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TETRAHEDRON: *ASYMMETRY*

# Reactivity as glycine templates of 1,2-dialkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones

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**Abstract**—The 1-methyl(*iso*-propyl)-2-benzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones **8** and **9** could be regio- and diastereoselectively alkylated at C(4) with retention of configuration at both stereocentres. 

## 1. Introduction

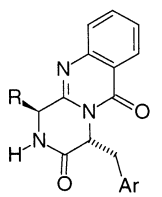
Several fungal metabolites such as fumiquinazolines F **1** and **2**,[1,2] fiscalin B **3**,[3,4] and *N*-acetylardeemin **4**[5,6] are 1,4-dialkyl derivatives of the 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione system. A common strategy in the synthesis of compounds **1**–**3** uses tripeptide starting materials bearing two residues with the desired substituents at the final C(1) and C(4) positions and anthranilic acid as the third residue. These tripeptides give the target molecules through cyclodehydration to 4-imino-4*H*-3,1-benzoxazines.[7–14] Other alternatives generally start from appropriately substituted piperazine-2,5-diones and either involve *N*-acylation with *o*-azidobenzoyl chloride followed by an intramolecular Staudinger reaction, or condensation of their lactim derivatives with anthranilic acid.[15–17]

In the synthesis of analogues of **4**, our group has shown that enantiomerically pure 2,4-dialkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazolinediones **5** can be used as glycine templates for regio- and diastereoselective alkylation at C(1). The kinetically controlled products usually have *anti*-configuration at C(1) and C(4) and equilibrate to the more stable *syn*-isomers under thermodynamic conditions (to minimise the 1,2-interactions between the C(1) and *N*(2) pseudoequatorial substituents). Thus, the bulk of the C(1) and C(4) substituents influences the resultant diastereomeric excess.[18–21] In this context we study herein how 1,2-dialkyl - 2,4 - dihydro - 1*H* - pyrazino[2,1 - *b*]quinazolinediones behave in the alkylation process.

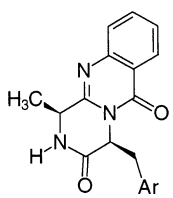
## 2. Results and discussion

Condensation of anthranilic acid with the iminoether derived from 1-benzyl-6-methylpiperazine-2,5-dione **6** gave **8** as a racemate, while no cyclisation was observed with the *iso*-propyl derivative **7** (Scheme 1). These results contrast with those obtained with 1,3-dialkylpiperazine-2,5-diones, which gave enantiomerically pure **5**.[18,20,21]

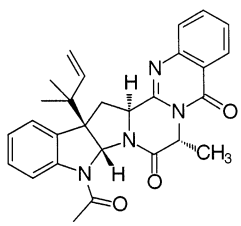
The alternative route outlined in Scheme 2, which involves the *N*-acylation of piperazinediones **6** and **7**



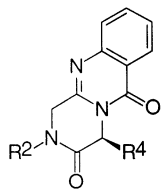
**1** Fumiquinazoline F (R = $CH_3$)
**3** Fiscalin B (R = $CH(CH_3)_2$)
Ar = 3-indolyl



**2** Fumiquinazoline G
Ar = 3-indolyl



**4** (*N*-Acetylardeemin)



**5**
$R^2$ = Me, Bn
$R^4$ = Me, *i*-Pro

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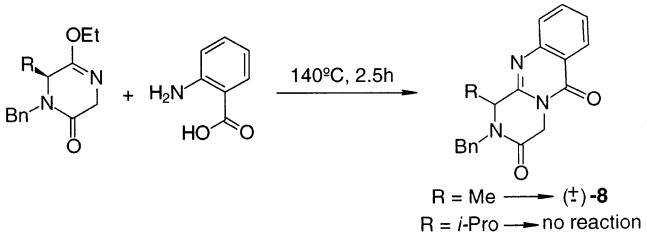
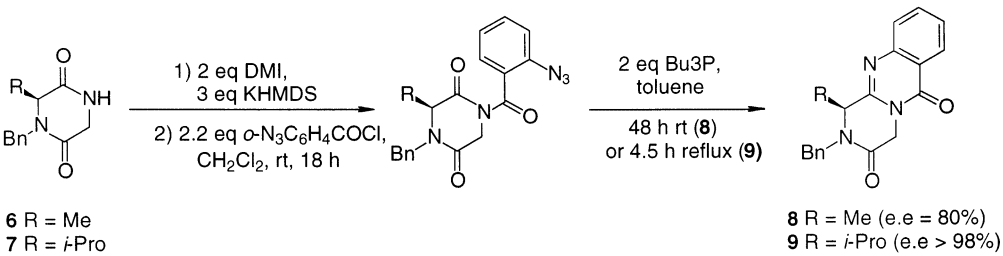



**Scheme 1.**

followed by an intramolecular Staudinger reaction, was more convenient in this case. Thus, **8** and **9** were obtained in acceptable yields, but only the 1-*iso*-propyl derivative **9** showed satisfactory enantiomeric purity (e.e. >95%). In the case of the 1-methyl derivative **8** the e.e. (80%) could not be optimised, although a very good separation of both enantiomers by analytical chiral HPLC was observed. It is significant that this e.e. value is in accordance with C(1) epimerisation observed by Ganesan et al. in the synthesis of fumiquinazolines F and G through the corresponding alanylanthranyltryptophan.[12] These stereochemical results allow us to conclude that while the synthesis of C(4)-alkylated tricyclic systems always leads to enantiomerically pure compounds, in C(1) methyl systems such as **8**, epimerisation at C(1) occurs. The C(1)-*iso*-propyl derivatives **9** are exceptions to this general behaviour because epimerisation is prevented by the steric bulk of the C(1) substituent.

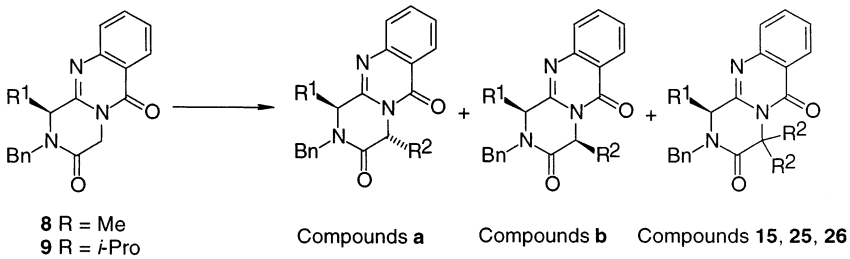
The alkylations of compounds **8** and **9** were performed under reaction conditions similar to those used for their 4-alkyl analogues,[18,20,21] using THF as solvent and lithium hexamethyldisilazide as a base. The obtained results are summarised in Table 1.

To favour kinetic conditions and avoid possible dialkylation processes, alkylations of **8** were performed at




**Scheme 2.**

**Table 1.** Alkylation of compounds **8** and **9**




| Entry | $R^1$ | $R^2$ | % *anti* compounds **a** | % *syn* compounds **b** | D.e.[a] (%) | % 4,4-dialkyl |
|---|---|---|---|---|---|---|
| 1 | $CH_3$ | $CH_3$[b] | 25 (**10a**) | 74 (**10b**) | 49 | |
| 2 | $CH_3$ | $CH_2CH{=}CH_2$[c] | 48 (**11a**) | 5 (**11b**) | 81 | |
| 3 | $CH_3$ | $CH_2C_6H_5$ | 72 (**12a**) | 2 (**12b**) | 94 | |
| 4 | $CH_3$ | $CH_2C_6H_4$-*p*-$CH_3$ | 88 (**13a**) | 7 (**13b**) | 84 | |
| 5 | $CH_3$ | $CH_2C_6H_4$-*p*-$NO_2$[d] | 62 (**14a**) | 10 (**14b**) | 72 | 9 (**15**) |
| 6 | $CH(CH_3)_2$ | $CH_3$[b] | 41 (**19a**) | – | >99 | 50 (**25**) |
| 7 | $CH(CH_3)_2$ | $CH_2CH{=}CH_2$ | 47 (**20a**) | – | >99 | 21 (**26**) |
| 8 | $CH(CH_3)_2$ | $CH_2C_6H_5$ | 71 (**21a**) | – | >99 | |
| 9 | $CH(CH_3)_2$ | $CH_2C_6H_4$-*p*-$CH_3$ | 70 (**22a**) | – | >99 | |
| 10 | $CH(CH_3)_2$ | $CH_2C_6H_4$-*p*-F | 78 (**23a**) | – | >99 | |
| 11 | $CH(CH_3)_2$ | $CH_2C_6H_4$-*p*-$NO_2$ | 85 (**24a**) | – | >99 | |

General reaction conditions: THF as solvent, LHMDS (1.2 equiv.) and alkyl halide (1 equiv.), 20 min at −78°C (entries 1, 3, 4 and 11) or 10 min at −78°C plus 40 min at 0°C (entries 6–10).

[a] The ratios given are of the isolated products.

[b] Excess iodomethane was employed.

[c] Reaction times: 10 min at −78°C plus 10 min at 0°C.

[d] Reaction times: 10 min at −78°C.

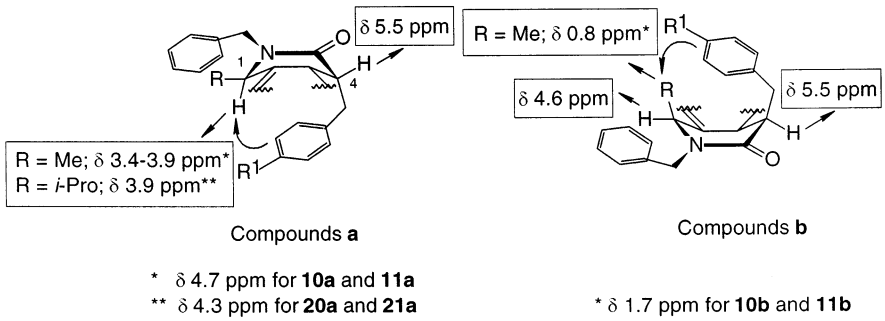



**Figure 1.** Significant NOEs and chemical shifts for compounds **a** and **b**.

−78°C. Except in the reaction with iodomethane (compounds **10**, entry 1), the reactions were highly diastereoselective in favour of the *anti*-isomers, with d.e. values of about 80%. It is notable that although the *syn*-isomer **10b** was the main isomer in this case (d.e. 49%), methylation of the 4-methyl derivatives **5** only gave the *syn*-isomer.[18] In the reaction with *p*-nitrobenzyl bromide (entry 5) small amounts of the 4,4-dialkyl derivative **15** were also formed, even when short reaction times were used. Since the enantiomeric excess of compounds **10**–**14** (both isomers), was similar to that of the starting compound **8** (about 80%), we concluded that the alkylation process does not affect the stereogenic centre at C-(1).

The configuration and conformation of compounds **10**–**14** were determined by NOESY experiments and were supported by the $^1$H NMR chemical shifts of significant protons (Fig. 1). The piperazine ring adopts a boat conformation in both diastereoisomers, the C(4)-substituent always being in a pseudoaxial disposition. The C(4) proton resonates at $\delta = 5.5$ ppm in all compounds showing the characteristic anisotropic effect of the coplanar carbonyl group at C(6) on this *quasi* equatorial proton.[18] As well as the observed NOEs between the axial substituents at C(1) and C(4) in the *syn*-isomers, the chemical shift at $\delta = 0.8$ ppm for the C(1)-methyl group in compounds **12b** and **13b** indicates folding of the C(4)-benzyl substituent over the piperazine ring. In accordance, the *anti*-isomers **12a** and **13a** show a shielding effect of the phenyl ring on the C(1) protons.

When alkylation of **8** was forced by using 2 equiv. of base and 2 equiv. of *p*-methylbenzyl bromide (10 min at −78°C plus 20 min at 0°C) the 4,4-dialkyl derivative **16** was obtained in quantitative yield, while addition of DMI as co-solvent in this reaction also gave the 1,4-dialkyl **17**[22] and the 1,4,4-trialkyl **18** derivatives.

Although the *iso*-propyl derivative **9** required longer reaction times and higher temperatures than **8**, alkylation was completely diastereoselective, giving the *anti*-isomers **19a**–**24a** exclusively in enantiomerically pure form. The boat conformation of the piperazine ring and the axial disposition of the C(4) substituent in compounds **19a**–**24a** (*anti*-isomers) were also deduced from NOESY experiments and $^1$H NMR data: chemical shift values $\delta = 5.5$ ppm for H-4 in all compounds and $\delta = 3.9$ ppm for H-1, which is shielded by the phenyl ring, in compounds **21a**–**24a**.

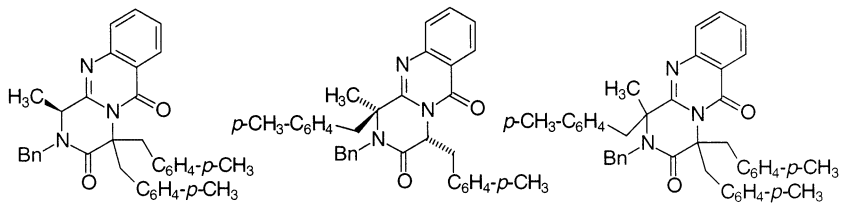
## 3. Conclusion

We conclude that, in contrast to their 2-benzyl-4-methyl(*iso*-propyl) analogues **5**, the 2-benzyl-1-methyl(*iso*-propyl) derivatives **8** and **9** can be alkylated to give the 1,4-*anti*-isomers with much greater diastereoselectivity, the *anti*-isomer being the only product that is obtained in the case of compounds **9**.

## 4. Experimental

### 4.1. General methods

All reagents were of commercial quality and were used as received. Solvents were dried and purified using standard techniques. 'Petroleum ether' refers to the fraction boiling at 40–60°C. TLC was carried out on precoated plates (Merck Kieselgel 60 $F_{254}$), spots visualised with UV light. Column chromatography was performed on silica gel (Merck 60, 230–400 mesh). Melting points were measured in a Reichert 723 hot stage microscope and are uncorrected. NMR spectra were obtained on Bruker AC-250 (250 MHz for $^1$H, 62.5 MHz for $^{13}$C) and Bruker Avance DPX-300 (300 MHz for $^1$H, 75 MHz for $^{13}$C) spectrometers, in $CDCl_3$



unless otherwise mentioned. (Servicio de RMN, Universidad Complutense). Protons were assigned according to COSY, HMQC and/or 1D-NOE experiments; carbons were assigned according to DEPT, HMQC, and/or HMBC experiments. Optical rotation values were determined in a Perkin–Elmer 241 polarimeter equipped with a 1 mL cell measuring 10 cm at 25°C, using the emission wavelength of a sodium lamp; concentrations are given in g/100 mL. The enantiomeric purity was determined by $^1$H NMR (addition of europium (III) tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorate] [(+)-Eu(HFC)$_3$] as shift reagent) and by chiral HPLC (comparison to racemic products), employing a Constrometric 4100 system equipped with a chiral column (Chiracel OD; 25 cm× 0.25 mm) and UV-detection at 254 nm; mobil phase: hexane/propan-2-ol (9:1) at 1 mL/min IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer, with solid compounds compressed into KBr pellets and liquid compounds placed as films on NaCl disks. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense on a Leco 932 microanalyser.

### 4.2. (6*S*)-1-Benzyl-6-alkylpiperazine-2,5-diones 6 and 7

To a stirred solution of Cbz–glycine (11.0 g, 52 mmol) and DCC (10.9 g, 52 mmol) in dry $CH_2Cl_2$ (150 mL), 52 mmol of freshly distilled ethyl *N*-benzylalaninate (for **6**) or ethyl *N*-benzylvalinate (for **7**) was added, and stirring was continued overnight. The reaction mixture was filtered, washed successively with HCl (1 N), $NaHCO_3$ (1 N) and water, dried over anhydrous $Na_2SO_4$ and evaporated. The syrupy residue was hydrogenated at 35 psi for 18 h with C/Pd (10%, 1.7 g) in ethanol (200 mL), filtered (Celite) and evaporated. The obtained white solid **6** or syrup **7** was recrystallised from ether.

**4.2.1. (6*S*)-1-Benzyl-6-methylpiperazine-2,5-dione 6**. Yield 88%; mp 175–176.5°C; $[\alpha]_D^{25}=+30.0$ (*c* 0.26, $CHCl_3$); $\nu_{max}$ (KBr) 3246, 1696, 1654 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.29 (5H, m, ArH), 6.14 (1H, s, NH), 5.21 (1H, d, $J=14.8$ Hz, *N*-$CH_2$-Ar), 4.08 (1H, d, $J=17.3$ Hz, H-5), 4.02 (1H, d, $J=14.8$ Hz, *N*-$CH_2$-Ar), 3.98 (1H, dd, $J=17.3$ Hz, $J=3.5$ Hz, H-5), 3.86 (1H, q, $J=7.1$ Hz, H-2), 1.45 (3H, d, $J=7.1$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 169.8, 164.0, 135.6, 129.0, 128.3, 128.2, 55.1, 47.3, 44.9, 17.5. $C_{12}H_{14}O_2N_2$ requires: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.77; H, 6.55; N, 12.72%.

**4.2.2. (6*S*)-1-Benzyl-6-*iso*-propylpiperazine-2,5-dione 7**. Yield 91%; mp: 84–85°C. $[\alpha]_D^{25}=+12$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (KBr) 3210, 1671, 1647 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 7.3 (5H, m, ArH), 6.83 (1H, s, NH), 5.41 (1H, d, $J=15$ Hz, *N*-$CH_2$-Ar), 4.11 (1H, d, $J=17.5$ Hz, H-5), 3.95 (1H, d, $J=17.5$ Hz, H-5), 3.89 (1H, d, $J=15$ Hz, *N*-$CH_2$-Ar), 3.64 (1H, d, $J=4.7$ Hz, H-1), 2.24 (1H, m, $J=6.9$, $J=4.9$ Hz, C<u>H</u>$(CH_3)_2$), 1.1 (3H, d, $J=6.9$ Hz, $CH_3$), 1.02 (3H, d, $J=6.9$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 167.9, 164.6, 135.4, 128.8, 127.9, 127.9, 64.5, 48.1, 45.1, 38.0, 19.7, 17.6. $C_{14}H_{18}O_2N_2$ requires: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.16; H, 7.45; N, 11.25%.

### 4.3. (1*S*)-2-Benzyl-1-methyl(*iso*-propyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones 8 and 9

To a cold (−78°C), magnetically stirred solution of compound **6** or **7** (2 mmol) in dry THF (40 mL) under argon was added, dropwise via a syringe, DMI (0.4 mL, 4 mmol) and a solution of potassium hexamethyldisilazide in dry toluene (0.5 M, 6 mL), followed 15 min later by addition of a solution of 2-azidobenzoyl chloride (5 mmol). Stirring was continued for 15 min at −78°C and then for a further 18 h at room temperature. The reaction mixture was quenched with ice and diluted with $CHCl_3$. The organic layer was dried over anhydrous $Na_2SO_4$ evaporated and isolated by column chromatography ($CH_2Cl_2$:EtOAc 9:1 for **6** and petroleum ether:EtOAc 1:1 for **7**).

**(3*S*)-1-(*o*-Azidobenzoyl)-4-benzyl-3-methylpiperazine-2,5-dione** was obtained as a pale yellow oil; yield 84%; $[\alpha]_D^{25}=-78.8$ (*c* 0.27, $CHCl_3$); $\nu_{max}$ (NaCl) 2129, 1726, 1674 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.46 (1H, ddd, $J=8.0$ Hz, $J=7.5$ Hz, $J=1.5$ Hz, H-4′), 7.31 (1H, d, $J=8.1$ Hz, H-6′), 7.30 (5H, m, ArH), 7.19 (1H, dt, $J=7.6$ Hz, $J=1.8$ Hz, H-5′), 7.08 (1H, d, $J=8.3$ Hz, H-3′), 5.32 (1H, d, $J=15.0$ Hz, *N*-$CH_2$-Ar), 4.96 (1H, d, $J=17.5$ Hz, H-6), 4.20 (1H, d, $J=17.5$ Hz, H-6), 4.00 (1H, d, $J=15.0$ Hz, *N*-$CH_2$-Ar), 3.96 (1H, q, $J=7.2$ Hz, CH), 1.43 (3H, d, $J=7.2$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 169.0, 168.0, 164.1, 136.8, 135.3, 131.9, 129.3, 129.0, 128.1, 127.9, 127.0, 125.2, 118.1, 56.2, 46.9, 46.1, 17.1. $C_{19}H_{17}O_3N_5$ requires: C, 62.80; H, 4.72; N, 19.27. Found: C, 62.89; H, 4.77; N, 19.10%.

**(3*S*)-1-(*o*-Azidobenzoyl)-4-benzyl-3-*iso*-propylpiperazine-2,5-dione** was obtained as a syrup; yield 70%; $[\alpha]_D^{25}=-108.3$ (*c* 0.26, $CHCl_3$); $\nu_{max}$ (NaCl) 2129, 1724, 1676 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 7.44 (1H, ddd, $J=8.0$ Hz, $J=7.6$ Hz, $J=1.5$ Hz, H-4′), 7.33 (3H, m, ArH), 7.25 (3H, m, ArH), 7.18 (1H, ddd, $J=7.6$ Hz, $J=7.5$ Hz, $J=1.0$ Hz, H-5′), 7.06 (1H, dd, $J=8.1$ Hz, $J=0.5$ Hz, H-3′), 5.57 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 4.89 (1H, d, $J=17.8$ Hz, H-6), 4.26 (1H, d, $J=17.8$ Hz, H-6), 3.85 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 3.70 (1H, d, $J=6.0$ Hz, H-3), 2.27 (1H, sep, $J=6.7$ Hz, C<u>H</u>$(CH_3)_2$), 1.06 (3H, d, $J=6.9$ Hz, $CH_3$), 1.02 (3H, d, $J=6.9$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 168.2, 167.2, 164.5, 136.6, 135.3, 131.9, 129.2, 128.4, 128.3, 128.1, 125.2, 118.0, 65.9, 48.4, 46.7, 32.4, 20.0, 18.6. $C_{21}H_{21}O_3N_5$ requires: C, 64.44; H, 5.41; N, 17.89. Found: C, 64.03; H, 5.42; N, 17.75%.

To a solution of the corresponding 1-(*o*-azidobenzoyl)-4-benzyl-3-alkylpiperazine-2,5-dione (1.9 mmol) in dry toluene (10 mL) was added tributylphosphine (3.8 mmol). The mixture was stirred under argon for 48 h at room temperature **8**, or was heated under reflux for 4.5 h under argon **9**, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (ether).

**4.3.1. (1*S*)-2-Benzyl-1-methyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione 8**. Compound **8** was obtained as a pale yellow solid; yield 73%; mp 136–137°C (ether); $\nu_{max}$ (KBr) 1667, 1610 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.27

(1H, dd, $J=8.0$ Hz, $J=1.5$ Hz, H-7), 7.74 (1H, ddd, $J=8.1$ Hz, $J=7.2$ Hz, $J=1.5$ Hz, H-9), 7.56 (1H, dd, $J=8.1$ Hz, $J=1.0$ Hz, H-10), 7.48 (1H, ddd, $J=8.0$ Hz, $J=7.2$ Hz, $J=1.0$ Hz, H-8), 7.30 (5H, m, ArH), 5.36 (1H, d, $J=18.3$ Hz, H-4), 5.10 (1H, d, $J=14.8$ Hz, *N*-$CH_2$-Ar), 4.53 (1H, q, $J=7.1$ Hz, H-1), 4.33 (1H, d, $J=14.8$ Hz, *N*-$CH_2$-Ar), 4.16 (1H, d, $J=18.3$ Hz, H-4), 1.46 (3H, d, $J=7.1$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 163.9, 160.2, 151.6, 147.1, 135.5, 134.6, 128.9, 128.3, 128.1, 127.1, 126.9, 126.7, 119.9, 56.3, 47.8, 44.4, 19.0. $C_{19}H_{17}O_2N_3$ requires: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.21; H, 5.40; N, 13.00%.

**4.3.2. (1*S*)-2-Benzyl-1-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 9**. Compound **9** was obtained as a yellow oil; yield 80%; $[\alpha]_D^{25}=-82.5$ (*c* 0.27, $CHCl_3$); $\nu_{max}$ (NaCl) 1676, 1608 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 8.24 (1H, dd, $J=8$, $J=1.4$ Hz, H-7), 7.72 (1H, ddd, $J=8.1$, $J=6.9$, $J=1.4$ Hz, H-9), 7.57 (1H, dd, $J=8.1$, $J=1.1$ Hz, H-10), 7.46 (1H, ddd, $J=8$, $J=6.9$, $J=1.1$ Hz, H-8), 7.21 (5H, m, ArH), 5.54 (1H, d, $J=15$ Hz, *N*-$CH_2$-Ar), 5.26 (1H, d, $J=18.6$ Hz, H-4), 4.31 (1H, d, $J=18.6$ Hz, H-4), 4.20 (1H, d, $J=7.1$ Hz, H-1), 4.03 (1H, d, $J=15$ Hz, *N*-$CH_2$-Ar), 2.28 (1H, m, $J=6.8$ Hz, C<u>H</u>$(CH_3)_2$), 1.14 (3H, d, $J=6.8$ Hz, $CH_3$), 0.95 (3H, d, $J=6.8$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 164.3, 160.4, 149.5, 146.7, 135.2, 134.6, 128.8, 128.0, 127.9, 127.2, 127.1, 126.7, 119.8, 65.9, 49.5, 45.2, 33.7, 20.1, 18.9. $C_{21}H_{21}O_2N_3$ requires: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.65; H, 5.93; N, 11.98%.

### 4.4. General alkylation procedures

**4.4.1. Monoalkylation of 8**. To a cold (−78°C), magnetically stirred solution of **8** (0.5 mmol) in dry THF (10 mL) was added, under argon, dropwise via syringe, a solution of lithium hexamethyldisilazide in THF (1 M, 0.6 mL), followed by a solution of the appropriate halide (0.5 mmol dissolved in THF (5 mL)) 10 min later. The reaction mixture was stirred at −78°C for 20 min (10 min for **14**; 10 min at −78°C and 10 min at 0°C for **11**), quenched with ice, and diluted with $CH_2Cl_2$. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. Column chromatography of the residue on silica gel (toluene:EtOAc or $CH_2Cl_2$: EtOAc) afforded first the dialkylated, if any, followed by the *anti*-4-alkylated and the *syn*-4-alkylated compounds.

**4.4.1.1. (1*S*,4*R*)-2-Benzyl-1,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 10a**. Compound **10a** was obtained (toluene:EtOAc 8:2) as a pale yellow oil; yield 25%; $\nu_{max}$ (NaCl) 1682, 1602 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.27 (1H, dd, $J=1.4$ Hz, $J=8.1$ Hz, H-7), 7.74 (1H, ddd, $J=1.4$ Hz, $J=7.0$ Hz, $J=8.4$ Hz, H-9), 7.63 (1H, dd, $J=1.3$ Hz, $J=8.4$ Hz, H-10), 7.47 (1H, ddd, $J=1.3$ Hz, $J=7.0$ Hz, $J=8.1$ Hz, H-8), 7.33 (5H, m, ArH), 5.60 (1H, q, $J=7.1$ Hz, H-4), 5.45 (1H, d, $J=15.7$ Hz, *N*-$CH_2$-Ar), 4.67 (1H, q, $J=6.7$ Hz, H-1), 4.30 (1H, d, $J=15.7$ Hz, *N*-$CH_2$-Ar), 1.79 (3H, d, $J=6.7$ Hz, $CH_3$), 1.69 (3H, d, $J=7.1$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.8, 160.2, 150.8, 147.0, 136.5, 134.5, 128.9, 127.6, 127.4, 127.1, 127.0, 126.7, 120.4, 52.7, 51.9, 45.4, 17.1, 16.1. $C_{20}H_{19}O_2N_3$ requires: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.95; H, 5.97; N, 12.32%.

**4.4.1.2. (1*S*,4*S*)-2-Benzyl-1,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 10b**. Compound **10b** was obtained (toluene:EtOAc 8:2) as a pale yellow oil; yield 74%; $\nu_{max}$ (NaCl) 1684, 1659 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.22 (1H, dd, $J=8.0$ Hz, $J=1.2$ Hz, H-7), 7.69 (1H, ddd, $J=8.2$ Hz, $J=7.0$ Hz, $J=1.5$ Hz, H-9), 7.52 (1H, ddd, $J=8.0$ Hz, $J=1.5$ Hz, $J=0.6$ Hz, H-10), 7.42 (1H, ddd, $J=8.2$ Hz, $J=7.3$ Hz, $J=1.2$ Hz, H-8), 7.26 (5H, m, ArH), 5.39 (1H, q, $J=7.0$ Hz, H-4), 5.30 (1H, d, $J=15.0$ Hz, *N*-$CH_2$-Ar), 4.53 (1H, q, $J=7.0$ Hz, H-1), 4.13 (1H, d, $J=15.0$ Hz, *N*-$CH_2$-Ar), 1.73 (3H, d, $J=7.0$ Hz, C(4)-$CH_3$), 1.63 (3H, d, $J=7.0$ Hz, C(1)-$CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.2, 160.4, 151.7, 147.4, 135.6, 134.8, 128.9, 128.3, 128.1, 126.9, 126.7, 126.6, 120.1, 55.8, 52.2, 47.6, 21.4, 19.2. $C_{20}H_{19}O_2N_3$ requires: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.90; H, 5.75; N, 12.72%.

**4.4.1.3. (1*S*,4*R*)-4-Allyl-2-benzyl-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 11a**. Compound **11a** was obtained (toluene:EtOAc 8:2 or $CH_2Cl_2$:EtOAc 9:1) as a pale yellow oil; yield 48%; $\nu_{max}$ (NaCl) 1682, 1603 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.26 (1H, dd, $J=8.0$ Hz, $J=1.5$ Hz, H-7), 7.74 (1H, ddd, $J=8.4$ Hz, $J=7.1$ Hz, $J=1.5$ Hz, H-9), 7.62 (1H, dd, $J=8.4$ Hz, $J=1.2$ Hz, H-10), 7.47 (1H, ddd, $J=8.0$ Hz, $J=7.1$ Hz, $J=1.2$ Hz, H-8), 7.29 (5H, m, ArH), 5.76 (1H, ddt, $J=16.2$ Hz, $J=10.8$ Hz, $J=7.4$ Hz, H-2′), 5.60 (1H, t, $J=6.0$ Hz, H-4), 5.47 (1H, d, $J=15.5$ Hz, *N*-$CH_2$-Ar), 5.02 (1H, d, $J=10.8$ Hz, H-3′), 4.97 (1H, dd, $J=16.2$ Hz, $J=1.4$ Hz, H-3′), 4.68 (1H, q, $J=6.7$ Hz, H-1), 4.25 (1H, d, $J=15.5$ Hz, *N*-$CH_2$-Ar), 2.90 (1H, ddd, $J=14.1$ Hz, $J=7.4$ Hz, $J=6.0$ Hz, H-1′), 2.88 (1H, ddd, $J=14.1$ Hz, $J=7.4$ Hz, $J=6.0$ Hz, H-1′), 1.77 (3H, d, $J=6.7$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.1, 160.4, 151.3, 147.0, 136.2, 134.5, 131.2, 128.8, 127.7, 127.5, 127.3, 127.1, 126.7, 120.2, 120.0, 55.4, 53.2, 45.8, 36.2, 17.4. $C_{22}H_{21}O_2N_3$ requires: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.34; H, 5.99; N, 11.82%.

**4.4.1.4. (1*S*,4*S*)-4-Allyl-2-benzyl-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 11b**. Compound **11b** was obtained (toluene:ethyl acetate 8:2 or $CH_2Cl_2$:EtOAc 9:1) as a pale yellow oil; yield 5%; $\nu_{max}$ (NaCl) 1680, 1666 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.25 (1H, dd, $J=8.0$ Hz, $J=1.5$ Hz, H-7), 7.72 (1H, ddd, $J=8.2$ Hz, $J=7.1$ Hz, $J=1.5$ Hz, H-9), 7.54 (1H, dd, $J=8.2$ Hz, $J=1.2$ Hz, H-10), 7.46 (1H, ddd, $J=8.2$ Hz, $J=7.1$ Hz, $J=1.2$ Hz, H-8), 7.31 (5H, m, ArH), 5.94 (1H, ddt, $J=14.6$ Hz, $J=10.2$ Hz, $J=7.3$ Hz, H-2′), 5.47 (1H, t, $J=7$ Hz, H-4), 5.30 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 5.10 (1H, d, $J=10.2$ Hz, H-3′), 5.05 (1H, d, $J=14.6$ Hz, H-3′), 4.57 (1H, q, $J=7.1$ Hz, H-1), 4.19 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 2.84 (2H, t, $J=7$ Hz, H-1′), 1.69 (3H, d, $J=7.1$ Hz, $CH_3$), $\delta_C$ (62.5 MHz, $CDCl_3$) 165.5, 160.5, 151.8, 147.1, 135.4, 134.7, 132.5, 128.9, 128.3, 128.1, 126.9, 126.8, 126.7, 120.3, 119.1, 55.8, 55.6, 47.6, 38.4, 21.7. $C_{22}H_{21}O_2N_3$ requires: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.60; H, 5.95; N, 11.72%.

**4.4.1.5. (1*S*,4*R*)-2,4-Dibenzyl-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 12a**. Compound **12a** was obtained (toluene:EtOAc 8:2) as a wax; yield 72%; $\nu_{max}$ (KBr) 1682, 1595 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.31 (1H, dd, $J$=8.0 Hz, $J$=1.4 Hz, H-7), 7.75 (1H, ddd, $J$=8.0 Hz, $J$=7.0 Hz, $J$=1.4 Hz, H-9), 7.59 (1H, dd, $J$=8.0 Hz, $J$=1.0 Hz, H-10), 7.50 (1H, dd, $J$=8.0 Hz, $J$=7.0 Hz, $J$=1.0 Hz, H-8), 7.29 (3H, m, ArH), 7.15 (3H, m, ArH), 7.02 (2H, m, ArH), 6.79 (2H, m, ArH), 5.73 (1H, dd, $J$=6.6 Hz, $J$=5.0 Hz, H-4), 4.84 (1H, d, $J$=15.4 Hz, $N$-$CH_2$-Ar), 4.50 (1H, d, $J$=15.4 Hz, $N$-$CH_2$-Ar), 3.53 (1H, dd, $J$=5.0 Hz, $J$=14.0 Hz, C(4)-$CH_2$), 3.47 (1H, dd, $J$=14.0 Hz, $J$=6.6 Hz, C(4)-$CH_2$), 3.35 (1H, q, $J$=6.7 Hz, H-1), 1.52 (1H, d, $J$=6.7 Hz, $CH_3$), $\delta_C$ (62.5 MHz, $CDCl_3$) 166.8, 160.5, 151.6, 147.0, 136.3, 134.9, 134.7, 129.6, 128.5, 127.8, 127.5, 127.4, 127.2, 127.0, 126.7, 120.1, 56.7, 53.6, 46.7, 37.2, 18.6. $C_{26}H_{23}O_2N_3$ requires: C, 76.26; H, 5.66; N, 10.25. Found: C, 75.90; H, 5.42; N, 10.05%.

**4.4.1.6. (1*S*,4*S*)-2,4-Dibenzyl-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 12b**. Compound **12b** was obtained (toluene:EtOAc 8:2) as a white solid; yield 2%; mp 124–126°C; $\nu_{max}$ (KBr) 1684, 1654 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.30 (1H, dd, $J$=8.0 Hz, $J$=1.3 Hz, H-7), 7.75 (1H, ddd, $J$=8.1 Hz, $J$=7.1 Hz, $J$=1.3 Hz, H-9), 7.55 (1H, dd, $J$=8.1 Hz, $J$=1.0 Hz, H-10), 7.48 (1H, ddd, $J$=8.0 Hz, $J$=7.1 Hz, $J$=1.0 Hz, H-8), 7.25 (5H, m, ArH), 7.18 (3H, m, ArH), 7.03 (2H, m, ArH), 5.59 (1H, t, $J$=5.0 Hz, H-4), 5.15 (1H, d, $J$=14.8 Hz, $N$-$CH_2$-Ar), 4.37 (1H, q, $J$=7.0 Hz, H-1), 3.93 (1H, d, $J$=14.8 Hz, $N$-$CH_2$-Ar), 3.59 (1H, dd, $J$=14.1 Hz, $J$=5.2 Hz, C(4)-$CH_2$), 3.52 (1H, dd, $J$=14.1 Hz, $J$=4.8 Hz, C(4)-$CH_2$), 0.75 (3H, d, $J$=7.0 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 164.7, 160.4, 151.9, 146.8, 135.5, 135.1, 134.8, 130.1, 128.8, 128.7, 128.5, 128.1, 127.5, 126.9, 126.8, 126.4, 119.8, 57.2, 54.8, 46.7, 37.2, 19.8. $C_{26}H_{23}O_2N_3$ requires: C, 76.26; H, 5.66; N, 10.25. Found: C, 76.01; H, 5.74; N, 10.34%.

**4.4.1.7. (1*S*,4*R*)-2-Benzyl-1-methyl-4-*p*-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 13a**. Compound **13a** was obtained (toluene:EtOAc 9:1) as an oil; yield 88%; $\nu_{max}$ (NaCl) 1682 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.32 (1H, dd, $J$=8.0 Hz, $J$=1.5 Hz, H-7), 7.75 (1H, ddd, $J$=8.4 Hz, $J$=7.2 Hz, $J$=1.5 Hz, H-9), 7.59 (1H, dd, $J$=8.4 Hz, $J$=1.1 Hz, H-10), 7.50 (1H, ddd, $J$=8.0 Hz, $J$=7.2 Hz, $J$=1.1 Hz, H-8), 7.28 (3H, m, ArH), 7.12 (2H, m, ArH), 6.86 (2H, d, $J$=8.0 Hz, H-3′,5′), 6.68 (2H, d, $J$=8.0 Hz, H-2′,6′), 5.71 (1H, dd, $J$=6.6 Hz, $J$=5.0 Hz, H-4), 4.85 (1H, d, $J$=15.4 Hz, $N$-$CH_2$-Ar), 4.51 (1H, d, $J$=15.4 Hz, $N$-$CH_2$-Ar), 3.48 (1H, dd, $J$=14.2 Hz, $J$=5.0 Hz, C(4)-$CH_2$), 3.42 (1H, dd, $J$=14.2 Hz, $J$=6.6 Hz, C(4)-$CH_2$), 3.41 (1H, q, $J$=6.7 Hz, H-1), 2.23 (3H, s, $CH_3$), 1.52 (3H, d, $J$=6.7 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.8, 160.5, 151.7, 147.0, 137.1, 136.3, 134.6, 131.7, 129.5, 129.2, 128.5, 127.7, 127.4, 127.2, 127.0, 126.7, 120.1, 56.8, 53.7, 46.7, 36.8, 21.0, 18.7. $C_{27}H_{25}O_2N_3$ requires: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.65; H, 5.85; N, 9.79%.

**4.4.1.8. (1*S*,4*S*)-2-Benzyl-1-methyl-4-*p*-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 13b**. Compound **13b** was obtained (toluene:EtOAc 9:1) as an oil; yield 7%; $\nu_{max}$ (NaCl) 1684 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.30 (1H, dd, $J$=8.0 Hz, $J$=1.5 Hz, H-7), 7.75 (1H, ddd, $J$=8.4 Hz, $J$=7.1 Hz, $J$=1.5 Hz, H-9), 7.53 (1H, dd, $J$=8.4 Hz, $J$=1.1 Hz, H-10), 7.48 (1H, ddd, $J$=8.0 Hz, $J$=7.1 Hz, $J$=1.1 Hz, H-8), 7.27 (5H, m, ArH), 7.00 (2H, d, $J$=8.0 Hz, H-3′,5′), 6.90 (2H, d, $J$=8.0 Hz, H-2′,6′), 5.58 (1H, t, $J$=5.0 Hz, H-4), 5.45 (1H, d, $J$=14.7 Hz, $N$-$CH_2$-Ar), 4.35 (1H, q, $J$=7.0 Hz, H-1), 3.90 (1H, d, $J$=14.7 Hz, $N$-$CH_2$-Ar), 3.56 (1H, dd, $J$=14.3 Hz, $J$=5.2 Hz, C(4)-$CH_2$), 3.49 (1H, dd, $J$=14.3 Hz, $J$=4.8 Hz, C(4)-$CH_2$), 2.25 (3H, s, $CH_3$), 0.8 (3H, d, $J$=7.0 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 164.8, 160.5, 151.8, 147.1, 137.1, 135.2, 134.7, 132.4, 129.9, 129.4, 128.8, 128.5, 128.0, 126.7, 126.6, 120.0, 57.3, 54.9, 46.6, 36.9, 20.9, 19.7. $C_{27}H_{25}O_2N_3$ requires: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.71; H, 5.98; N, 9.81%.

**4.4.1.9. (1*S*,4*R*)-2-Benzyl-1-methyl-4-*p*-nitrobenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 14a**. Compound **14a** was obtained (toluene:EtOAc 9:1) as a pale yellow solid; yield 62%; mp 82–84°C; $\nu_{max}$ (KBr) 1669, 1647, 1343 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J$=7.9 Hz, $J$=1.5 Hz, H-7), 7.82 (2H, d, $J$=8.6 Hz, H-3′,5′), 7.76 (1H, ddd, $J$=8.0 Hz, $J$=7.1 Hz, $J$=1.5 Hz, H-9), 7.60 (1H, dd, $J$=8.0 Hz, $J$=1.0 Hz, H-10), 7.50 (1H, ddd, $J$=7.9 Hz, $J$=7.1 Hz, $J$=1.0 Hz, H-8), 7.30 (3H, m, ArH), 7.18 (2H, m, ArH), 6.95 (2H, d, $J$=8.6 Hz, H-2′,6′), 5.69 (1H, dd, $J$=5.9 Hz, $J$=4.3 Hz, H-4), 5.24 (1H, d, $J$=15.2 Hz, $N$-$CH_2$-Ar), 4.27 (1H, d, $J$=15.2 Hz, $N$-$CH_2$-Ar), 3.92 (1H, q, $J$=6.7 Hz, H-1), 3.57 (1H, dd, $J$=13.8 Hz, $J$=5.9 Hz, C(4)-$CH_2$), 3.48 (1H, dd, $J$=13.8 Hz, $J$=4.3 Hz, C(4)-$CH_2$), 1.67 (3H, d, $J$=6.7 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 165.6, 160.5, 150.9, 147.1, 146.8, 142.7, 135.7, 135.0, 130.4, 128.7, 128.1, 128.0, 127.4, 127.3, 126.6, 123.5, 120.0, 56.2, 53.5, 46.2, 36.9, 18.9. $C_{26}H_{22}O_4N_4$ requires: C, 68.71; H, 4.88; N, 12.33. Found: C, 68.91; H, 5.00; N, 12.61%.

**4.4.1.10. (1*S*,4*S*)-2-Benzyl-1-methyl-4-*p*-nitrobenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 14b**. Compound **14b** was obtained (toluene:EtOAc 9:1) as a pale yellow oil; yield 10%; $\nu_{max}$ (NaCl) 1682, 1602, 1346 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.27 (1H, dd, $J$=8.0 Hz, $J$=1.5 Hz, H-7), 8.15 (2H, d, $J$=8.4 Hz, H-3′,5′), 7.77 (1H, ddd, $J$=8.1 Hz, $J$=7.0 Hz, $J$=1.5 Hz, H-9), 7.57 (1H, dd, $J$=8.1 Hz, $J$=1.0 Hz, H-10), 7.51 (1H, ddd, $J$=8.0 Hz, $J$=7.0 Hz, $J$=1.0 Hz, H-8), 7.40 (2H, d, $J$=8.4 Hz, H-2′,6′), 7.28 (5H, m, ArH), 5.56 (1H, dd, $J$=7.5 Hz, $J$=4.2 Hz, H-4), 5.31 (1H, d, $J$=14.7 Hz, $N$-$CH_2$-Ar), 4.53 (1H, q, $J$=7.0 Hz, H-1), 4.07 (1H, d, $J$=14.7 Hz, $N$-$CH_2$-Ar), 3.55 (1H, dd, $J$=13.6 Hz, $J$=4.2 Hz, C(4)-$CH_2$), 3.45 (1H, dd, $J$=13.6 Hz, $J$=7.5 Hz, C(4)-$CH_2$), 1.26 (1H, d, $J$=7.0 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 164.3, 163.3, 151.4, 147.2, 146.5, 143.6, 135.2, 135.0, 130.7, 129.0, 128.5, 128.3, 127.4, 126.8, 126.6, 123.8, 119.7, 56.7, 55.1, 47.4, 38.6, 21.7. $C_{26}H_{22}O_4N_4$ requires: C, 68.71; H, 4.88; N, 12.33. Found: C, 68.49; H, 4.63; N, 12.29%.

**4.4.1.11. (1*S*)-2-Benzyl-1-methyl-4,4-bis(*p*-nitrobenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 15**. Compound **15** was obtained (toluene:EtOAc 9:1) as an oil; $\nu_{max}$ (NaCl) 1681, 1653 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.41 (1H, dd, $J=8.0$ Hz, $J=1.5$ Hz, H-7), 8.05 (2H, d, $J=8.7$ Hz, H-3″,5″), 7.78 (1H, ddd, $J=8.0$ Hz, $J=7.0$ Hz, $J=1.5$ Hz, H-9), 7.63 (2H, d, $J=8.7$ Hz, H-3′,5′), 7.57 (1H, ddd, $J=8.0$ Hz, $J=7.0$ Hz, $J=1.0$ Hz, H-8), 7.43 (1H, d, $J=8.0$ Hz, H-10), 7.32 (2H, d, $J=8.7$ Hz, H-2″,6″), 7.27 (3H, m, ArH), 7.00 (2H, m, ArH), 6.86 (2H, d, $J=8.7$ Hz, H-2′,6′), 5.35 (1H, d, $J=14.5$ Hz, *N*-$CH_2$-Ar), 4.85 (1H, d, $J=13.2$ Hz, C(4)-$CH_2$), 4.50 (1H, d, $J=13.5$ Hz, C(4)-$CH_2$), 3.95 (1H, q, $J=6.8$ Hz, H-1), 3.88 (1H, d, $J=13.2$ Hz, C(4)-$CH_2$), 3.84 (1H, d, $J=13.5$ Hz, C(4)-$CH_2$), 3.72 (1H, d, $J=14.5$ Hz, *N*-$CH_2$-Ar), 0.38 (3H, d, $J=6.8$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 165.4, 163.1, 151.2, 147.2, 146.9, 145.9, 143.6, 142.7, 135.4, 133.9, 131.3, 130.4, 128.8, 128.7, 128.1, 127.7, 126.9, 126.6, 123.8, 123.3, 120.6, 72.9, 53.7, 47.4, 40.9, 40.6, 21.4. $C_{33}H_{27}O_6N_5$ requires: C, 67.22; H, 4.62; N, 11.88. Found: C, 67.35; H, 4.82; N, 11.93%.

**4.4.2. 4,4-Dialkylation of 8**. To a cold (−78°C), magnetically stirred solution of **8** (0.5 mmol) in dry THF (10 mL) under argon was added, dropwise via syringe, a solution of lithium hexamethyldisilazide in THF (1 M, 1.1 mL), followed 10 min later by the addition of a solution of *p*-methylbenzyl bromide (1 mmol dissolved in THF (5 mL)). The reaction mixture was stirred at −78°C for 3 min and 20 min at 0°C, quenched with ice and diluted with $CH_2Cl_2$. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. Column chromatography of the residue on silica gel (toluene:EtOAc 9:1) afforded **16** in quantitative yield.

**4.4.2.1. (1*S*)-2-Benzyl-1-methyl-4,4-bis(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 16**. Compound **16** was obtained (toluene:EtOAc 9:1) as an oil; $\nu_{max}$ (NaCl) 1682, 1654 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.42 (1H, dd, $J=8.0$ Hz, $J=1.5$ Hz, H-7), 7.72 (1H, ddd, $J=8.5$ Hz, $J=7.1$ Hz, $J=1.5$ Hz, H-9), 7.51 (1H, ddd, $J=8.0$ Hz, $J=7.1$ Hz, $J=1.1$ Hz, H-8), 7.39 (1H, dd, $J=8.5$ Hz, $J=1.1$ Hz, H-10), 7.25 (3H, m, ArH), 6.99 (2H, d, $J=8.1$ Hz, H-3′,5′), 6.94 (2H, d, $J=8.1$ Hz, H-2′,6′), 6.78 (2H, m, ArH), 6.72 (2H, d, $J=8.2$ Hz, H-3″,5″), 6.68 (2H, d, $J=8.2$ Hz, H-2″,6″), 5.47 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 4.65 (1H, d, $J=13.4$ Hz, C(4)-$CH_2$), 4.39 (1H, d, $J=13.7$ Hz, C(4)-$CH_2$), 3.78 (1H, q, $J=6.8$ Hz, H-1), 3.68 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 3.66 (1H, d, $J=13.4$ Hz, C(4)-$CH_2$), 3.65 (1H, d, $J=13.7$ Hz, C(4)-$CH_2$), 2.19 (3H, s, $CH_3$), 2.17 (3H, s, $CH_3$), 0.28 (3H, d, $J=6.8$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.4, 162.9, 152.5, 146.3, 136.7, 136.2, 134.6, 134.3, 133.4, 132.7, 130.2, 129.5, 129.2, 128.9, 128.5, 128.4, 127.7, 127.0, 126.7, 126.2, 121.2, 74.5, 53.2, 46.5, 40.5, 40.1, 20.9, 20.8, 20.3. $C_{35}H_{33}O_2N_3$ requires: C, 79.67; H, 6.30; N, 7.96. Found: C, 79.82; H, 6.42; N, 8.15%.

**4.4.3. Alkylation of 8 in presence of DMI**. To a cold (−78°C), magnetically stirred solution of 0.5 mmol of **8** in dry THF (10 mL) and DMI (1 mmol) under argon was added, dropwise via syringe, a solution of lithium hexamethyldisilazide in THF (1 M, 1.1 mL), followed 10 min later by addition of a solution of *p*-methylbenzyl bromide (1 mmol) in THF (5 mL). The reaction mixture was stirred at −78°C for 10 min and 15 min at 0°C, quenched with ice and diluted with $CH_2Cl_2$. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. Column chromatography of the residue on silica gel (toluene:EtOAc 9:1) afforded **18**, **17**, and **16** in 4, 19 and 30% yield, respectively.

**4.4.3.1. 2-Benzyl-1,4,4-tris(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18**. Compound **18** was obtained (toluene:EtOAc 9:1) as a wax; $\nu_{max}$ (NaCl) 1681, 1651 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.41 (1H, dd, $J=8.0$ Hz, $J=1.5$ Hz, H-7), 7.68 (1H, ddd, $J=8.5$ Hz, $J=7.2$ Hz, $J=1.5$ Hz, H-9), 7.51 (1H, ddd, $J=8.0$ Hz, $J=7.2$ Hz, $J=1.2$ Hz, H-8), 7.23 (3H, m, ArH); 7.15 (5H, m, ArH, H-3′,5′,10), 6.98 (2H, d, $J=7.8$ Hz, H-2′,6′), 6.75 (2H, d, $J=7.7$ Hz, H-3″,5″), 6.63 (2H, d, $J=7.8$ Hz, H-3‴,5‴), 6.48 (2H, d, $J=7.8$ Hz, H-2‴,6‴), 6.32 (2H, d, $J=7.8$ Hz, H-2″,6″), 4.80 (1H, d, $J=15.2$ Hz, *N*-$CH_2$-Ar), 4.48 (1H, d, $J=13.5$ Hz, C(4)-$CH_2$), 4.28 (1H, d, $J=13.7$ Hz, C(4)-$CH_2$), 4.19 (1H, d, $J=15.2$ Hz, *N*-$CH_2$-Ar), 3.73 (1H, d, $J=13.5$ Hz, C(4)-$CH_2$), 3.47 (1H, d, $J=13.7$ Hz, C(4)-$CH_2$), 2.25 (1H, d, $J=13.8$ Hz, C(1)-$CH_2$), 2.18 (3H, s, $CH_3$), 2.10 (3H, s, $CH_3$), 2.09 (3H, s, $CH_3$), 1.56 (1H, d, $J=13.8$ Hz, C(1)-$CH_2$), 1.20 (3H, s, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.5, 163.3, 152.4, 145.6, 137.3, 136.8, 136.1, 135.9, 134.2, 133.8, 132.8, 132.6, 130.5, 130.2, 129.6, 129.1, 128.6, 128.5, 128.0, 127.9, 127.0, 126.9, 126.8, 126.7, 121.3, 73.5, 64.6, 48.2, 47.5, 40.9, 40.6, 25.6, 20.9, 20.8. $C_{43}H_{41}O_2N_3$ requires: C, 81.74; H, 6.54; N, 6.65. Found: C, 81.83; H, 6.64; N, 6.75%.

**4.4.3.2. (1*S*,4*R*)-2-Benzyl-1-methyl-1,4-bis(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 17**. $\nu_{max}$ (NaCl) 1680, 1655 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.26 (1H, dd, $J=8$ Hz, $J=1.5$ Hz, H-7), 7.81 (1H, ddd, $J=8.3$ Hz, $J=7.1$ Hz, $J=1.5$ Hz, H-9), 7.70 (1H, dd, $J=8.3$ Hz, $J=1.2$ Hz, H-10), 7.51 (1H, ddd, $J=8$ Hz, $J=7.1$ Hz, $J=1.2$ Hz, H-8), 7.30 (5H, m, ArH), 6.71 (2H, d, $J=8$ Hz, H-3′,5′), 6.63 (2H, d, $J=8$ Hz, H-3″,5″), 6.37 (2H, d, $J=8$ Hz, H-2′,6′), 6.28 (2H, d, $J=8$ Hz, H-2″,6″), 5.28 (1H, d, $J=14.8$ Hz, *N*-$CH_2$-Ar), 4.61 (1H, dd, $J=5$ Hz, $J=3$ Hz, H-4), 4.28 (1H, d, $J=14.8$ Hz, *N*-$CH_2$-Ar), 3.37 (1H, dd, $J=14.1$ Hz, $J=5$ Hz, C(4)-$CH_2$), 3.23 (1H, d, $J=13.7$ Hz, C(1)-$CH_2$), 3.14 (1H, dd, $J=14.1$ Hz, $J=3$ Hz, C(4)-$CH_2$), 3.11 (1H, d, $J=13.7$ Hz, C(1)-$CH_2$), 2.20 (3H, s, $CH_3$), 2.16 (3H, s, $CH_3$), 1.42 (3H, s, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 165.5, 160.2, 153.3, 146.8, 137.2, 136.9, 136.2, 134.5, 131.5, 131.2, 129.8, 129.3, 129.1, 128.9, 128.7, 128.0, 127.2, 127.1, 126.7, 126.6, 120.0, 67.0, 55.5, 47.8, 46.9, 36.5, 26.8, 20.9, 20.8. $C_{35}H_{33}O_2N_3$ requires: C, 79.67; H, 6.30; N, 7.96. Found: C, 79.35; H, 6.40; N, 7.90%.

**4.4.4. Monoalkylation of 9**. To a cold (−78°C), magnetically stirred solution of **9** (0.5 mmol) in dry THF (10 mL) under argon was added, dropwise via syringe, a solution of lithium hexamethyldisilazide in THF (1 M, 0.6 mL), followed 10 min later by a solution of the

appropriate halide (0.5 mmol) in THF (5 mL); in the case of **19**, excess iodomethane was employed). The reaction mixture was maintained at −78°C for 10 min, and at 0°C for 40 min, quenched with ice and diluted with $CH_2Cl_2$. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. Column chromatography of the residue on silica gel (toluene:EtOAc or $CH_2Cl_2$:EtOAc) afforded first the 4,4-dialkylated, if any, followed by the *anti*-4-alkylated compound.

**4.4.4.1. (1*S*,4*R*)-2-Benzyl-1-*iso*-propyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19a**. Compound **19a** was obtained (toluene:EtOAc 8:2) as a yellow oil; yield 41%; $[\alpha]_D^{25}=-122$ (*c* 0.19, $CHCl_3$); $\nu_{max}$ (NaCl) 1683, 1667 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 8.23 (1H, dd, $J=8$, $J=1.5$ Hz, H-7), 7.72 (1H, ddd, $J=8.2$. $J=6.8$, $J=1.5$ Hz, H-9), 7.5 (1H, dd, $J=8.2$, $J=1.2$ Hz, H-10), 7.45 (1H, ddd, $J=8$, $J=6.8$, $J=1.2$ Hz, H-8), 7.3 (5H, m, ArH), 5.62 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 5.16 (1H, q, $J=6.5$ Hz, H-4), 4.34 (1H, d, $J=2.7$ Hz, H-1), 3.96 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 2.42 (1H, sepd, $J=6.9$, $J=2.7$ Hz, C$\underline{H}(CH_3)_2$), 1.74 (3H, d, $J=6.5$ Hz, $CH_3$), 1.03 (3H, d, $J=6.9$ Hz, $CH_3$), 0.73 (3H, d, $J=6.9$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 167.7, 160.7, 147.9, 146.2, 135.4, 134.6, 129.0, 128.1, 128.0, 126.9, 126.8, 126.6, 120.6, 63.6, 53.3, 47.5, 34.1, 23.0, 19.8, 16.5. $C_{22}H_{23}O_2N_3$ requires: C, 73.11; H, 6.41; N, 11.63. Found: C, 72.83; H, 6.14; N, 11.58%.

**4.4.4.2. (1*S*)-2-Benzyl-1-*iso*-propyl-4,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 25**. Compound **25** was obtained (toluene:EtOAc 8:2) as a pale yellow solid; yield 50%; mp 118–120°C; $[\alpha]_D^{25}=-63$ (*c* 0.26, $CHCl_3$); $\nu_{max}$ (KBr) 1674, 1654 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 8.22 (1H, dd, $J=8.0$, $J=1.5$ Hz, H-7), 7.69 (1H, ddd, $J=8.2$. $J=6.8$, $J=1.5$ Hz, H-9), 7.53 (1H, dd, $J=8.2$. $J=1.2$ Hz, H-10), 7.42 (1H, ddd, $J=8.2$, $J=6.8$, $J=1.2$ Hz, H-8), 7.24 (5H, m, ArH), 5.59 (1H, d, $J=15$ Hz, *N*-$CH_2$-Ar), 4.25 (1H, d, $J=5.5$ Hz, H-1), 3.99 (1H, d, $J=15$ Hz, *N*-$CH_2$-Ar), 2.29 (1H, m, $J=6.9$ Hz, C$\underline{H}(CH_3)_2$), 2.15 (3H, s, $CH_3$), 1.98 (3H, s, $CH_3$), 1.15 (3H, d, $J=6.9$ Hz, $CH_3$), 0.87 (3H, d, $J=6.9$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 172, 162.2, 149.1, 146.0, 135.9, 134.6, 129.1, 129.0, 128.1, 128.0, 127.1, 126.9, 126.8, 64.8, 64.7, 49.7, 35.3. 26.8, 24.9, 20.7, 19.0. $C_{23}H_{25}O_2N_3$ requires: C, 73.58; H, 6.71; N, 11.19. Found: C, 73.49; H, 6.86; N, 10.96%.

**4.4.4.3. (1*S*,4*R*)-4-Allyl-2-benzyl-1-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 20a**. Compound **20a** was obtained (toluene:EtOAc 9:1) as a pale yellow oil; yield 47%; $[\alpha]_D^{25}=-220.4$ (*c* 0.24, $CHCl_3$); $\nu_{max}$ (NaCl) 1682, 1662 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 8.23 (1H, dd, $J=8$ Hz, $J=1.5$ Hz, H-7), 7.71 (1H, ddd, $J=8.2$ Hz, $J=7.2$ Hz, $J=1.5$ Hz, H-9), 7.56 (1H, dd, $J=8.2$ Hz, $J=1.1$ Hz, H-10), 7.45 (1H, ddd, $J=8$ Hz, $J=7.2$ Hz, $J=1.1$ Hz, H-8), 7.25 (5H, m, ArH), 5.66 (1H, d, $J=14.8$ Hz, *N*-$CH_2$-Ar), 5.30 (1H, dddd, $J=16.2$ Hz, $J=10.8$ Hz, $J=8.1$ Hz, $J=7$ Hz, H-2′), 5.24 (1H, dd, $J=4.4$ Hz, $J=2.7$ Hz, H-4), 4.78 (1H, dd, $J=10.8$ Hz, $J=1.8$ Hz, H-3′), 4.75 (1H, dd, $J=16.2$ Hz, $J=1.8$ Hz, H-3′), 4.32 (1H, d, $J=2.7$ Hz, H-1), 3.97 (1H, d, $J=14.8$ Hz, *N*-$CH_2$-Ar), 3.22 (1H, ddd, $J=13.2$ Hz, $J=8.1$ Hz, $J=4.4$ Hz, H-1′), 2.99 (1H, ddd, $J=13.2$ Hz, $J=7$ Hz, $J=2.7$ Hz, H-1′), 2.42 (1H, sepd, $J=6.9$ Hz, $J=2.7$ Hz, C$\underline{H}(CH_3)_2$), 1.00 (3H, d, $J=6.9$ Hz, $CH_3$), 0.75 (3H, d, $J=6.9$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 165.9, 160.8, 148.6, 146.3, 135.2, 134.8, 130.5, 129.1, 128.9, 128.3. 127.1, 126.8, 120.7, 120.6, 63.5, 56.6, 47.7, 36.1, 33.8, 19.9, 16.4. $C_{24}H_{25}O_2N_3$ requires: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.17; H, 6.65; N, 10.62%.

**4.4.4.4. (1*S*)-2-Benzyl-4,4-diallyl-1-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 26**. Compound **26** was obtained (toluene:EtOAc 9:1) as a yellow oil; yield 21%; $[\alpha]_D^{25}=-80$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (NaCl) 1685, 1656 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 8.21 (1H, dd, $J=8.2$ Hz, $J=1.5$ Hz, H-7), 7.69 (1H, ddd, $J=8.2$ Hz, $J=7$ Hz, $J=1.2$ Hz, H-8), 7.53 (1H, dd, $J=8.1$ Hz, $J=1.2$ Hz, H-10), 7.43 (1H, ddd, $J=8.1$ Hz, $J=7$ Hz, $J=1.5$ Hz, H-9), 7.29 (5H, m, ArH), 5.85 (1H, dddd, $J=17$ Hz, $J=10$ Hz, $J=8.2$ Hz, $J=7.9$ Hz, H-2′), 5.52 (1H, d, $J=14.7$ Hz, *N*-$CH_2$-Ar), 5.2 (1H, dd, $J=17$ Hz, $J=2$ Hz, H-3′), 5.06 (1H, dd, $J=10$ Hz, $J=2.0$ Hz, H-3′), 5.03 (1H, dddd, $J=17$ Hz, $J=10$ Hz, $J=8.5$ Hz, $J=6.3$ Hz, H-2″), 4.72 (1H, dd, $J=17.1$ Hz, $J=2.1$ Hz, H-3″), 4.61 (1H, dd, $J=10$ Hz, $J=2.1$ Hz, H-3″), 4.18 (1H, d, $J=6.9$ Hz, H-1), 4.05 (1H, d, $J=14.8$ Hz, *N*-$CH_2$-Ar), 3.56 (1H, dd, $J=13.8$ Hz, $J=8.5$ Hz, H-1″), 3.53 (1H, dd, $J=13.9$ Hz, $J=8.2$ Hz, H-1′), 3.33 (1H, dd, $J=13.9$ Hz, $J=7.9$ Hz, H-1′), 3.0 (1H, dd, $J=13.8$ Hz, $J=6.3$ Hz, H-1″), 2.25 (1H, m, $J=6.9$ Hz, C$\underline{H}(CH_3)_2$), 1.17 (3H, d, $J=6.9$ Hz, $CH_3$), 0.86 (3H, d, $J=6.8$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 167.9, 162.5, 150.4, 145.8, 135.7, 134.6, 133.2, 133.0, 128.9, 128.7, 128.1, 127.1, 126.9, 126.8, 121.7, 120.2. 119.5, 71.2. 65.1, 51.0, 41.3, 40.5, 36.5, 21.2, 19.7. $C_{27}H_{29}O_2N_3$ requires: C, 75.85; H, 6.84; N, 9.83. Found: C, 75.69; H, 6.77; N, 9.67%.

**4.4.4.5. (1*S*,4*R*)-2,4-Dibenzyl-1-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 21a**. Compound **21a** was obtained ($CH_2Cl_2$:EtOAc 95:5) as a colourless oil; yield 71%; $[\alpha]_D^{25}=-357.6$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (NaCl) 1683. 1661 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 8.33 (1H, dd, $J=7.9$ Hz, $J=1.5$ Hz, H-7), 7.75 (1H, ddd, $J=8.4$ Hz, $J=6.9$ Hz, $J=1.5$ Hz, H-9), 7.54 (1H, dd, $J=8.4$ Hz, $J=1$ Hz, H-10), 7.50 (1H, ddd, $J=7.9$ Hz, $J=6.9$ Hz, $J=1$ Hz, H-8), 7.19 (4H, m, ArH), 6.98 (2H, m, ArH), 6.8 (2H, m, ArH), 6.63 (2H, m, ArH), 5.49 (1H, t, $J=3.7$ Hz, H-4), 5.38 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 3.94 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 3.85 (1H, d, $J=2.6$ Hz, H-1), 3.79 (1H, dd, $J=14.0$ Hz, $J=4.6$ Hz, C(4)-$CH_2$), 3.53 (1H, dd, $J=14.0$ Hz, $J=3.0$ Hz, C(4)-$CH_2$), 2.25 (1H, sepd, $J=6.9$ Hz, $J=2.6$ Hz, C$\underline{H}(CH_3)_2$), 0.87 (3H, d, $J=6.9$ Hz, $CH_3$), 0.61 (3H, d, $J=6.9$, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 165.1, 160.9, 148.2, 146.0, 134.8, 134.7, 134.1, 129.6, 128.7, 128.6, 128.4, 127.8, 127.0, 126.9, 126.7, 120.4, 62.5, 57.3. 47.0, 36.5, 33.0, 19.8, 16.0. $C_{28}H_{27}O_2N_3$ requires: C, 76.86; H, 6.22; N, 9.60. Found: C, 76.64; H, 5.95; N, 9.54%.

**4.4.4.6. (1*S*,4*R*)-2-Benzyl-1-*iso*-propyl-4-*p*-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 22a**. Compound **22a** was obtained (toluene:EtOAc 95:5)

as a yellow oil; yield 70%; $[\alpha]_D^{25}=-389.6$ (*c* 0.28, $CHCl_3$); $\nu_{max}$ (NaCl) 1683, 1661 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 8.33 (1H, dd, $J=8.0$ Hz, $J=1.5$ Hz, H-7), 7.75 (1H, ddd, $J=8.4$ Hz, $J=6.8$ Hz, $J=1.5$ Hz, H-9), 7.55 (1H, dd, $J=8.4$ Hz, $J=1.1$ Hz, H-10), 7.5 (1H, ddd, $J=8.0$ Hz, $J=6.8$ Hz, $J=1.1$ Hz, H-8), 7.20 (3H, m, ArH), 6.80 (2H, m, ArH), 6.78 (2H, d, $J=8$ Hz, H-3′,5′), 6.50 (2H, d, $J=8.0$ Hz, H-2′,6′), 5.47 (1H, t, $J=3.7$ Hz, H-4), 5.38 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 3.91 (1H, d, $J=14.9$ Hz, *N*-$CH_2$-Ar), 3.85 (1H, d, $J=2.6$ Hz, H-1), 3.73 (1H, dd, $J=14.1$ Hz, $J=4.4$ Hz, C(4)-$CH_2$), 3.48 (1H, dd, $J=14.1$ Hz, $J=3.1$ Hz, C(4)-$CH_2$), 2.26 (1H, sepd, $J=6.9$ Hz, $J=2.6$ Hz, C$\underline{H}$($CH_3$)), 2.22 (3H, s, $CH_3$), 1.29 (3H, d, $J=6.9$ Hz, $CH_3$), 0.59 (3H, d, $J=6.9$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 165.4, 161.1, 148.5, 146.2, 136.5, 134.7, 134.1, 131.6, 129.5, 129.0, 128.7, 128.6, 127.8, 126.9, 126.95, 126.7, 120.6, 62.5, 57.6, 47.1, 36.4, 33.1, 21.1, 19.7, 15.9. $C_{29}H_{29}O_2N_3$ requires: C, 77.14; H, 6.47; N, 9.31. Found: C, 76.86; H, 6.40; N, 9.12%.

**4.4.4.7. (1*S*,4*R*)-2-Benzyl-4-*p*-fluorobenzyl-1-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 23a**. Compound **23a** was obtained (toluene:EtOAc 95:5) as a yellow solid; yield 78%; mp 91–93°C; $[\alpha]_D^{25}=-378$ (*c* 0.27, $CHCl_3$); $\nu_{max}$ (KBr) 1678, 1659 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 8.32 (1H, dd, $J=8.2$ Hz, $J=1.3$ Hz, H-7), 7.77 (1H, ddd, $J=8.5$ Hz, $J=7.0$ Hz, $J=1.3$ Hz, H-9), 7.56 (1H, dd, $J=8.5$ Hz, $J=1.2$ Hz, H-10), 7.52 (1H, ddd, $J=8.2$ Hz, $J=7.0$ Hz, $J=1.2$ Hz, H-8), 7.25 (3H, m, ArH), 6.84 (2H, m, ArH), 6.60 (4H, m, ArF-H), 5.44 (1H, t, $J=3.5$ Hz, H-4), 5.39 (1H, d, $J=14.3$ Hz, *N*-$CH_2$-Ar), 3.95 (1H, d, $J=2.7$ Hz, H-1), 3.92 (1H, d, $J=14.3$ Hz, *N*-$CH_2$-Ar), 3.75 (1H, dd, $J=14.2$ Hz, $J=4.6$ Hz, C(4)-$CH_2$), 3.5 (1H, dd, $J=14.2$ Hz, $J=3.0$ Hz, C(4)-$CH_2$), 2.31 (1H, sepd, $J=6.9$ Hz, $J=2.7$ Hz, C$\underline{H}$($CH_3$)$_2$), 0.89 (3H, d, $J=6.9$ Hz, $CH_3$), 0.62 (3H, d, $J=6.9$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 165.0, 164.1, 162.0 (d, $J=244.3$ Hz, C-4′), 160.9, 148.2, 145.9, 134.9, 134.3, 131.1 (d, $J=7.8$ Hz, C-2′,6′), 130.5 (d, $J=3.3$ Hz, C-1′), 128.7, 128.5, 128.0, 127.1, 126.9, 126.6, 120.3, 115.2 (d, $J=21$ Hz, C-3′,5′), 62.9, 57.5, 47.3, 35.8, 33.4, 19.7, 16.0. $C_{28}H_{26}O_2N_3F$ requires: C, 73.83; H, 5.75; N, 9.22. Found: C, 73.46; H, 5.83; N, 9.09%.

**4.4.4.8. (1*S*,4*R*)-2-Benzyl-1-*iso*-propyl-4-*p*-nitrobenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 24a**. Compound **24a** was obtained ($CH_2Cl_2$:EtOAc 95:5) as a yellow oil; yield 85%; $[\alpha]_D^{25}=-322.5$ (*c* 0.28, $CHCl_3$); $\nu_{max}$ (NaCl) 1682, 1658, 1347 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$), 8.32 (1H, dd, $J=8.0$ Hz, $J=1.4$ Hz, H-7), 7.78 (1H, ddd, $J=8.4$ Hz, $J=7.0$ Hz, $J=1.4$ Hz, H-9), 7.69 (2H, d, $J=8.7$ Hz, H-3″,5″), 7.58 (1H, dd, $J=8.4$ Hz, $J=1.1$ Hz, H-10), 7.53 (1H, ddd, $J=8.0$ Hz, $J=7.0$ Hz, $J=1.1$ Hz, H-8), 7.22 (3H, m, ArH), 6.94 (2H, d, $J=8.1$ Hz, ArH), 6.74 (2H, d, $J=8.7$ Hz, H-2′,6′), 5.45 (1H, dd, $J=4.8$ Hz, $J=3.0$ Hz, H-4), 5.36 (1H, d, $J=14.6$ Hz, *N*-$CH_2$-Ar), 4.03 (1H, d, $J=2.8$ Hz, H-1), 3.9 (1H, d, $J=14.6$ Hz, *N*-$CH_2$-Ar), 3.87 (1H, dd, $J=13.8$ Hz, $J=4.8$ Hz, C(4)-$CH_2$), 3.63 (1H, dd, $J=13.8$ Hz, $J=3.0$ Hz, C(4)-$CH_2$), 2.33 (1H, sepd, $J=6.9$ Hz, $J=2.8$ Hz, C$\underline{H}$($CH_3$)$_2$), 0.93 (3H, d, $J=6.9$ Hz, $CH_3$), 0.65 (3H, d, $J=6.9$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$), 164.5, 161.0, 147.7, 146.8, 145.8, 142.6, 135.1, 134.4, 130.4, 128.7, 128.6, 128.3, 127.4, 127.2. 126.6, 123.2, 120.2, 63.6, 57.1, 47.6, 36.4, 33.7, 19.6, 16.0. $C_{28}H_{26}O_4N_4$ requires: C, 69.70; H, 5.43; N, 11.61. Found: C, 69.57; H, 5.44; N, 11.46%.

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