (*C*-Ar), 126.9, 127.1, 127.2, 127.6, 130.2, 130.8, 131.0, 131.9 (*C*H-Ar), 135.3, 137.8, 142.1, 142.3, 150.3, 151.8, 157.8 (*C*-Ar), 160.0 (*C*H-pteridine), 160.5 (*C*-pteridine-NH) ppm. IR: $\tilde{\nu}$ = 2956 (CH$_3$) cm^{-1}. MS (CI) *m*/*z*: [M + H] 382. HRMS: calcd. for $C_{24}H_{23}N_5$ $(M)^+$: 381.1954; found 381.1953.

8,12-Difluoro-*N*-(1-methylbutyl)-10*H*-dibenzo[3,4:6,7]cyclohepta-[1,2-*g*]pteridin-4-amine (6): The compound **6** (35.0 mg, 49%) was obtained after purification on HPLC using CH_2Cl_2/EtOAc (70:30) as eluent. M.p. 97–98 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, *T* = 55 °C): δ = 0.99 [t, *J* = 7.0 Hz, 3 H, CH_3(CH$_2$)$_2$CHCH_3], 1.38 [d, *J* = 6.4 Hz, 3 H, CH$_3$(CH$_2$)$_2$CHCH_3], 1.49 (quartet, *J* = 6.4 Hz, 2 H, CH$_3$CH$_2$CH_2CHCH$_3$), 1.62–1.75 (m, 2 H, CH$_3$CH_2CH$_2$CHCH$_3$), 3.81 (s, 2 H, ArCH_2Ar), 4.55 (sextet, *J* = 6.4 Hz, 1 H, CH$_3$CH$_2$CH$_2$C*H*CH$_3$), 6.98 (d, *J* = 6.4 Hz, 1 H, N*H*), 7.06 (d, *J* = 8.3 Hz, 2 H, Ar-*H*), 7.1 (d, *J* = 8.3 Hz, 2 H, Ar-*H*), 7.87 (dd, $^3J_{HH}$ = 9.1, $^4J_{HF}$ = 5.7 Hz, 1 H, Ar-*H*), 8.18 (dd, $^3J_{HH}$ = 9.1, $^4J_{HF}$ = 5.7 Hz, 1 H, Ar-*H*), 8.81 (s, 1 H, *H*-pteridine) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (*C*H$_3$), 19.3 (*C*H$_2$), 20.6 (*C*H$_3$), 38.9 (*C*H$_2$), 39.8 (Ar*C*H$_2$Ar), 46.9 (*C*HNH), 114.0 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 114.1 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 114.2 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 114.4 (d, $^2J_{CF}$ = 22.0 Hz, *C*H-Ar-F), 124.8 (*C*-Ar), 131.4 (d, $^4J_{CF}$ = 3.0 Hz, *C*-Ar-F), 131.5 (d, $^4J_{CF}$ = 3.0 Hz, *C*-Ar-F), 133.1 (d, $^3J_{CF}$ = 8.8 Hz, *C*H-Ar-F), 134.2 (d, $^3J_{CF}$ = 8.8 Hz, *C*H-Ar-F), 143.5 (d, $^3J_{CF}$ = 8.5 Hz, *C*-Ar-F), 143.6 (d, $^3J_{CF}$ = 8.5 Hz, *C*-Ar-F), 149.1, 151.7, 156.4 (*C*-Ar), 160.2 (*C*-pteridine-NH), 160.5 (*C*H-pteridine), 164.1 (d, $^1J_{CF}$ = 252.0 Hz, *C*-Ar-F), 164.4 (d, $^1J_{CF}$ = 252.0 Hz, *C*-Ar-F) ppm. IR: $\tilde{\nu}$ = 3398 (NH), 2929 (CH$_3$) cm^{-1}. MS (CI) *m*/*z*: [M + H] 418. HRMS: calcd. for $C_{24}H_{21}F_2N_5$ $(M)^+$: 417.1765; found 417.1758.

General Procedure for the Preparation of Compounds 7 and 8: To the crude compounds **3** (83.0 mg, 0.23 mmol) or **4** (84.0 mg, 0.23 mmol) dissolved in THF (10 mL), a mixture of *cis*/*trans* 4-methylcyclohexylamine (0.1 mL) was added. The reaction mixtures were stirred at reflux temperature for 12 h. After solvent evaporation, the residues were purified on HPLC using CH_2Cl_2/EtOAc

(70:30) to afford products **7**, **7′** and **8**, **8′**, respectively. The *trans* stereoisomer **7** and **8** eluted first and the *cis* isomers **7′**, **8′** eluted as a second fraction.

***N*-(10*H*-Dibenzo[3,4:6,7]cyclohepta[1,2-*g*]pteridin-4-yl)-*N*-(4-methylcyclohexyl)amine (7) and (7′):** Reaction of **3** yielded the *trans* isomer **7** (25.0 mg) and the *cis* isomer **7′** (24.0 mg).

***trans* Isomer 7:** M.p. 247.5–249 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96 (d, J = 6.4 Hz, 3 H, CH_3-cyclohexyl), 1.18–1.24 (m, 2 H, $H^{3'ax}$, $H^{5'ax}$), 1.36–1.47 (m, 3 H, $H^{2'ax}$, $H^{6'ax}$, C$H^{4'ax}$), 1.79–1.85 (m, 2 H, $H^{3'eq}$, $H^{5'eq}$), 2.16–2.27 (m, 2 H, $H^{6'eq}$, $H^{2'eq}$), 3.79 (d, J = 13.5 Hz, 1 H, ArCH_2Ar), 3.96 (d, J = 13.5 Hz, 1 H, ArCH_2Ar), 4.20–4.24 (m, values of constant couplings were derived from *homonuclear decoupling* experiments: $^3J_{HCNH}$ = 8.5, $^3J_{ax\text{-}ax}$ = 2×11.0, $^3J_{ax\text{-}eq}$ = 2×3.5 Hz, 1 H, $H^{1'ax}$), 7.10 (d, J = 8.5 Hz, 1 H, NH), 7.36–7.46 (m, 6 H, Ar-H), 7.91 (d, J = 7.2 Hz, 1 H, Ar-H), 8.17 (d, J = 7.2 Hz, 1 H, Ar-H), 8.83 (s, 1 H, H-pteridine) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.2 (CH_3-cyclohexyl), 32.0 (C-4′-cyclohexyl), 32.92 (C-2′-cyclohexyl), 32.93 (C-6′-cyclohexyl), 33.8 (2 C, C-3′,5′-cyclohexyl), 40.1 (ArCH_2Ar), 50.2 (cyclohexyl-CHNH), 124.7 (C-pteridine), 126.9, 127.1 (2 C), 127.2, 130.3, 130.8, 131.0, 131.9, (CH-Ar), 135.3 (2 C-Ar), 142.2, 142.3, 150.4, (C-Ar), 151.8 (C-pteridine-NH), 157.8 (C-Ar), 159.9 (CH-pteridine), 160.3 (C-pteridine) ppm. IR: $\tilde{\nu}$ = 3386 (NH) cm^{-1}. MS (CI) m/z: [M + H] 408. HRMS: calcd. for $C_{26}H_{25}N_5$ (M)$^+$: 407.2110 found 407.2105.

***cis* Isomer 7′:** M.p. 271–273.7 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (d, J = 6.4 Hz, 3 H, CH_3-cyclohexyl), 1.18–1.24 (m, 2 H, $H^{3'ax}$, $H^{5'ax}$), 1.36–1.47 (m, 3 H, $H^{2'ax}$, $H^{6'ax}$, $H^{4'ax}$), 1.79–1.85 (m, 2 H, $H^{3'eq}$, $H^{5'eq}$), 2.16–2.27 (m, 2 H, $H^{2'eq}$, $H^{6'eq}$), 3.80 (d, J = 13.5 Hz, 1 H, ArCH_2Ar), 3.97 (d, J = 13.5 Hz, 1 H, ArCH_2Ar), 4.46–4.47 (m, values of constant couplings were derived from *homonuclear decoupling* experiments: $^3J_{HCNH}$ = 7.6, $^3J_{eq\text{-}ax}$ = 2×2.7, $^3J_{eq\text{-}eq}$ = 2×2.7 Hz, 1 H, $H^{1'eq}$), 7.36–7.46 (m, 7 H, Ar-H, NH), 7.92 (d, J = 7.2 Hz, 1 H, Ar-H), 8.17 (d, J = 7.2 Hz, 1 H, Ar-H), 8.83 (s, 1 H, H-pteridine) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.9 (CH_3-cyclohexyl), 28.92 (C-2′-cyclohexyl), 28.99 (C-6′-cyclohexyl), 30.1 (2 C, C-3′,5′-cyclohexyl), 30.3 (C-4′-cyclohexyl), 40.1 (ArCH_2Ar), 47.4 (cyclohexyl-CHNH), 124.8 (C-pteridine), 127.0, 127.1 (2 C), 127.3, 130.2, 130.8, 130.9, 131.9, (CH-Ar), 135.4 (2 C-Ar), 142.2, 142.3, 150.4, (C-Ar), 151.7 (C-pteridine-NH), 157.8 (C-Ar), 159.9 (CH-pteridine), 160.2 (C-pteridine) ppm.

8,12-Difluoro-*N*-(4-methylcyclohexyl)-10*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*g*]pteridin-4-amine (8) and (8′): Reaction of compound **4** yielded the *trans* isomer **8** (30.0 mg) and the *cis* isomer **8′** (22.0 mg).

***trans* Isomer 8:** M.p. 285.7–286.3 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, T = 55 °C): δ = 0.96 (d, J = 6.5 Hz, 3 H, CH_3-cyclohexyl), 1.31–1.39 (m, 2 H, $H^{3'ax}$, $H^{5'ax}$), 1.67–1.75 (m, 3 H, $H^{2'ax}$, $H^{6'ax}$, $H^{4'ax}$), 1.80–1.86 (m, 2 H, $H^{3'eq}$, $H^{5'eq}$), 1.89–1.97 (m, 2 H, $H^{2'eq}$, $H^{6'eq}$), 3.8 (s, 2 H, ArCH_2Ar), 4.20–4.24 (m, values of constant couplings were derived from *homonuclear decoupling* experiments: $^3J_{HCNH}$ = 8.5, $^3J_{ax\text{-}ax}$ = 2×11.0, $^3J_{ax\text{-}eq}$ = 2×3.5 Hz, 1 H, $H^{1'ax}$), 7.0 (d, J = 8.5 Hz, 1 H, NH), 7.05–7.1 (m, 4 H, Ar-H), 7.87 (dd, $^3J_{HH}$ = 8.5, $^4J_{HF}$ = 5.7 Hz, 1 H, Ar-H), 8.18 (dd, $^3J_{HH}$ = 8.5, $^4J_{HF}$ = 5.7 Hz, 1 H, Ar-H), 8.81 (s, 1 H, H-pteridine) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.1 (CH_3), 31.9 (CH), 32.8 (CH_2), 33.8 (CH_2), 39.8 (ArCH_2Ar), 50.3 (CHNH), 114.1 (d, $^2J_{CF}$ = 22.0 Hz, CH-Ar-F), 114.2 (d, $^2J_{CF}$ = 22.0 Hz, CH-Ar-F), 114.3 (d, $^2J_{CF}$ = 21.5 Hz, CH-Ar-F), 114.5 (d, $^2J_{CF}$ = 21.5 Hz, CH-Ar-F), 124.7 (C-Ar), 131.5 (d, $^4J_{CF}$ = 3.5 Hz, C-Ar-F), 131.6 (d, $^4J_{CF}$ = 3.5 Hz, C-Ar-F), 133.2 (d, $^3J_{CF}$ = 9.0 Hz, CH-Ar-F), 134.3 (d, $^3J_{CF}$ = 9.0 Hz, CH-Ar-F), 143.5 (d, $^3J_{CF}$ = 8.4 Hz, C-Ar-F), 143.6 (d, $^3J_{CF}$ = 8.4 Hz, C-Ar-F), 149.1, 151.8, 156.5, 160.0 (C-Ar), 160.2 (CH-pteridine), 164.1 (d, $^1J_{CF}$ = 252.0 Hz, C-Ar-F), 164.5 (d, $^1J_{CF}$ = 252.0 Hz, C-Ar-F) ppm. IR: $\tilde{\nu}$ = 3389 (NH) cm^{-1}. MS (CI) m/z: [M + H] 444. HRMS: calcd. for $C_{26}H_{23}F_2N_5$ (M)$^+$: 443.1922; found 443.1923.

***cis* Isomer 8′:** M.p. 247.6–248.6 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (d, J = 6.3 Hz, 3 H, CH_3-cyclohexyl), 1.18–1.24 (m, 2 H, $H^{3'ax}$, $H^{5'ax}$), 1.36–1.47 (m, 3 H, $H^{2'ax}$, $H^{6'ax}$, $H^{4'ax}$), 1.79–1.86 (m, 2 H, $H^{3'eq}$, $H^{5'eq}$), 2.16–2.27 (m, 2 H, $H^{2'eq}$, $H^{6'eq}$), 3.80 (d, J = 13.5 Hz, 1 H, ArCH_2Ar), 3.97 (d, J = 13.5 Hz, 1 H, ArCH_2Ar), 4.47–4.48 (m, values of constant couplings were derived from *homonuclear decoupling* experiments: $^3J_{HCNH}$ = 7.6, $^3J_{eq\text{-}ax}$ = 2×2.7, $^3J_{eq\text{-}eq}$ = 2×2.7 Hz, 1 H, $H^{1'eq}$), 7.36–7.46 (m, 7 H, Ar-H, NH), 7.92 (d, J = 7.2 Hz, 1 H, Ar-H), 8.17 (d, J = 7.2 Hz, 1 H, Ar-H), 8.83 (s, 1 H, H-pteridine) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.9 (CH_3), 28.9 (CH), 30.1 (CH_2), 30.2 (CH_2), 39.8 (ArCH_2Ar), 47.4 (CHNH), 114.1 (d, $^2J_{CF}$ = 22.0 Hz, CH-Ar-F), 114.2 (d, $^2J_{CF}$ = 22.0 Hz, CH-Ar-F), 114.4 (d, $^2J_{CF}$ = 21.6 Hz, CH-Ar-F), 114.5 (d, $^2J_{CF}$ = 21.6 Hz, CH-Ar-F), 124.7 (C-Ar), 131.5 (d, $^4J_{CF}$ = 3.5 Hz, C-Ar-F), 131.6 (d, $^4J_{CF}$ = 3.5 Hz, C-Ar-F), 133.0 (d, $^3J_{CF}$ = 9.0 Hz, CH-Ar-F), 134.2 (d, $^3J_{CF}$ = 9.0 Hz, CH-Ar-F), 143.5 (d, $^3J_{CF}$ = 8.0 Hz, C-Ar-F), 143.6 (d, $^3J_{CF}$ = 8.0 Hz, C-Ar-F), 149.1, 151.6, 156.5, 160.0 (C-Ar), 160.1 (CH-pteridine), 164.1 (d, $^1J_{CF}$ = 252.0 Hz, C-Ar-F), 164.4 (d, $^1J_{CF}$ = 252.0 Hz, C-Ar-F) ppm.

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