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# Influence of *N*(2)-substitution in the alkylation of (4*S*)-alkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones

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**Abstract**—1-Alkylation of *O*(3)-lactim, *N*(11)-azaenolate dilithium species derived from *N*(2)–H compounds **1a** and **1b** and the lithium azaenolates derived from the *N*(2)-phenyl and *N*(2)-(1-arylethyl) substituted compounds **2**, **3** and **4** is studied. In **1** the *trans*-diastereoselectivity of 1-alkylation is controlled by 1,4-asymmetric induction, with some of these products precursors of the *ent*-ardeemin framework. By contrast in compounds **2**–**4**, the stabilization of the lithium azaenolate imposed by the phenyl substituent in **2**, and the repulsive steric 1,2-interactions present in the initially formed 1,4-*trans* derivatives of **3** and **4**, favour a C(1)-epimerization to the 1,4-*cis* isomers.


## 1. Introduction

In connection with the synthesis of the MDR reversal agent[1] *N*-acetylardeemin (Fig. 1) and other related natural products, we have extensively studied the reactivity of homochiral *N*(2)-methyl and *N*(2)-arylmethyl-pyrazino[2,1-*b*]quinazoline-3,6-diones as nucleophilic glycine templates. In the alkylation of the corresponding base-generated azaenolates, we have shown that the main factors leading the 1,4-asymmetric induction are the substituent size at the stereogenic centre (methyl or *iso*-propyl groups at C-1 or C-4 positions) and the existence of repulsive interactions between the C(1)- and *N*(2)-substituents in the 1,4-*trans*-isomers.[2–7]

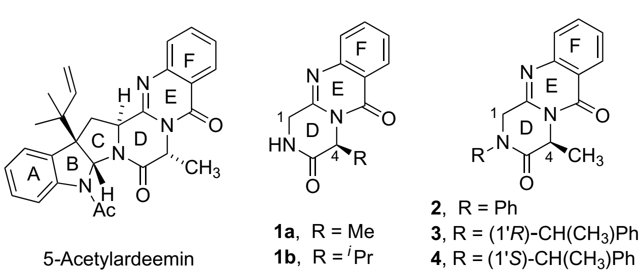


**Figure 1.**

According to these results, a greater diastereoselectivity was expected for *N*(2)–H compounds. In fact, the *O*(3)-lactim, C(4)-dilithium species originated from *N*(2)-unsubstituted-1-methylpyrazino[2,1-*b*]quinazoline-3,6-diones and an excess of base, were alkylated at C-4 to give the 1,4-*trans*-isomers with de >95%. However, when this method was applied to the less reactive 1-*iso*-propyl analogues for the synthesis of fiscalin B, the diastereomeric excess found was lower because of the much longer reaction times required.[8]

In order to complete the stage, we study here the alkylation of *O*(3)-lactim, *N*(11)-azaenolate dilithium species derived from compounds **1a** and **1b**. We also investigate in the as yet unexplored *N*(2)-phenyl and *N*(2)-(1-phenylethyl) lithium azaenolates derived from **2**, **3** and **4**, whether the electronic effects in **2**, or the presence of a stereocentre in **3** and **4**, have a diastereoselective influence on alkylation.

## 2. Results and discussion

Compounds **1** and **2** were obtained by *N*-acylation of the corresponding piperazine-2,5-diones **5** and **6** with *o*-azidobenzoyl chloride following the Eguchi aza-Wittig

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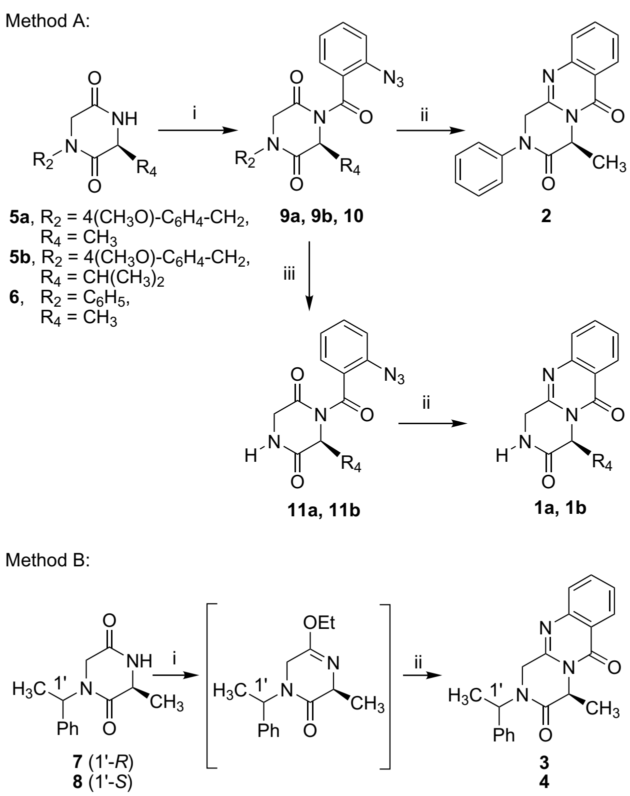
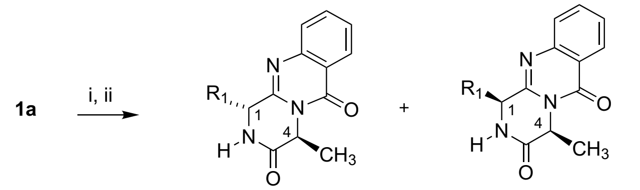
protocol (method A),[9] while compounds **3** and **4** were prepared by condensation of anthranilic acid with the lactim ether derivatives of piperazinediones **7** and **8** (method B, Scheme 1).[10] In the case of **1a** and **1b** the *N*-protected *N*-(4-methoxybenzyl)-*N*′-(2-azidobenzoyl)-piperazinediones **9a** and **9b** were submitted to oxidative cleavage before being cyclized to the corresponding pyrazino[2,1-*b*]quinazoline-3,6-diones.



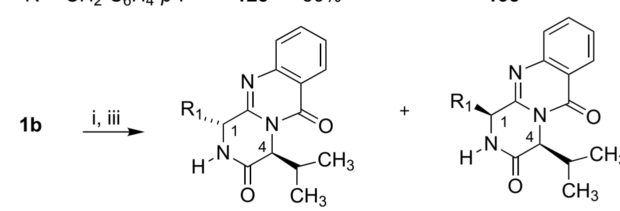

**Scheme 1.** Method A. Reagents and conditions: (i) KHMDS, THF, DMI, −78 °C, 16 h. (ii) $Bu_3P$, PhMe, Δ. (iii) CAN (2 equiv), MeCN/$H_2O$ (4:1.5), 1 h. Method B. Reagents and conditions: (i) $(Et)_3O^+F_4B^-$ (3 equiv), $Na_2CO_3$ (5 equiv), $CH_2Cl_2$, rt, overnight. (ii) Anthranilic acid (1 equiv), 130 °C, 3 h.

Alkylation of compounds **1a** and **1b** was performed by using a large excess of lithium hexamethyldisilazide. Reaction with allyl bromide and arylmethyl bromides gave the 1,4-*trans*-isomers **12** and **14** as the main or exclusive products, while reaction with methyl iodide afforded compounds **13a** and **15a** as the major or exclusive products (Scheme 2). In most cases small amounts of 1,1-dialkyl derivatives were also isolated. The diastereomeric ratio of the isolated products was in agreement with that observed in the $^1$H NMR spectra of the crude products. NOESY experiments allowed an easy assignment of the *cis*- and *trans*-isomers. The enantiomeric purity (>95%) was determined by chiral HPLC (see Section 4).

The apparent diastereoselectivity discrepancy found for the methyl derivatives **13a** and **15a** can be attributed to the small volume of the methyl group, which facilitates the epimerization at C(1) in the kinetic products **12a** and **14a**. Although the activation barrier for the *syn*-attack in the transition state might be lower for methyl iodide than for other alkylating agents,[7] the exclusive isolation of 1,1-dialkylderivatives as trace products in the alkylation of compounds **1**, proves that the incorporation of the second electrophile takes place solely at C-1, and also establishes the deprotonation/protonation equilibrium at this position to give the thermodynamic *cis*-products.



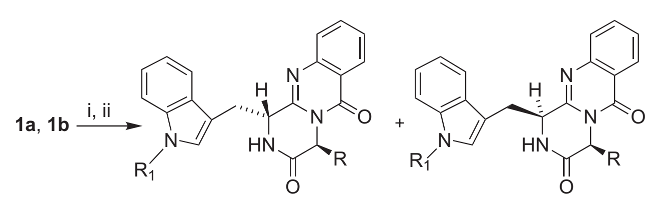

| | | | | |
|---|---|---|---|---|
| $R^1$= $CH_3$ | **12a** | 15% | **13a** | 54% |
| $R^1$= $CH_2$-CH=$CH_2$ | **12b** | 30% | **13b** | 2% |
| $R^1$= $CH_2$-$C_6H_5$ | **12c** | 44% | **13c** | 5% |
| $R^1$= $CH_2$-$C_6H_4$-*p*-$CH_3$ | **12d** | 43% | **13d** | 7% |
| $R^1$= $CH_2$-$C_6H_4$-*p*-F | **12e** | 36% | **13e** | --- |




| | | | | |
|---|---|---|---|---|
| $R^1$= $CH_3$ | **14a** | --- | **15a** | 46% |
| $R^1$= $CH_2$-CH=$CH_2$ | **14b** | 32% | **15b** | --- |
| $R^1$= $CH_2$-$C_6H_5$ | **14c** | 50% | **15c** | --- |
| $R^1$= $CH_2$-$C_6H_4$-*p*-$CH_3$ | **14d** | 58% | **15d** | 5% |
| $R^1$= $CH_2$-$C_6H_4$-*p*-F | **14e** | 48% | **15e** | 3% |

**Scheme 2.** Reagents and conditions: (i) LHMDS (6 equiv), THF, −78 °C, 10 min. (ii) $R^1$X (2 equiv), 16 h. (iii) $R^1$X (2 equiv), 3 d.

At this point, introduction of a 3-indolylmethyl substituent at the C(1)-position was specially interesting because these compounds are potential ardeemin skeleton precursors. The alkylation of **1a** and **1b** with *N*-Boc-3-indolylmethyl bromide (method A, Scheme 3)

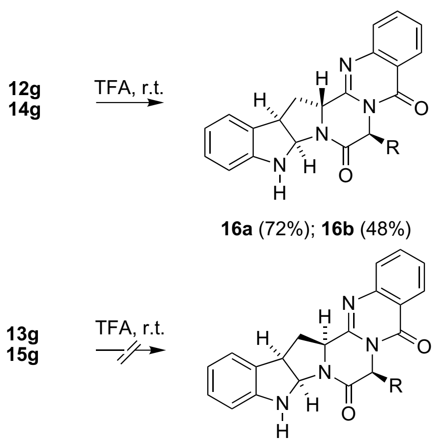



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **12f** R= Me | $R^1$= Boc | 7% | | **13f** R= Me | $R^1$= Boc | 28% |
| **14f** R= $^i$Pr | $R^1$= Boc | 20% | | **15f** R= $^i$Pr | $R^1$= Boc | 35% |
| **12g** R= Me | $R^1$= H | 23% | | **13g** R= Me | $R^1$= H | 11% |
| **14g** R= $^i$Pr | $R^1$= H | 24% | | **15g** R= $^i$Pr | $R^1$= H | 11% |

**Scheme 3.** Reagents and conditions: (i) LHMDS (6 equiv), THF, −78 °C, 10 min. (ii) Method A: *N*-Boc-3-indolylmethyl bromide, 6 h (R = Me) or 72 h (R = $^i$Pr). Method B: trimethyl-3-indolylmethyl ammonium iodide, 16 h (R = Me) or 72 h (R = $^i$Pr).

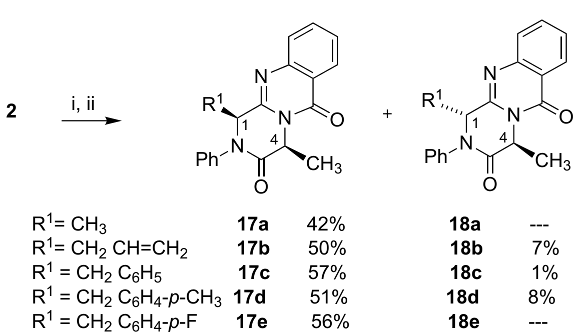
gave mainly the *cis*-isomer, showing here again the already reported *cis*/*trans* diastereomeric ratio for alkylation with *N*-Boc-3-indolylmethyl halides.[7,8] The reactions with trimethyl-3-indolylmethylammonium iodide (method B, Scheme 3) gave instead a diastereomeric ratio in favour of *trans*-isomers (see **12g** and **14g** vs **13g** and **15g**).

Compounds **12g** and **14g** were submitted to acid-promoted cyclization to give the de-'prenyl'-ardeemin derivatives **16a** and **16b**, while the 1,4-*cis* epimers **13g** and **15g** failed to cyclize in all acid catalyzed attempts due to the pseudoaxial disposition of the 3-indolylmethyl substituent (Scheme 4).[11]

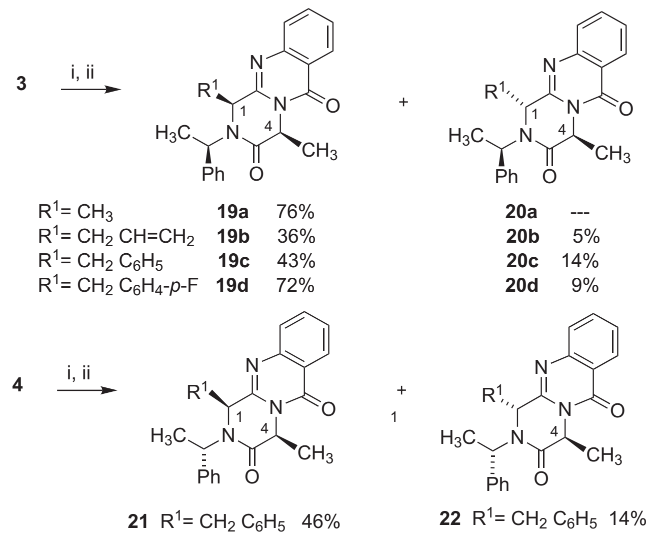



**Scheme 4.**

Alkylation of the lithium azaenolate derived from **2** required the use of DMI as a cosolvent[12] as the yields were very low in its absence (Scheme 5).[13] These findings can be explained taking into consideration that the *N*(2)-phenyl group stabilizes the negative charge. In contrast to all previously studied 4-alkyl-pyrazino[2,1-*b*]quinazoline-3,6-diones, the 1,4-*cis*-isomers **17** were the predominant products here. Small amounts of the 1,4-*trans*-isomers and traces of 1,1- and 1,4-dialkylated products were also detected. We assume that the 1,4-*trans*-isomers epimerize almost completely when formed, due to the more acidic character of the C(1)-protons. Alkylation




**Scheme 5.** Reagents and conditions: (i) LHMDS (1.2 equiv), DMI (1.2 equiv), THF, −78 °C, 10 min. (ii) $R^1X$ (1.2 equiv), 10 min (−78 °C), then 30 min at 0 °C.




**Scheme 6.** Reagents and conditions: (i) LHMDS (1.2 equiv), THF, −78 °C, 10 min. (ii) $R^1X$ (1.2 equiv), 10 min (−78 °C), then 30 min at 0 °C.

experiments on *N*-benzyl analogues of compounds **17** and **18** showed that under basic conditions the 1,4-*cis*-isomers are deprotonated at C-4, while the 1,4-*trans*-isomers are deprotonated at C-1.[4]

In spite of the precedents of the *N*-phenylethyl radical acting as an asymmetric inductor,[14] the benzyl bromide alkylation of lithium azaenolates derived from **3** and **4** afforded the same diastereomeric ratio for both epimers (Scheme 6). The observed predominance of the 1,4-*cis*-isomers **19** and **21** is attributed to the destabilizing steric interaction between the bulky *N*(2)-substituent and the C(1)-alkyl group in the quasiplanar 1,4-*trans*-isomers **20** and **22**, favouring the epimerization at C-1 as in preceding examples.[4] The enantiomeric purity of compounds **17**–**22** (ee >95%) was determined by $^1H$ NMR experiments (see Section 4).

## 3. Conclusion

In conclusion, we have shown that the alkylation of compounds **1** (*N*(2)–H) is diastereoselectively controlled by 1,4-asymmetric induction and affords 1,4-*trans*-derivatives as the main products, with some of them being precursors of the ardeemin framework. By contrast, the stabilization of the lithium azaenolate imposed by a phenyl substituent in **2**, as well as the repulsive steric 1,2-interactions present in the 1,4-*trans* isomers of the 2-(1-phenylethyl)-compounds **3** and **4**, favour the epimerization at C(1) to give predominantly or almost exclusively the corresponding 1,4-*cis* derivatives.

## 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 $F_{254}$) and spots visualized 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, Bruker Avance 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. NOE and NOESY experiments allowed the assignation of the *cis*- and *trans*-diastereoisomers. 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/or 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; mobile phase: hexane/2-propanol (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. (3*S*)-3-Alkyl-1-arylalkyl-(aryl)-piperazine-2,5-diones 5–8. General procedure

To a stirred solution of freshly distilled ethyl *N*-(arylalkyl or phenyl)-L-glycinate (20 mmol), and Cbz–alanine or Cbz–valine in dry $CH_2Cl_2$ (50 mL) DCC (or EDC for **5b**) (22 mmol) was added, and stirring was continued at room temperature for 16 h. The reaction mixture was filtered, washed successively with 1 N HCl, 1 N $NaHCO_3$ and water, dried over anhydrous $Na_2SO_4$ and evaporated. The syrupy residue was hydrogenated at 35 psi for 12 h with C/Pd (10%, 1.8 g) in ethanol (100 mL), filtered (Celite) and evaporated. Compounds **7** and **8** were directly isolated. In case of **5** and **6** the residue was heated under reflux in toluene (or methanol for **5b**) (25 mL) for 12 h affording the corresponding piperazinedione.

**4.2.1. (3*S*)-3-*iso*-Propyl-1-*p*-methoxybenzyl-piperazine-2,5-dione 5b.** Mp: 145 °C (EtOAc); yield 72%; $[\alpha]_D^{25} = +11.9$ (*c* 0.46, $CHCl_3$); $\nu_{max}$ (NaCl) 3236, 2962, 1684, 1654, 1612 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.53 (1H, s, NH), 7.17 (2H, d, $J$ = 8.6 Hz, H-2′ and H-6′), 6.83 (2H, d, $J$ = 8.6 Hz, H-3′ and H-5′), 4.68 (1H, d, $J$ = 14.2 Hz, *N*–$CH_2$–Ar), 4.32 (1H, d, $J$ = 14.7 Hz, *N*–$CH_2$–Ar) 3.86 (1H, t, $J$ = 8.8 Hz, H-3), 3.81 (1H, d, $J$ = 17,8 Hz, H-6), 3.76 (3H, s, $OCH_3$), 3.70 (1H, d, $J$ = 17,8 Hz, H-6), 2.40 (1H, m, $CH(CH_3)_2$), 0.98 (3H, d, $J$ = 6.9 Hz, $CH_3$), 0.82 (3H, d, $J$ = 6.9 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.5, 165.4, 159.4, 129.9, 127.2, 114.2, 60.6, 55.2, 49.0, 48.4, 33.1, 18.8, 16.0. $C_{15}H_{20}N_2O_3$ requires: C, 65.20; H, 7.30; N, 10.14. Found: C, 64.79; H, 7.17; N, 10.06%.

**4.2.2. (3*S*)-3-Methyl-1-phenylpiperazine-2,5-dione 6.** Mp: 148–150 °C (ethyl ether); yield 98%; $[\alpha]_D^{25} = -21.7$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (NaCl) 1689, 1646 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.42 (2H, m, Ar–H), 7.27 (3H, m, Ar–H), 6.56 (1H, s, NH), 4.33 (2H, 't', $J$ = 17.4 Hz, H-6), 4.24 (1H, q, $J$ = 7.0 Hz, H-3), 1.58 (3H, d, $J$ = 7.0 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.8, 166.1, 140.1, 129.3, 127.5, 125.2, 52.7, 51.4, 19.5. $C_{11}H_{12}N_2O_2$ requires: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.58; H, 5.86; N, 13.70%.

**4.2.3. (1′*R*,3*S*)-3-Methyl-1-(1-phenylethyl)piperazine-2,5-dione 7.** Mp: 114–115 °C (toluene); yield 98%; $[\alpha]_D^{25} = +148$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (NaCl) 3244, 1683, 1636 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.30 (5H, m, Ar–H), 6.80 (1H, s, NH), 5.98 (1H, q, $J$ = 7.1 Hz, Hα), 4.10 (1H, q, $J$ = 6.9 Hz, H-3), 3.74 (1H, d, $J$ = 17.6 Hz, H-6), 3.42 (1H, d, $J$ = 17.6 Hz, H-6), 1.51 (3H, d, $J$ = 7.0 Hz, $CH_3$), 1.48 (3H, d, $J$ = 7.0 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.6, 135.5, 128.9, 128.1, 127.5, 51.2, 50.4, 44.2, 19.9, 15.2. $C_{13}H_{16}N_2O_2$ requires: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.69; H, 6.80; N, 11.69%.

**4.2.4. (1′*S*,3*S*)-3-Methyl-1-(1-phenylethyl)piperazine-2,5-dione 8.** Mp: 126–128 °C ($CH_2Cl_2$/ether); yield 98%; $[\alpha]_D^{25} = -124$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (NaCl) 3276, 2929, 1675, 1620 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.30 (5H, m, Ar–H), 6.66 (1H, s, NH), 5.99 (1H, q, $J$ = 7.1 Hz, Hα), 4.08 (1H, q, $J$ = 6.9 Hz, H-3), 3.75 (1H, d, $J$ = 17.5 Hz, H-6), 3.43 (1H, d, $J$ = 17.6 Hz, H-6), 1.51 (3H, d, $J$ = 7.1 Hz, $CH_3$), 1.50 (3H, d, $J$ = 6.9 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.6, 138.4, 128.9, 128.2, 127.4, 51.3, 50.4, 44.1, 19.9, 15.2. $C_{13}H_{16}N_2O_2$ requires: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.81; H, 7.36; N, 11.64%.

### 4.3. (3*S*)-3-Alkyl-4-(*o*-azidobenzoyl)-1-*p*-methoxybenzyl-(1-phenyl)-piperazine-2,5-diones 9 and 10

To a cold (−78 °C), magnetically stirred solution of compounds **5a**,[4] **5b** or **6** (3 mmol) in dry THF (30 mL) under argon was added dropwise via syringe, DMI (0.6 mL, 6 mmol) and a solution of potassium hexamethyldisilazide in dry toluene (0.5 M. 7.2 mL, 3.6 mmol), followed 10 min later by addition of *o*-azidobenzoyl chloride (0.55 g, 3 mmol) in THF (10 mL). Stirring was continued for 15 min at −78 °C, and then for a further 16 h at room temperature. The reaction mixture was quenched with ice, washed with brine (3 × 15 mL) and extracted with chloroform (3 × 10 mL). The organic layer was dried over anhydrous $Na_2SO_4$, evaporated and isolated by column chromatography (petroleum ether–EtOAc, 7:3) for compounds **9** (**10** (97% yield) was used in the next step without further purification).

**4.3.1. (3*S*)-4-(*o*-Azidobenzoyl)-1-*p*-methoxybenzyl-3-methylpiperazine-2,5-dione 9a.** Compound **9a** was obtained as an oily product; yield 52%; $[\alpha]_D^{25} = -64.5$ (*c* 0.33, $CHCl_3$); $\nu_{max}$ (NaCl) 2129, 1720, 1676, 1610 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.44 (1H, dt, $J = 1.6$ and 8.0 Hz, H-4′), 7.42 (1H, dd, $J = 1.5$ and 7.9 Hz, H-6′), 7.20 (2H, d, $J = 8.7$ Hz, H-2″ and H-6″), 7.19 (1H, dt, $J = 0.9$ and 7.9 Hz, H-5′), 7.10 (1H, dd, $J = 8.1$ and 0.9 Hz, H-3′), 6.87 (2H, d, $J = 8.7$ Hz, H-3″ and H-5″), 5.10 1H, (q, $J = 7.2$ Hz, H-3), 4.81 (1H, d, $J = 14.1$ Hz, *N*–$CH_2$–Ar), 4.32 (1H, d, $J = 14.1$ Hz, *N*–$CH_2$–Ar), 3.98 (1H, d, $J = 18.8$ Hz, H-6), 3.88 (1H, d, $J = 18.8$ Hz, H-6), 3.78 3H, (s, $OCH_3$), 1.59 (3H, d, $J = 7.2$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.3, 167.1, 166.5, 159.5, 136.4, 131.9, 129.4, 127.7, 126.8, 125.0, 117.9, 114.4, 55.2, 53.9, 49.2, 48.2, 18.4. $C_{20}H_{19}N_5O_4$ requires: C, 61.06; H, 4.86; N, 17.80. Found: C, 60.91; H, 4.98; N, 17.92%.

**4.3.2. (3*S*)-4-(*o*-Azidobenzoyl)-1-*p*-methoxybenzyl-3-*iso*-propylpiperazine-2,5-dione 9b.** Compound **9b** was obtained as an oily product; yield 54%; $[\alpha]_D^{25} = -38.8$ (*c* 0.08, $CHCl_3$); $\nu_{max}$ (NaCl) 2129, 1729, 1674 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.43 (1H, ddt, $J = 0.5$, 1.6 and 8.0 Hz, H-4′), 7.35 (1H, dd, $J = 1.6$ and 7.7 Hz, H-6′), 7.21 (2H, d, $J = 8.9$ Hz, H-2″ and H-6″), 7.16 (1H, dt, $J = 0.9$ and 7.7 Hz, H-5′), 7.04 (1H, dd, $J = 0.9$ and 8.0 Hz, H-3′), 6.86 (2H, d, $J = 8.7$ Hz, H-3″ and H-5″), 4.92 (1H, d, $J = 7.8$ Hz, H-3), 4.72 (1H, d, $J = 14.4$ Hz, *N*–$CH_2$–Ar), 4.40 (1H, d, $J = 14.4$ Hz, *N*–$CH_2$–Ar), 4.00 (1H, d, $J = 19.2$ Hz, H-6), 3.89 (1H, d, $J = 19.2$ Hz, H-6), 3.77 (3H, s, $OCH_3$), 2.14 (1H, m, $J = 7.0$ Hz, $CH(CH_3)_2$), 1.08 (6H, d, $J = 7.0$ Hz, $2CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.6, 167.2, 165.5, 159.4, 135.9, 131.6, 129.7, 129.6, 127.9, 127.1, 125.0, 117.8, 114.4, 62.2, 55.2, 49.7, 48.3, 32.8, 19.5, 18.9. $C_{22}H_{23}N_5O_4$ requires: C, 62.70; H, 5.50; N, 16.62. Found: C, 62.59; H, 5.46; N, 16.41%.

**4.3.3. (3*S*)-4-*o*-Azidobenzoylmethyl-3-methyl-1-phenylpiperazine-2,5-dione 10.** White solid, mp: 138–140 °C (EtOAc); yield 97%; $[\alpha]_D^{25} = +10.8$ (*c* 0.35, $CHCl_3$); $\nu_{max}$ (KBr) 2193, 1692, 1596 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.52–7.13 (9H, m, Ar–H), 5.24 (1H, q, $J = 7.2$ Hz, H-3), 4.63 (1H, d, $J = 18.1$ Hz, H-6), 4.29 (1H, d, $J = 18.1$ Hz, H-6), 1,71 (3H, d, $J = 7.2$ Hz, $CH_3$), $\delta_C$ (62.5 MHz, $CDCl_3$) 167.5, 166.9, 166.0, 139.4, 136.6, 132.0, 129.5, 129.1, 127.8, 127.6, 125.1, 124.9, 118.2, 54.5, 53.5, 18.2. $C_{12}H_{11}O_3N_5$ requires: C. 61,89; H, 4.33; N, 20.05. Found: C, 61.75; H, 4.20; N, 19.91%.

### 4.4. (6*S*)-6-Alkyl-1-(*o*-azidobenzoyl)piperazine-2,5-diones 11a and 11b

A solution of **9a** or **9b** (3 mmol) in 50 mL acetonitrile–water (5:2) and CAN 3.3 g, 6 mmol) was stirred for 1 h at room temperature. The reaction mixture was extracted with $CH_2Cl_2$, dried ($Na_2SO_4$) and evaporated. Column chromatography (EtOAc–petroleum ether, 1:1 or 3:7) afforded **11a** or **11b**, respectively.

**4.4.1. (6*S*)-1-(*o*-Azidobenzoyl)-6-methylpiperazine-2,5-dione 11a.** Mp: 150–152 °C (EtOAc); yield: 60%; $[\alpha]_D^{25} = -14.7$ (*c* 0.09, $CHCl_3$); $\nu_{max}$ (NaCl) 3234, 2193, 1692 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.62 (1H, s, *N*–H), 7.48 (1H, ddd, $J = 1.7$, 7.5 and 8.3 Hz, H-4′), 7.39 (1H, dd, $J = 1.5$ and 8.4 Hz, H-6′), 7.20 (1H, ddd, $J = 0.8$, 7.5 and 8.4 Hz, H-5′), 7.14 (1H, dd, $J = 0.8$ and 8.3 Hz, H-3′), 5.00 (1H, q, $J = 7.2$ Hz, H-6), 4.14 (1H, d, $J = 18.4$ Hz, H-3), 4.06 (1H, d, $J = 18.4$ Hz, H-6), 1.62 (3H, d, $J = 7.2$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 170.0, 167.8, 166.1, 136.5, 131.9, 129.0, 127.9, 124.9, 118.1, 53.5, 45.7, 18.1. $C_{12}H_{11}N_5O_3$ requires: C, 52.74; H, 4.02; N, 25.64. Found: C, 52.45; H, 3.93; N, 25.41%.

**4.4.2. (6*S*)-1-(*o*-Azidobenzoyl)-6-*iso*-propylpiperazine-2,5-dione 11b.** Yield: 45%; mp: 165–167 °C (EtOAc); $[\alpha]_D^{25} = +14.3$ (c 0.28, $CHCl_3$); $\nu_{max}$ (NaCl) 2969, 2129, 1689 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 7.82 (1H, d, *N*-H), 7.45 (1H, dt, $J = 1.5$ and 8.0 Hz, H-4′), 7.35 (1H, dd, $J = 1.5$ and 7.7 Hz, H-6′), 7.18 (1H, dt, $J = 1.0$ and 7.7 Hz, H-5′), 7.12 (1H, dd, $J = 1.0$ and 8.0 Hz, H-3′), 4.81 (1H, d, $J = 7.4$ Hz, H-6), 4.15 (1H, d, $J = 19.1$ Hz, H-3), 4.05 (1H, d, $J = 19.1$ Hz, H-3), 2.19 (1H, m, $J = 7.4$ and 6.8 Hz, $CH(CH_3)_2$), 1.13 (3H, d, $J = 6.8$ Hz, $CH_3$), 1.12 (3H, d, $J = 6.8$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.9, 167.7, 167.4, 136.2, 131.6, 128.8, 128.0, 125.0, 118.0, 62.2, 46.0, 32.4, 19.5, 18.8. $C_{14}H_{15}N_5O_3$ requires: C, 55.75; H, 4.97; N, 23.23. Found: C, 55.38; H, 4.88; N, 23.11%.

### 4.5. Synthesis of compounds 1 and 2 (method A)

To a stirred solution of **11a**, **11b** or **10** (3 mmol) in dry toluene (10 mL) tributylphosphine (3 mmol) was added with syringe. The mixture was stirred under argon for 16 h at room temperature, and evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc (**1**) or EtOAc/petroleum ether 3:7 (**2**) yielding 60%, 45% and 68% of **1a**,[8] **1b**[8] and **2**, respectively.

**4.5.1. (4*S*)-4-Methyl-2-phenyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]-quinazoline-3,6-dione 2.** White solid, mp: 151–152 °C; $[\alpha]_D^{25} = +11.4$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (KBr) 1679, 1608 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.29 (1H, dd, $J = 8.0$ Hz, $J = 1.2$ Hz, H-7), 7.77 (1H, ddd, $J = 8.4$, 7.1 and 1.5 Hz, H-9), 7.63 (1H, dd, $J = 8.4$ and 1.1 Hz, H-10), 7.50 (1H, ddd, $J = 8.0$, 7.1 and 1.1 Hz H-8), 7.46–7.30 (5H, m, Ar–H), 5.66 (1H, q, $J = 7.3$ Hz, H-4), 5.15 (1H, d, $J = 16.3$ Hz, H-1), 4.78 (1H, d, $J = 16.3$ Hz, H-1), 1.72 (3H, d, $J = 7.3$ Hz, $CH_3$), $\delta_C$ (62.5 MHz, $CDCl_3$) 167.1, 159.9, 147.8, 147,2, 139.9, 134.8, 129,4, 127.5, 127.1, 126.9, 124.8, 120.5, 52.6, 16.8. $C_{18}H_{15}O_2N_3$ requires: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.72; H, 4.83; N, 13.68%.

### 4.6. Synthesis of compounds 3 and 4 (method B)

A mixture of 1 g (4 mmol) of the piperazine-2,5-dione **7** or **8**, triethyloxonium tetrafluoroborate (2.6 g, 12 mmol) and anhydrous $Na_2CO_3$ (2.3 g, 20 mmol) in 40 mL dry $CH_2Cl_2$ was stirred overnight at room temperature, poured on ice water, extracted with $CH_2Cl_2$, dried over anhydrous $Na_2SO_4$ and evaporated. Anthranilic acid (0.74 g, 5.4 mmol) was added to the syrupy residue, the mixture was stirred vigorously at 120 °C for 3 h under argon, dissolved in $CH_2Cl_2$, extracted with diluted ammonium hydroxide, dried ($Na_2SO_4$) and concentrated. Column chromatography (EtOAc) afforded 0.72 g of **3** and 0.84 g of **4**, respectively.

**4.6.1. (+)-(1′*R*,4*S*)-4-Methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 3.** White solid, yield 48%; mp: 120–122 °C (ethyl ether); $[\alpha]_D^{25} = +141$ (*c* 0.26, $CHCl_3$); $\nu_{max}$ (KBr) 1693, 1654 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.21 (1H, dd, *J* = 8.0 and 1.5 Hz, H-7), 7.69 (1H, ddd, *J* = 8.5, 7.2 and 1.5 Hz, H-9), 7.53 (1H, dd, *J* = 8.5 and 1.1 Hz, H-10), 7.42 (1H, ddd, *J* = 8.0, 7.2 and 1.1 Hz, H-8), 7.32 (5H, m, Ar–H), 6.05 (1H, q, *J* = 7.0 Hz, H-1′), 5.48 (1H, q, *J* = 7.1 Hz, H-4), 4.15 (1H, d, *J* = 17.0 Hz, H-1), 3.92 (1H, d, *J* = 17.0 Hz, H-1), 1.54 (3H, d, *J* = 7.1 Hz, $CH_3$), 1.53 (3H, d, *J* = 7.0 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.2, 159.9, 148.5, 147.2, 138.4, 129.1, 128.3, 127.3, 126.9, 120.5, 52.3, 50.3, 44.8, 16.6, 15.3. $C_{20}H_{19}O_2N_3$ requires: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.76; H, 5.68; N, 12.22%.

**4.6.2. (−)-(1′*S*,4*S*)-4-Methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 4.** White oil, yield 59%, $[\alpha]_D^{25} = -38$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (NaCl) 1672, 1608 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.24 (1H, dd, *J* = 8.0 and 1.5 Hz, H-7), 7.70 (1H, ddd, *J* = 8.3, 6.9 and 1.4 Hz, H-9), 7.50 (1H, dd, *J* = 8.3 and 1.1 Hz, H-10), 7.45 (1H, ddd, *J* = 8.0, 6.9 and 1.1 Hz, H-8), 7.27 (5H, m, Ar–H), 6.02 (1H, q, *J* = 7.0 Hz, H-1′), 5.54 (1H, q, *J* = 7.1 Hz, H-4), 4.45 (1H, d, *J* = 16.6 Hz, H-1), 4.14 (1H, d, *J* = 16.6 Hz, H-1), 1.62 (3H, d, *J* = 7.1 Hz, $CH_3$), 1.61 (3H, d, *J* = 7.0 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.3, 160.0, 148.5, 147.2, 138.4, 129.1, 128.3, 127.3, 126.9, 120.5, 52.3, 50.3, 44.8, 16.6, 15.3. $C_{20}H_{19}O_2N_3$ requires: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.50; H, 5.62; N, 12.32%.

### 4.7. General alkylation procedures

**4.7.1. Alkylation of 1a.** To a cold (−78 °C), magnetically stirred solution of **1a** (0.5 mmol) in dry THF (10 mL) was added, under argon, dropwise via syringe a solution of lithium hexamethyldisilazide in THF (1M, 3.0 mL), followed after 10 min by a solution of the appropriate halide (1.0 mmol dissolved in THF (5 mL)). The reaction mixture was stirred at −78 °C for 16 h, quenched with drops of glacial acetic acid followed by a saturated aqueous solution of ammonium chloride (5 mL), and extracted with $CHCl_3$. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. Column chromatography of the residue on silica gel (EtOAc–$CH_2Cl_2$, 3:7 unless otherwise mentioned) afforded traces of 1,1-dialkylated compounds, followed from the expected *anti*-1-alkyl compounds and small amounts of *syn*-1-alkyl derivatives.

**4.7.1.1. (+)-(1*R*,4*S*)-1,4-Dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*] quinazoline-3,6-dione 12a.** Compound **12a** was obtained as a solid (EtOAc–MeOH, 9:1); mp: 89–90 °C (ethyl ether); yield 15%; $[\alpha]_D^{25} = +98.2$ (*c* 0.28, $CHCl_3$); $\nu_{max}$ (NaCl) 3239, 2931, 1688, 1607 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.26 (1H, dd, *J* = 1.5 Hz, *J* = 8.1 Hz, H-7), 7.75 (1H, ddd, *J* = 1.5 Hz, *J* = 7.0 Hz, *J* = 8.2 Hz, H-9), 7.67 (1H, dd, *J* = 1.4 Hz, *J* = 8.2 Hz, H-10), 7.48 (1H, ddd, *J* = 1.4 Hz, *J* = 7.0 Hz, *J* = 8.1 Hz, H-8), 7.36 (1H, sa, NH), 5.47 (1H, dq, *J* = 1.0 Hz, *J* = 7.2 Hz H-4), 4.71 (1H, q, *J* = 6.6 Hz H-1), 1.79 (3H, d, *J* = 6.6 Hz, $CH_3$-1), 1.63 (3H, d, *J* = 7.2 Hz, $CH_3$-4);$\delta_C$ (62.5 MHz, $CDCl_3$) 170.3, 160.3, 150.6, 146.9, 134.5, 127.4, 127.2, 126.7, 120.3, 52.3, 49.2, 17.4, 16.4. $C_{13}H_{13}O_2N_3$ requires: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.91; H, 5.43; N, 17.04%.

**4.7.1.2. (+)-(1*S*,4*S*)-1,4-Dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 13a.** Compound **13a** was obtained as a solid (EtOAc–MeOH, 9:1); mp: 205 °C (ethyl ether); yield 54%; $[\alpha]_D^{25} = +110.5$ (*c* 0.41, $CHCl_3$); $\nu_{max}$ (NaCl) 3169, 3063, 2978, 1684, 1600, 1569, 1473 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.25 (1H, dd, *J* = 1.4 Hz, *J* = 8.1 Hz, H-7), 7.83 (1H, sa, NH), 7.75 (1H, ddd, *J* = 1.4 Hz, *J* = 7.1 Hz, *J* = 8.4 Hz, H-9), 7.61 (1H, dd, *J* = 1.1 Hz, *J* = 8.4 Hz, H-10), 7.47 (1H, ddd, *J* = 1.1 Hz, *J* = 7.1 Hz, *J* = 8.1 Hz, H-8), 5.27 (1H, q, *J* = 7.1 Hz, H-4), 4.73 (1H, dq, *J* = 4.0 Hz, *J* = 7.1 Hz H-1), 1.74 (3H, d, *J* = 7.1 Hz, $CH_3$-1), 1.73 (3H, d, *J* = 7.1 Hz, $CH_3$-4); $\delta_C$ (62.5 MHz, $CDCl_3$) 169.6, 160.4, 151.0, 147.1, 134.7, 127.0, 126.8, 126.7, 120.0, 52.3, 51.6, 24.8, 19.2. $C_{13}H_{13}O_2N_3$ requires: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.90; H, 5.38; N, 17.12%.

**4.7.1.3. (+)-(1*R*,4*S*)-1-Allyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 12b.** Compound **12b** was obtained as a solid (EtOAc–$CH_2Cl_2$, 1:1); mp: 185–186 °C (ethyl ether); yield 30%; $[\alpha]_D^{25} = +175.6$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (NaCl) 3253, 2980, 2922, 1686, 1606, 1566, 1470 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.26 (1H, dd, *J* = 1.4 Hz, *J* = 8.1 Hz, H-7), 7.75 (1H, ddd, *J* = 1.4 Hz, *J* = 7.1 Hz, *J* = 8.3 Hz, H-9), 7.65 (1H, dd, *J* = 1.3 Hz, *J* = 8.3 Hz, H-10), 7.48 (1H, ddd, *J* = 1.3 Hz, *J* = 7.1 Hz, *J* = 8.1 Hz, H-8), 6.35 (1H, sa, NH), 5.88 (1H, dddd, *J* = 5.7 Hz, *J* = 8.9 Hz, *J* = 10.0 Hz, *J* = 17.1 Hz, H-2′), 5.46 (1H, dq, *J* = 0.9 Hz, *J* = 7.2 Hz, H-4), 5.33 (1H, dd, *J* = 0.9 Hz, *J* = 10.1 Hz, H-3′), 5.32 (1H, dd, *J* = 0.9 Hz, *J* = 17.2 Hz, H-3′), 4.60 (1H, dd, *J* = 3.6 Hz, *J* = 8.9 Hz, H-1), 3.36 (1H, ddd, *J* = 3.6 Hz, *J* = 5.7 Hz, *J* = 14.7 Hz, H-1′), 2.66 (1H, dt, *J* = 8.9 Hz, *J* = 14.7 Hz, H-1′), 1.62 (3H, d, *J* = 7.2 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 169.2, 160.2, 149.2, 146.7, 134.6, 132.5, 127.4, 127.3, 126.7, 121.0, 120.3, 52.1, 51.6, 36.2, 16.7. $C_{15}H_{15}O_2N_3$ requires: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.67; H, 5.47; N, 15.43%.

**4.7.1.4. (+)-(1*S*,4*S*)-1-Allyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 13b.** Compound **13b** was obtained as an oil (EtOAc–$CH_2Cl_2$, 1:1); yield 2%; $[\alpha]_D^{25} = +92.0$ (*c* 0.05, $CHCl_3$); $\nu_{max}$ (NaCl) 3258, 2962, 2932, 1723, 1689, 1607 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.28 (1H, dd, *J* = 1.3 Hz, *J* = 8.0 Hz, H-7), 7.77 (1H, ddd, *J* = 1.3 Hz, *J* = 7.1 Hz, *J* = 8.4 Hz, H-9), 7.64 (1H, dd, *J* = 1.1 Hz, *J* = 8.4 Hz, H-10), 7.49 (1H, ddd, *J* = 1.1 Hz, *J* = 7.1 Hz, *J* = 8.0 Hz, H-8), 6.57 (1H, sa, NH), 5.88 (1H, dddd, *J* = 6.1 Hz, *J* = 9.4 Hz, *J* = 10.3 Hz, *J* = 16.8 Hz, H-2′), 5.30 (1H, q, *J* = 7.1 Hz, H-4), 5.27 (1H, ddd, $J = 1.0$ Hz, $J = 3.8$ Hz, $J = 16.8$ Hz, H-3′), 5.26 (1H, dd, $J = 1.0$ Hz, $J = 10.3$ Hz, H-3′), 4.60 (1H, dt, $J = 3.8$ Hz, $J = 10.3$ Hz, H-1), 2.94 (1H, ddd, $J = 3.8$ Hz, $J = 6.1$ Hz, $J = 13.7$ Hz, H-1′), 2.56 (1H, ddd, $J = 9.4$ Hz, $J = 10.3$ Hz, $J = 13.7$ Hz, H-1′), 1.73 (3H, d, $J = 7.1$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.8, 160.4, 149.7, 147.0, 134.8, 131.7, 130.8, 126.8, 126.7, 120.9, 120.1, 56.1, 52.5, 42.7, 19.3. $C_{15}H_{15}O_2N_3$ requires: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.71; H, 5.64; N, 15.52%.

**4.7.1.5. (+)-(1*R*,4*S*)-1-Benzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazolino-3,6-dione 12c.** Mp: 204–206 °C (ethyl ether); yield 44%; $[\alpha]_D^{25} = +167.8$ (*c* 0.14, $CHCl_3$); $\nu_{max}$ (NaCl) 2920, 1684, 1605 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J = 1.3$ Hz, $J = 8.1$ Hz, H-7), 7.79 (1H, ddd, $J = 1.3$ Hz, $J = 6.9$ Hz, $J = 8.2$ Hz, H-9), 7.71 (1H, dd, $J = 1.3$ Hz, $J = 8.2$ Hz, H-10), 7.51 (1H, ddd, $J = 1.3$ Hz, $J = 6.9$ Hz, $J = 8.1$ Hz, H-8), 7.35 (5H, m, Ar–H), 5.92 (1H, sa, NH), 5.42 (1H, q, $J = 7.2$ Hz, H-4), 4.80 (1H, dd, $J = 3.6$ Hz, $J = 10.4$ Hz, H-1), 4.12 (1H, dd, $J = 3.6$ Hz, $J = 14.5$ Hz, $CH_2$–Ar–H), 2.96 (1H, dd, $J = 10.4$ Hz, $J = 14.5$ Hz, $CH_2$–Ar–H), 1.59 (3H, d, $J = 7.2$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 169.1, 160.2, 149.5, 146.7, 135.3, 134.7, 129.4, 129.2, 128.1, 127.8, 127.4, 126.9, 120.4, 53.9, 52.1, 37.9, 16.9. $C_{19}H_{17}O_2N_3$ requires: C, 71,46; H, 5,37; N, 13,16. Found: C, 71,16; H, 5,64; N, 12,84%.

**4.7.1.6. (+)-(1*S*,4*S*)-1-Benzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazolino-3,6-dione 13c.** Mp: 71–73 °C (ethyl ether); yield 5%; $[\alpha]_D^{25} = +41.4$ (*c* 0.15, $CHCl_3$); $\nu_{max}$ (NaCl) 2926, 1682, 1597, 1567 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.29 (1H, dd, $J = 1.2$ Hz, $J = 8.1$ Hz, H-7), 7.80 (1H, ddd, $J = 1.2$ Hz, $J = 7.1$ Hz, $J = 8.4$ Hz, H-9), 7.69 (1H, dd, $J = 1.2$ Hz, $J = 8.4$ Hz, H-10), 7.51 (1H, ddd, $J = 1.2$ Hz, $J = 7.1$ Hz, $J = 8.1$ Hz, H-8), 7.33 (2H, m, Ar–H), 7.24 (3H, m, Ar–H), 6.12 (1H, da, $J = 3.7$ Hz, NH), 5.24 (1H, q, $J = 7.1$ Hz, H-4), 4.78 (1H, dt, $J = 3.7$ Hz, $J = 10.1$ Hz, H-1), 3.47 (1H, dd, $J = 3.7$ Hz, $J = 13.5$ Hz, $CH_2$–Ar–H), 3.12 (1H, dd, $J = 10.1$ Hz, $J = 13.5$ Hz, $CH_2$–Ar–H), 1.53 (3H, d, $J = 7.1$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.4, 160.4, 149.6, 147.1, 135.1, 134.8, 129.5, 129.2, 127.7, 127.1, 126.8, 126.7, 120.1, 58.0, 51.8, 44.8, 18.9. $C_{19}H_{17}O_2N_3$ requires: C, 71,46; H, 5,37; N, 13,16. Found: C, C, 71.23; H, 5.34; N, 13.04%.

**4.7.1.7. (+)-(1*R*,4*S*)-4-Methyl-1-(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 12d.** Mp: 134–135 °C (ethyl ether); yield 43%; $[\alpha]_D^{25} = +152.7$ (*c* 0.15, $CHCl_3$); $\nu_{max}$ (NaCl) 3234, 2924, 1687, 1605 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J = 1.3$ Hz, $J = 8.1$ Hz, H-7), 7.78 (1H, ddd, $J = 1.3$ Hz, $J = 6.9$ Hz, $J = 8.1$ Hz, H-9), 7.70 (1H, dd, $J = 1.2$ Hz, $J = 8.1$ Hz, H-10), 7.50 (1H, ddd, $J = 1.2$ Hz, $J = 6.9$ Hz, $J = 8.1$ Hz, H-8), 7.18 (4H, 't', Ar–$CH_3$), 5.89 (1H, sa, NH), 5.42 (1H, q, $J = 7.3$ Hz, H-4), 4.76 (1H, dd, $J = 4.0$ Hz, $J = 10.5$ Hz, H-1), 4.06 (1H, dd, $J = 4.0$ Hz, $J = 14.4$ Hz, $CH_2$–Ar–$CH_3$), 2.91 (1H, dd, $J = 10.5$ Hz, $J = 14.4$ Hz, $CH_2$–Ar–$CH_3$), 2.34 (3H, s, Ar–$CH_3$), 1.58 (3H, d, $J = 7.2$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 169.0, 160.2, 149.6, 146.8, 137.5, 134.6, 132.1, 130.1, 129.0, 128.1, 127.4, 127.3, 126.8, 120.4, 53.9, 52.1, 37.5, 20.9, 16.9. $C_{20}H_{19}O_2N_3$ requires: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.16; H, 5.64; N, 12.64%.

**4.7.1.8. (+)-(1*S*,4*S*)-4-Methyl-1-(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 13d.** Mp: 221–222 °C (ethyl ether); yield 7%; $[\alpha]_D^{25} = +23.4$ (*c* 0.16, $CHCl_3$); $\nu_{max}$ (NaCl) 3211, 2925, 1682, 1598, 1473, 1406, 1333, 1174 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.30 (1H, dd, $J = 1.0$ Hz, $J = 8.0$ Hz, H-7), 7.81 (1H, ddd, $J = 1.0$ Hz, $J = 7.1$ Hz, $J = 7.6$ Hz, H-9), 7.70 (1H, dd, $J = 1.1$ Hz, $J = 7.6$ Hz, H-10), 7.52 (1H, ddd, $J = 1.1$ Hz, $J = 7.1$ Hz, $J = 8.0$ Hz, H-8), 7.16* (2H, d, $J = 9.1$ Hz, H-3′ y 5′), 7.13* (2H, d, $J = 9.1$ Hz, H-2′ y 6′), 6.62 (1H, da, $J = 2.8$ Hz, NH), 5.26 (1H, q, $J = 7.1$ Hz, H-4), 4.78 (1H, dt, $J = 3.7$ Hz, $J = 9.9$ Hz, H-1), 3.44 (1H, dd, $J = 3.7$ Hz, $J = 13.5$ Hz, $CH_2$–Ar–$CH_3$), 3.11 (1H, dd, $J = 9.9$ Hz, $J = 13.5$ Hz, $CH_2$–Ar–$CH_3$), 2.33 (3H, s, Ar–$CH_3$), 1.50 (3H, d, $J = 7.1$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.8, 160.6, 149.9, 147.3, 137.6, 135.0, 132.2, 130.0, 129.6, 127.3, 127.0, 126.9, 120.3, 58.2, 51.9, 43.9, 21.2, 19.0. $C_{20}H_{19}O_2N_3$ requires: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.72; H, 5.94; N, 12.25%.

**4.7.1.9. (+)-(1*R*,4*S*)-1-(*p*-Fluorobenzyl)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazolino-3,6-dione 12e.** Mp: 168–171 °C (ethyl ether); yield 36%; $[\alpha]_D^{25} = +175.3$ (*c* 0.31, $CHCl_3$); $\nu_{max}$ (NaCl) 3209, 3072, 2926, 1686, 1605, 1568, 1510 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.26 (1H, dd, $J = 1.4$ Hz, $J = 8.1$ Hz, H-7), 7.78 (1H, ddd, $J = 1.4$ Hz, $J = 7.0$ Hz, $J = 8.2$ Hz, H-9), 7.69 (1H, dd, $J = 1.1$ Hz, $J = 8.2$ Hz, H-10), 7.50 (1H, ddd, $J = 1.1$ Hz, $J = 7.0$ Hz, $J = 8.1$ Hz, H-8), 7.27 (2H, m, $J_{H-F} = 9.5$ Hz, H-3′ y 5′), 7.04 (2H, m, $J_{H-F} = 5.2$ Hz, H-2′ y 6′), 6,31 (1H, sa, NH), 5,40 (1H, q, $J = 7.2$ Hz, H-4), 4.78 (1H, dd, $J = 3.8$ Hz, $J = 9.6$ Hz, H-1), 4.01 (1H, dd, $J = 3.8$ Hz, $J = 14.9$ Hz, $CH_2$–Ar–F), 3.04 (1H, dd, $J = 9.6$ Hz, $J = 14.9$ Hz, $CH_2$–Ar–F), 1.58 (3H, d, $J = 7.2$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 169.3, 162.2 (d, $J = 247.0$ Hz), 160.2, 149.3, 146.6, 134.7, 131.1 (d, $J = 3.4$ Hz), 130.9 (d, $J = 8.0$ Hz), 127.4, 127.3, 126.8, 120.4, 116.1 (d, $J = 21.4$ Hz), 54.0, 52.0, 37.0, 16.9. $C_{19}H_{16}O_2N_3F$ requires: C, 67.65; H, 4.78; N, 12.46. Found: C, 66.55; H, 4.84; N, 12.21%.

**4.7.1.10. (+)-(1*R*,4*S*)-1-(*N*-Boc-3-indolylmethyl)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazolino-3,6-dione 12f.** Compound **12f** was obtained as a solid ($CH_2Cl_2$); mp: 108–110 °C ($CH_2Cl_2$); yield: 7%; $[\alpha]_D^{25} = +35.3$ (*c* 0.09, $CHCl_3$); $\nu_{max}$ (NaCl) 3214, 2978, 2929, 1732, 1689, 1606, 1570 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.30 (1H, dd, $J = 1.5$ Hz, $J = 8.0$ Hz, H-7), 8.19 (1H, da, $J = 7.9$ Hz, H-7′), 7.80 (1H, ddd, $J = 1.5$ Hz, $J = 6.6$ Hz, $J = 8.1$ Hz, H-9), 7.74 (1H, dd, $J = 1.3$ Hz, $J = 8.1$ Hz, H-10), 7.59 (1H, dd, $J = 1.0$ Hz, $J = 7.9$ Hz, H-4′), 7.58 (1H, d, $J = 2.4$ Hz, H-2′), 7.53 (1H, ddd, $J = 1.5$ Hz, $J = 6.6$ Hz, $J = 8.0$ Hz, H-8), 7.38 (1H, dt, $J = 1.0$ Hz, $J = 7.9$ Hz, H-6′), 7.27 (1H, dt, $J = 1.0$ Hz, $J = 7.9$ Hz, H-5′), 5.97 (1H, sa, NH), 5.45 (1H, q, $J = 7.2$ Hz, H-4), 4.89 (1H, dd, $J = 3.5$ Hz, $J = 10.5$ Hz, H-1), 4.21 (1H, ddd, $J = 1.1$ Hz, $J = 3.5$ Hz, $J = 15.1$ Hz, $CH_2$–Ar), 3.09 (1H, dd, $J = 10.5$ Hz, $J = 15.1$ Hz, $CH_2$–Ar), 1.68 (9H, s, $C(CH_3)_3$), 1.58 (3H, d, $J = 7.2$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.9, 160.2, 149.4, 149.2, 146.8, 135.8, 134.7, 129.3, 127.4, 126.8, 125.2, 124.9, 122.9, 120.4, 118.4, 115.7, 114.1, 84.2, 52.2, 51.8, 28.1, 27.8, 16.8. $C_{26}H_{26}O_4N_4$ requires: C, 68.11; H, 5.72; N, 12.22. Found: C, 68.43; H, 5.85; N, 12.09%.

**4.7.1.11. (+)-(1*S*,4*S*)-1-(*N*-Boc-3-indolylmethyl)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazolino-3,6-dione 13f.** Compound **13f** was obtained as a solid ($CH_2Cl_2$); mp: 189–191 °C ($CH_2Cl_2$); yield 28%; $[\alpha]_D^{25} = +84.6$ (*c* 0.24, $CHCl_3$); $\nu_{max}$ (NaCl) 3200, 2928, 1732, 1683, 1599, 1568 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J = 1.5$ Hz, $J = 8.1$ Hz, H-7), 8.14 (1H, da, $J = 8.2$ Hz, H-7′), 7.80 (1H, ddd, $J = 1.5$ Hz, $J = 7.0$ Hz, $J = 8.3$ Hz, H-9), 7.72 (1H, dd, $J = 1.3$ Hz, $J = 8.3$ Hz, H-10), 7.60 (1H, dd, $J = 1.2$ Hz, $J = 7.2$ Hz, H-4′), 7.56 (1H, s, H-2′), 7.51 (1H, ddd, $J = 1.2$ Hz, $J = 7.0$ Hz, $J = 8.1$ Hz, H-8), 7.33 (1H, dt, $J = 1.2$ Hz, $J = 8.2$ Hz, H-6′), 7.24 (1H, dt, $J = 1.2$ Hz, $J = 8.2$ Hz, H-5′), 6.48 (1H, da, $J = 3.4$ Hz, NH), 5.26 (1H, q, $J = 7.1$ Hz, H-4), 4.87 (1H, dt, $J = 3.5$ Hz, $J = 10.6$ Hz, H-1), 3.61 (1H, ddd, $J = 1.0$ Hz, $J = 3.5$ Hz, $J = 14.2$ Hz, $CH_2$–Ar), 3.16 (1H, dd, $J = 10.6$ Hz, $J = 14.2$ Hz, $CH_2$–Ar), 1.68 (3H, d, $J = 7.1$ Hz, $CH_3$), 1.65 (9H, s, $C(CH_3)_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.4, 160.4, 149.7, 149.3, 147.1, 135.5, 134.8, 129.4, 127.1, 126.9, 126.7, 124.9, 124.8, 122.9, 120.1, 118.6, 115.5, 114.2, 84.1, 56.7, 51.7, 34.6, 28.1, 19.3. $C_{26}H_{26}O_4N_4$ requires: C, 68.11; H, 5.72; N, 12.22. Found: C, 67.92; H, 5.63; N, 12.18%.

**4.7.2. Alkylation of 1b.** To a cold (−78 °C), magnetically stirred solution of **1b** (0.5 mmol) in dry THF (10 mL) was added, under argon, dropwise via syringe a solution of lithium hexamethyldisilazide in THF (1 M, 3.0 mL), followed after 10 min by a solution of the appropriate halide (1.0 mmol dissolved in THF (5 mL)). The reaction mixture was stirred at −78 °C for 3 d, quenched with drops of glacial acetic acid followed by a saturated aqueous solution of ammonium chloride (5 mL), and extracted with $CHCl_3$. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. Column chromatography of the residue on silica gel ($CH_2Cl_2$, unless otherwise mentioned) afforded traces of 1,1-dialkylated compounds, followed from the expected *anti*-1-alkyl compounds and small amounts of *syn*-1-alkyl derivatives.

**4.7.2.1. (+)-(1*S*,4*S*)-4-*iso*-Propyl-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 15a.** Compound **15a** was obtained (EtOAc) as a solid; mp: 161–163 °C (EtOAc); yield 46%; $[\alpha]_D^{25} = +82.9$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (NaCl) 2956, 2928, 1685, 1608, 1472, 1388, 1327 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.26 (1H, dd, $J = 1.3$ Hz, $J = 8.1$ Hz, H-7), 7.75 (1H, ddd, $J = 1.3$ Hz, $J = 7.0$ Hz, $J = 8.2$ Hz, H-9), 7.66 (1H, dd, $J = 1.3$ Hz, $J = 8.2$ Hz, H-10), 7.48 (1H, ddd, $J = 1.3$ Hz, $J = 7.0$ Hz, $J = 8.1$ Hz, H-8), 6.77 (1H, sa, NH), 5.30 (1H, dd, $J = 1.2$ Hz, $J = 8.5$ Hz, H-4), 4.76 (1H, q, $J = 6.6$ Hz, H-1), 2.29 (1H, m, $CH_3$–$CH$–$CH_3$), 1.74 (3H, d, $J = 6.6$ Hz, $CH_3$-(1)), 1.17 (3H, d, $J = 6.8$ Hz, $CH_3$–CH–$CH_3$), 1.04 (3H, d, $J = 6.8$ Hz, $CH_3$–CH–$CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.6, 160.9, 151.5, 146.9, 134.6, 127.4, 127.2, 127.1, 120.3, 61.4, 49.5, 31.3, 19.9, 19.1, 18.0. $C_{15}H_{17}O_2N_3$ requires: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.38; H, 6.28; N, 15.41%.

**4.7.2.2. (+)-(1*R*,4*S*)-1-Allyl-4-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 14b.** Compound **14b** was obtained (EtOAc–$CH_2Cl_2$, 3:7) as a solid; mp: 178–179 °C (EtOAc/$CH_2Cl_2$); yield 32%; $[\alpha]_D^{25} = +175.2$ (*c* 0.23, $CHCl_3$); $\nu_{max}$ (NaCl) 3262, 2978, 1683, 1605, 1568, 1470, 1386, 1331 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.26 (1H, dd, $J = 1.5$ Hz, $J = 8.0$ Hz, H-7), 7.76 (1H, ddd, $J = 1.5$ Hz, $J = 7.2$ Hz, $J = 8.3$ Hz, H-9), 7.65 (1H, dd, $J = 1.2$ Hz, $J = 8.3$ Hz, H-10), 7.48 (1H, ddd, $J = 1.2$ Hz, $J = 7.2$ Hz, $J = 8.0$ Hz, H-8), 6.24 (1H, sa, NH), 5.85 (1H, dddd, $J = 5.6$ Hz, $J = 8.9$ Hz, $J = 10.2$ Hz, $J = 17.0$ Hz, H-2′), 5.30 (3H, m, H-4 y 3′), 4.65 (1H, dd, $J = 3.7$ Hz, $J = 8.9$ Hz, H-1), 3.35 (1H, ddd, $J = 3.7$ Hz, $J = 5.4$ Hz, $J = 14.9$ Hz, H-1′), 2.61 (1H, dt, $J = 8.9$ Hz, $J = 14.9$ Hz, H-1′), 2.28 (1H, m, $J = 6.9$ Hz, $CH_3$ –$CH$–$CH_3$), 1.13 (3H, d, $J = 6.9$ Hz, $CH_3$–CH–$CH_3$), 1.04 (3H, d, $J = 6.9$ Hz, $CH_3$–CH–$CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.7, 160.9, 150.1, 147.6, 134.7, 132.6, 127.3, 127.2, 127.1, 121.0, 120.3, 61.1, 52.1, 36.6, 31.6, 19.9, 18.9. $C_{17}H_{19}O_2N_3$ requires: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.74; H, 6.35; N, 14.26%.

**4.7.2.3. (+)-(1*R*,4*S*)-1-Benzyl-4-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 14c.** Mp: 73–75 °C ($CH_2Cl_2$); yield 50%; $[\alpha]_D^{25} = +138.4$ (*c* 0.32, $CHCl_3$); $\nu_{max}$ (NaCl) 3207, 2965, 2932, 1688, 1605, 1570 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.28 (1H, ddd, $J = 0.8$ Hz, $J = 1.5$ Hz, $J = 8.1$ Hz, H-7), 7.76 (1H, ddd, $J = 1.5$ Hz, $J = 6.9$ Hz, $J = 8.3$ Hz, H-9), 7.74 (1H, dd, $J = 1.4$ Hz, $J = 8.3$ Hz, H-10), 7.51 (1H, ddd, $J = 1.4$ Hz, $J = 6.9$ Hz, $J = 8.1$ Hz, H-8), 7.33 (5H, m, Ar–H), 5.86 (1H, sa, NH), 5.28 (1H, dd, $J = 1.1$ Hz, $J = 7.8$ Hz, H-4), 4.85 (1H, dd, $J = 3.7$ Hz, $J = 10.5$ Hz, H-1), 4.11 (1H, dd, $J = 3.7$ Hz, $J = 14.5$ Hz, $CH_2$–Ar–H), 2.89 (1H, dd, $J = 10.5$ Hz, $J = 14.5$ Hz, $CH_2$–Ar–H), 2.26 (1H, m, $CH_3$–$CH$–$CH_3$), 1.07 (3H, d, $J = 6.9$ Hz, $CH_3$–CH–$CH_3$), 1.04 (3H, d, $J = 6.9$ Hz, $CH_3$–CH–$CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.5, 160.8, 150.4, 146.7, 135.5, 134.7, 129.5, 129.2, 127.8, 127.4, 127.3, 127.1, 120.4, 61.0, 54.4, 38.5, 31.7, 19.8, 18.8. $C_{21}H_{21}O_2N_3$ requires: C, 72.60; H, 6.09; N, 12.09. Found: C, 72.24; H, 6.29; N, 12.29%.

**4.7.2.4. (+)-(1*R*,4*S*)-4-*iso*-Propyl-1-*p*-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 14d.** Mp: 79 °C ($CH_2Cl_2$); yield 58%; $[\alpha]_D^{25} = +200.0$ (*c* 0.06, $CHCl_3$); $\nu_{max}$ (NaCl) 3209, 3063, 2967, 2929, 1683, 1606, 1471, 1387, 1330 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J = 1.3$ Hz, $J = 8.1$ Hz, H-7), 7.79 (1H, ddd, $J = 1.3$ Hz, $J = 7.0$ Hz, $J = 8.3$ Hz, H-9), 7.70 (1H, dd, $J = 1.2$ Hz, $J = 8.3$ Hz, H-10), 7.51 (1H, ddd, $J = 1.2$ Hz, $J = 7.0$ Hz, $J = 8.1$ Hz, H-8), 7.18 (4H, 't', $J = 8.3$ Hz, Ar–$CH_3$), 5.80 (1H, sa, NH), 5.28 (1H, dd, $J = 1.1$ Hz, $J = 7.8$ Hz, H-4), 4.81 (1H, dd, $J = 3.8$ Hz,

$J = 10.6$ Hz, H-1), 4.06 (1H, dd, $J = 3.8$ Hz, $J = 14.4$ Hz, *CH*$_2$–Ar–CH$_3$), 2.84 (1H, dd, $J = 10.6$ Hz, $J = 14.4$ Hz, *CH*$_2$–Ar–CH$_3$), 2.35 (3H, s, Ar–*CH*$_3$), 2.25 (1H, m, $J = 6.9$ Hz, CH$_3$–*CH*–CH$_3$), 1.07 (3H, d, $J = 6.9$ Hz, *CH*$_3$–CH–CH$_3$), 1.03 (3H, d, $J = 6.9$ Hz, CH$_3$–CH–*CH*$_3$); $\delta_C$ (62.5 MHz, CDCl$_3$) 167.5, 160.9, 150.5, 146.7, 137.6, 134.9, 132.3, 130.2, 129.1, 127.4, 120.4, 61.0, 54.4, 38.1, 31.8, 20.9, 19.8, 18.8. $C_{22}H_{23}O_2N_3$ requires: C, 73.11; H, 6.41; N, 11.63.Found: C, 72.65; H, 6.57; N, 11.08%.

**4.7.2.5. (+)-(1*S*,4*S*)-4-*iso*-Propyl-1-*p*-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 15d.** Mp: 82–84 °C (CH$_2$Cl$_2$); yield 5%; $[\alpha]_D^{25} = +73.7$ ($c$ 0.18, CHCl$_3$); $\nu_{max}$ (NaCl) 3246, 2954, 2824, 1686, 1607, 1471, 1389, 1329 cm$^{-1}$; $\delta_H$ (250 MHz, CDCl$_3$) 8.28 (1H, dd, $J = 1.3$ Hz, $J = 8.1$ Hz, H-7), 7.79 (1H, ddd, $J = 1.3$ Hz, $J = 7.1$ Hz, $J = 8.3$ Hz, H-9), 7.68 (1H, dd, $J = 1.3$ Hz, $J = 8.3$ Hz, H-10), 7.49 (1H, ddd, $J = 1.3$ Hz, $J = 7.1$ Hz, $J = 8.1$ Hz, H-8), 7.18 (4H, 't', $J = 8.4$ Hz, Ar–CH$_3$), 5.96 (1H, da, $J = 3.3$ Hz, NH), 5.21 (1H, dd, $J = 0.6$ Hz, $J = 7.2$ Hz, H-4), 4.71 (1H, dt, $J = 3.7$ Hz, $J = 11.6$ Hz, H-1), 3.65 (1H, dd, $J = 3.7$ Hz, $J = 13.4$ Hz, *CH*$_2$–Ar–CH$_3$), 3.01 (1H, dd, $J = 11.6$ Hz, $J = 13.4$ Hz, *CH*$_2$–Ar–CH$_3$), 2.71 (1H, m, CH$_3$–*CH*–CH$_3$), 2.34 (3H, s, Ar–*CH*$_3$), 1.21 (3H, d, $J = 6.9$ Hz, *CH*$_3$–CH–CH$_3$), 1.10 (3H, d, $J = 6.9$ Hz, CH$_3$–CH–*CH*$_3$); $\delta_C$ (62.5 MHz, CDCl$_3$) 166.6, 161.1, 150.2, 146.9, 137.4, 134.9, 132.5, 129.9, 129.3, 127.1, 126.8, 120.1, 59.9, 58.3, 43.0, 33.7, 21.1, 19.9, 19.5. $C_{22}H_{23}O_2N_3$ requires: C, 73.11; H, 6.41; N, 11.63.Found: C, 73.15; H, 6.38; N, 11.84%.

**4.7.2.6. (+)-(1*R*,4*S*)-1-*p*-Fluorobenzyl-4-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 14e.** Compound **14e** was obtained (EtOAc–CH$_2$Cl$_2$, 3:7) as a solid; mp: 64–66 °C (EtOAc/CH$_2$Cl$_2$); yield 48%; $[\alpha]_D^{25} = +119.0$ ($c$ 0.20, CHCl$_3$); $\nu_{max}$ (NaCl) 3207, 2965, 1687, 1606 cm$^{-1}$; $\delta_H$ (250 MHz, CDCl$_3$) 8.28 (1H, dd, $J = 1.3$ Hz, $J = 8.1$ Hz, H-7), 7.79 (1H, ddd, $J = 1.3$ Hz, $J = 7.0$ Hz, $J = 8.3$ Hz, H-9), 7.70 (1H, dd, $J = 1.3$ Hz, $J = 8.3$ Hz, H-10), 7.51 (1H, ddd, $J = 1.3$ Hz, $J = 7.0$ Hz, $J = 8.1$ Hz, H-8), 7.26 (2H, m, H-2′ y 6′), 7.06 (2H, m, H-3′ y 5′), 5.91 (1H, sa, NH), 5.28 (1H, dd, $J = 1.1$ Hz, $J = 7.8$ Hz, H-4), 4.82 (1H, dd, $J = 3.7$ Hz, $J = 10.2$ Hz, H-1), 4.05 (1H, dd, $J = 3.7$ Hz, $J = 14.6$ Hz, *CH*$_2$–Ar–F), 2.92 (1H, dd, $J = 10.2$ Hz, $J = 14.6$ Hz, *CH*$_2$–Ar–F), 2.26 (1H, m, CH$_3$–*CH*-CH$_3$), 1.08 (3H, d, $J = 6.9$ Hz, *CH*$_3$–CH–CH$_3$), 1.04 (3H, d, $J = 6.9$ Hz, CH$_3$–CH–*CH*$_3$); $\delta_C$ (62.5 MHz, CDCl$_3$) 167.5, 162.3 (d, $J = 246.9$ Hz), 160.8, 150.1, 146.6, 134.8, 131.2 (d, $J = 3.3$ Hz), 130.8 (d, $J = 8.1$ Hz), 127.5, 127.3, 127.2, 120.4, 116.3 (d, $J = 21.5$ Hz), 60.9, 54.4, 37.6, 31.7, 19.8, 18.8. $C_{21}H_{20}O_2N_3$ F requires: C, 69.03; H, 5.52; N, 11.50.Found: C, 68.67; H, 5.81; N, 11.39%.

**4.7.2.7. (+)-(1*S*,4*S*)-1-*p*-Fluorobenzyl-4-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 15e.** Compound **15e** was obtained (EtOAc–CH$_2$Cl$_2$, 3:7) as a solid; yield 3%; $[\alpha]_D^{25} = +18.0$ ($c$ 0.20, CHCl$_3$); $\nu_{max}$ (NaCl) 3221, 2965, 1687, 1601, 1510 cm$^{-1}$; $\delta_H$ (250 MHz, CDCl$_3$) 8.28 (1H, dd, $J = 1.3$ Hz, $J = 8.1$ Hz, H-7), 7.79 (1H, ddd, $J = 1.3$ Hz, $J = 7.1$ Hz, $J = 8.5$ Hz, H-9), 7.67 (1H, dd, $J = 1.3$ Hz, $J = 8.5$ Hz, H-10), 7.50 (1H, ddd, $J = 1.3$ Hz, $J = 7.1$ Hz, $J = 8.1$ Hz, H-8), 7.27 (2H, m, H-3′ y 5′), 7.08 (2H, m, H-2′ y 6′), 5.95 (1H, sa, NH), 5.19 (1H, dd, $J = 0.8$ Hz, $J = 7.5$ Hz, H-4), 4.71 (1H, dt, $J = 3.7$ Hz, $J = 11.4$ Hz, H-1), 3.66 (1H, dd, $J = 3.7$ Hz, $J = 13.6$ Hz, *CH*$_2$–Ar–F), 3.05 (1H, dd, $J = 11.4$ Hz, $J = 13.6$ Hz, *CH*$_2$–Ar–F), 2.25 (1H, m, $J = 7.0$ Hz, CH$_3$ –*CH*–CH$_3$), 1.21 (3H, d, $J = 7.0$ Hz, *CH*$_3$–CH–CH$_3$), 1.10 (3H, d, $J = 7.0$ Hz, CH$_3$–CH–*CH*$_3$).

**4.7.2.8. (+)-(1*R*,4*S*)-1-(*N*-Boc-3-indolylmethyl)-4-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 14f.** Mp: 149–151 °C (CH$_2$Cl$_2$); yield 20%; $[\alpha]_D^{25} = +56.7$ ($c$ 0.06, CHCl$_3$); $\nu_{max}$ (NaCl) 3240, 2971, 1734, 1685, 1606 cm$^{-1}$; $\delta_H$ (250 MHz, CDCl$_3$) 8.32 (1H, dd, $J = 1.5$ Hz, $J = 8.1$ Hz, H-7), 8.22 (1H, da, $J = 7.7$ Hz, H-7′), 7.83 (1H, ddd, $J = 1.5$ Hz, $J = 6.7$ Hz, $J = 8.2$ Hz, H-9), 7.77 (1H, dd, $J = 1.4$ Hz, $J = 8.2$ Hz, H-10), 7.63 (1H, d, $J = 7.7$ Hz, H-4′), 7.59 (1H, s, H-2′), 7.55 (1H, ddd, $J = 1.4$ Hz, $J = 6.7$ Hz, $J = 8.1$ Hz, H-8), 7.41 (1H, dt, $J = 1.2$ Hz, $J = 7.7$ Hz, H-6′), 7.30 (1H, dt, $J = 1.2$ Hz, $J = 7.7$ Hz, H-5′), 5.97 (1H, sa, NH), 5.32 (1H, dd, $J = 1.0$ Hz, $J = 6.8$ Hz, H-4), 4.96 (1H, dd, $J = 3.5$ Hz, $J = 10.5$ Hz, H-1), 4.20 (1H, ddd, $J = 1.0$ Hz, $J = 3.5$ Hz, $J = 15.0$ Hz, *CH*$_2$–Ar), 3.06 (1H, dd, $J = 10.5$ Hz, $J = 15.0$ Hz, *CH*$_2$–Ar), 2.25 (1H, m, CH$_3$–*CH*–CH$_3$), 1.69 (9H, s, C(*CH*$_3$)$_3$), 1.07 (3H, d, $J = 6.5$ Hz, *CH*$_3$–CH–CH$_3$), 1.05 (3H, d, $J = 6.5$ Hz, CH$_3$–CH–*CH*$_3$); $\delta_C$ (62.5 MHz, CDCl$_3$) 167.4, 160.8, 150.3, 146.7, 135.9, 134.8, 129.5, 127.5, 127.4, 127.2, 125.2, 124.9, 123.0, 120.4, 118.5, 115.8, 114.3, 84., 61.1 (C-1), 52.3, 31.7, 29.2, 28.2, 19.8, 18.9. $C_{28}H_{30}O_4N_4$ requires: C, 69.12; H, 6.21; N, 11.51.Found: C, 68.96; H, 6.12; N, 11.38%.

**4.7.2.9. (+)-(1*S*,4*S*)-1-(*N*-Boc-3-indolylmethyl)-4-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 15f.** Compound **15f** was obtained (EtOAc–CH$_2$Cl$_2$, 3:7) as a solid; mp: 111–113 °C (CH$_2$Cl$_2$); yield 35%; $[\alpha]_D^{25} = +47.9$ ($c$ 0.14, CHCl$_3$); $\nu_{max}$ (NaCl) 3271, 2976, 1685, 1606 cm$^{-1}$; $\delta_H$ (250 MHz, CDCl$_3$) 8.29 (1H, dd, $J = 1.5$ Hz, $J = 8.2$ Hz, H-7), 8.17 (1H, da, $J = 7.6$ Hz, H-7′), 7.81 (1H, ddd, $J = 1.5$ Hz, $J = 6.9$ Hz, $J = 8.3$ Hz, H-9), 7.73 (1H, dd, $J = 1.3$ Hz, $J = 8.3$ Hz, H-10), 7.69 (1H, dd, $J = 1.3$ Hz, $J = 6.8$ Hz, H-4′), 7.56 (1H, s, H-2′), 7.51 (1H, ddd, $J = 1.3$ Hz, $J = 6.9$ Hz, $J = 8.2$ Hz, H-8), 7.37 (1H, dt, $J = 1.3$ Hz, $J = 7.4$ Hz, H-6′), 7.29 (1H, dt, $J = 1.3$ Hz, $J = 7.4$ Hz, H-5′), 6.05 (1H, da, $J = 3.6$ Hz, NH), 5.22 (1H, d, $J = 6.4$ Hz, H-4), 4.91 (1H, dt, $J = 3.6$ Hz, $J = 11.4$ Hz, H-1), 3.83 (1H, dd, $J = 3.6$ Hz, $J = 14.1$ Hz, *CH*$_2$–Ar), 3.19 (1H, dd, $J = 11.4$ Hz, $J = 14.1$ Hz, *CH*$_2$–Ar), 2.29 (1H, m, CH$_3$–*CH*–CH$_3$), 1.68 (9H, s, C(*CH*$_3$)$_3$ ), 1.21 (3H, d, $J = 6.9$ Hz, *CH*$_3$–CH–CH$_3$), 1.12 (3H, d, $J = 6.9$ Hz, CH$_3$–CH–*CH*$_3$); $\delta_C$ (62.5 MHz, CDCl$_3$) 166.3, 161.0, 150.2, 149.4, 147.0, 134.9, 129.4, 127.2, 126.8, 125.1, 124.8, 123.0, 120.1, 118.8, 115.7, 114.6, 84.2, 59.9, 56.5, 33.8, 33.7, 28.2, 19.9, 19.3. $C_{28}H_{30}O_4N_4$ requires: C, 69.12; H, 6.21; N,11.51.Found: C, 69.01; H, 6.11; N, 11.39%.

**4.7.3. Alkylation with gramine methiodide.** To a cold (−78 °C), magnetically stirred solution of **1a**,**b** (0.5 mmol) in dry THF (10 mL) was added, under argon, dropwise via syringe a solution of lithium hexamethyldisilazide in THF (1 M, 3.0 mL). After 10 min this solution was added dropwise over a solution of the gramine methiodide (1.0 mmol dissolved in THF (15 mL)). The reaction mixture was stirred at −78 °C for 16 h (**1a**) or for 3 d (**1b**), quenched with drops of glacial acetic acid followed by a saturated aqueous solution of ammonium chloride (5 mL), and extracted with $CHCl_3$. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. Column chromatography of the residue on silica gel (EtOAc–$CH_2Cl_2$, 6:4 (**1a**) or 3:7 (**1b**)) afforded the expected *anti*-1-indolylmethyl compounds and smaller amounts of its *syn*-isomers.

**4.7.3.1. (+)-(1*R*,4*S*)-1-(3-Indolylmethyl)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 12g.** Mp: 109–111 °C (EtOAc/$CH_2Cl_2$); yield 23%; $[\alpha]_D^{25} = +30.6$ (*c* 0.16, $CHCl_3$); $\nu_{max}$ (NaCl) 3282, 1684 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.17 (1H, dd, *J* = 1.4 Hz, *J* = 8.1 Hz, H-7), 7.74 (1H, ddd, *J* = 1.4 Hz, *J* = 6.9 Hz, *J* = 8.2 Hz, H-9), 7.69 (1H, dd, *J* = 1.1 Hz, *J* = 8.2 Hz, H-10), 7.52 (1H, d, *J* = 8.0 Hz, H-4′), 7.45 (1H, ddd, *J* = 1.1 Hz, *J* = 6.9 Hz, *J* = 8.1 Hz, H-8), 7.34 (1H, d, *J* = 8.0 Hz, H-7′), 7.12 (1H, dt, *J* = 1.0 Hz, *J* = 8.0 Hz, H-6′), 7.11 (1H, s, H-2′), 7.00 (1H, dt, *J* = 1.0 Hz, *J* = 8.0 Hz, H-5′), 5.24 (1H, q, *J* = 7.2 Hz, H-4), 4.82 (1H, dd, *J* = 3.5 Hz, *J* = 10.0 Hz, H-1), 4.11 (1H, dd, *J* = 3.5 Hz, *J* = 14.9 Hz, *CH*$_2$–Ar), 3.10 (1H, dd, *J* = 10.0 Hz, *J* = 14.9 Hz, *CH*$_2$–Ar), 1.47 (3H, d, *J* = 7.2 Hz, *CH*$_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 169.0, 160.5, 149.8, 146.8, 136.7, 134.8, 127.3, 126.5, 124.0, 122.2, 120.2, 119.4, 118.0, 111.6, 108.2, 52.4, 52.1, 28.2, 16.7. $C_{21}H_{18}O_2N_4$ requires: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.38; H, 5.38; N, 15.89%.

**4.7.3.2. (+)-(1*S*,4*S*)-1-(3-Indolylmethyl)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 13g.** Mp: 215 °C (EtOAc/$CH_2Cl_2$); yield 11%; $[\alpha]_D^{25} = +6.9$(*c* 0.13, $CHCl_3$); $\nu_{max}$ (NaCl) 3264, 2925, 1682, 1596 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.29 (1H, sa, NH$^i$), 8.28 (1H, dd, *J* = 1.3 Hz, *J* = 8.0 Hz, H-7), 7.81 (1H, ddd, *J* = 1.3 Hz, *J* = 6.8 Hz, *J* = 8.2 Hz, H-9), 7.74 (1H, dd, *J* = 1.3 Hz, *J* = 8.2 Hz, H-10), 7.60 (1H, d, *J* = 7.8 Hz, H-4′), 7.51 (1H, ddd, *J* = 1.3 Hz, *J* = 6.8 Hz, *J* = 8.0 Hz, H-8), 7.37 (1H, d, *J* = 8.1 Hz, H-7′), 7.20 (1H, dt, *J* = 1.0 Hz, *J* = 7.2 Hz, H-6′), 7.12 (1H, d, *J* = 2.2 Hz, H-2′), 7.09 (1H, dt, *J* = 1.0 Hz, *J* = 7.9 Hz, H-5′), 6.33 (1H, da, *J* = 3.2 Hz, NH), 5.23 (1H, q, *J* = 7.1 Hz, H-4), 4.85 (1H, dt, *J* = 3.4 Hz, *J* = 10.1 Hz, H-1), 3.65 (1H, dd, *J* = 3.4 Hz, *J* = 14.3 Hz, *CH*$_2$–Ar), 3.28 (1H, dd, *J* = 10.1 Hz, *J* = 14.3 Hz, *CH*$_2$–Ar), 1.54 (3H, d, *J* = 7.1 Hz, *CH*$_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.5, 160.4, 150.9, 147.2, 136.2, 134.7, 127.0, 126.9, 126.7, 123.6, 122.6, 120.1, 120.0, 118.5, 111.4, 109.4, 57.2, 51.8, 34.8, 19.0. $C_{21}H_{18}O_2N_4$ requires: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.06; H, 5.31; N, 15.20%.

**4.7.3.3. (+)-(1*R*,4*S*)-1-(3-Indolylmethyl)-4-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 14g.** Mp: 64 °C (EtOAc/$CH_2Cl_2$); yield 24%; $[\alpha]_D^{25} = +66.2$ (*c* 0.07, $CHCl_3$); $\nu_{max}$ (NaCl) 3366, 1682 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.38 (1H, sa, NH$^i$), 8.30 (1H, ddd, *J* = 0.7 Hz, *J* = 1.5 Hz, *J* = 8.2 Hz, H-7), 7.80 (1H, ddd, *J* = 1.5 Hz, *J* = 6.5 Hz, *J* = 8.2 Hz, H-9), 7.76 (1H, dd, *J* = 1.9 Hz, *J* = 8.2 Hz, H-10), 7.65 (1H, d, *J* = 7.9 Hz, H-4′), 7.52 (1H, ddd, *J* = 1.9 Hz, *J* = 6.5 Hz, *J* = 8.2 Hz, H-8), 7.42 (1H, d, *J* = 7.9 Hz, H-7′), 7.25 (1H, dt, *J* = 1.1 Hz, *J* = 7.9 Hz, H-6′), 7.15 (1H, dt, *J* = 1.1 Hz, *J* = 7.9 Hz, H-5′), 7.13 (1H, d, *J* = 1.4 Hz, H-2′), 5.98 (1H, sa, NH-2), 5.29 (1H, dd, *J* = 1.1 Hz, *J* = 7.9 Hz, H-4), 4.94 (1H, dd, *J* = 3.7 Hz, *J* = 10.5 Hz, H-1), 4.22 (1H, ddd, *J* = 0.8 Hz, *J* = 3.7 Hz, *J* = 15.0 Hz, *CH*$_2$–Ar), 3.09 (1H, dd, *J* = 10.5 Hz, *J* = 15.0 Hz, *CH*$_2$–Ar), 2.24 (1H, hept, *J* = 6.8 Hz, $CH_3$–*CH*–$CH_3$), 1.05 (3H, d, *J* = 6.8 Hz, *CH*$_3$–CH–$CH_3$), 1.03 (3H, d, *J* = 6.8 Hz, $CH_3$–CH–*CH*$_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.4, 160.9, 150.7, 146.8, 136.7, 134.7, 127.4, 127.3, 127.1, 126.8, 123.7, 122.9, 120.4, 120.1, 118.4, 111.7, 109.4, 61.1, 52.7, 31.7, 28.8, 19.8, 18.8. $C_{23}H_{22}O_2N_4$ requires: C, 71.48; H, 5.74; N, 14.31. Found: C, 71.25; H, 5.83; N, 14.31%.

**4.7.3.4. (+)-(1*S*,4*S*)-1-(3-Indolylmethyl)-4-*iso*-propyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 15g.** Mp: 97 °C (EtOAc/$CH_2Cl_2$); yield 11%; $[\alpha]_D^{25} = +78.2$ (*c* 0.17, $CHCl_3$); $\nu_{max}$ (NaCl) 3326, 3269, 2926, 1682, 1600 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.48 (1H, sa, NH$^i$), 8.29 (1H, dd, *J* = 1.5 Hz, *J* = 8.2 Hz, H-7), 7.80 (1H, ddd, *J* = 1.5 Hz, *J* = 6.9 Hz, *J* = 8.2 Hz, H-9), 7.74 (1H, dd, *J* = 1.4 Hz, *J* = 8.2 Hz, H-10), 7.68 (1H, d, *J* = 7.8 Hz, H-4′), 7.50 (1H, ddd, *J* = 1.4 Hz, *J* = 6.9 Hz, *J* = 8.2 Hz, H-8), 7.37 (1H, d, *J* = 7.8 Hz, H-7′), 7.20 (1H, dt, *J* = 1.1 Hz, *J* = 7.8 Hz, H-6′), 7.12 (1H, dt, *J* = 1.1 Hz, *J* = 7.8 Hz, H-5′), 7.11 (1H, m, H-2′), 6.24 (1H, da, *J* = 3.3 Hz, NH-2), 5.20 (1H, dd, *J* = 0.7 Hz, *J* = 7.0 Hz, H-4), 4.80 (1H, dt, *J* = 3.4 Hz, *J* = 11.4 Hz, H-1), 3.84 (1H, dd, *J* = 3.4 Hz, *J* = 14.3 Hz, *CH*$_2$–Ar), 3.22 (1H, dd, *J* = 11.4 Hz, *J* = 14.3 Hz, *CH*$_2$–Ar), 2.27 (1H, hept, *J* = 6.9 Hz, $CH_3$–*CH*-$CH_3$), 1.19 (3H, d, *J* = 6.9 Hz, *CH*$_3$–CH–$CH_3$), 1.09 (3H, d, *J* = 6.9 Hz, $CH_3$–CH–*CH*$_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.7, 161.2, 150.5, 147.0, 136.4, 134.8, 127.1, 127.0, 126.9, 126.7, 123.6, 122.6, 120.1, 120.0, 118.5, 111.5, 109.8, 59.9, 57.2, 33.8, 19.9, 19.5. $C_{23}H_{22}O_2N_4$ requires: C, 71.48; H, 5.74; N, 14.31. Found: C, 71.36; H, 5.66; N, 14.24%.

**4.7.4. Alkylation of 2.** To a cold (−78 °C), magnetically stirred solution of **2** (0.5 mmol) and 0.1 mL (1 mmol) of DMI in dry THF (10 mL) was added, under argon, dropwise via syringe a solution of lithium hexamethyldisilazide in THF (1 M, 0.6 mL, 0.6 mmol), followed after 15 min by a solution of the appropriate halide (1.2 mmol dissolved in THF (5 mL)). The reaction mixture was stirred at −78 °C for 10 min (45 min for *p*-tolylbromide) and at 0 °C for 45 min (90 min for *p*-fluorobenzyl bromide and 3 h for *p*-tolyl bromide), quenched with ice followed by a saturated aqueous solution of ammonium chloride (5 mL), and extracted with $CHCl_3$. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. Column chromatography of the residue on silica gel (toluene/EtOAc 8:2) afforded traces of 1,1-dialkylated and 1,4-dialkylated compounds, followed by the *anti*-1-alkyl compounds (small amounts) and the expected *syn*-1-alkyl derivatives.

**4.7.4.1. (+)-(1*S*,4*S*)-1,4-Dimethyl-2-phenyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 17a.** Mp: 84–85 °C (ethyl ether); yield 42%; $[\alpha]_D^{25} = +12.4$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (KBr) 1686, 1606 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.30 (1H, dd, *J* = 1.5 Hz, *J* = 8.0 Hz, H-7), 7.76 (1H, ddd, *J* = 1.5 Hz, *J* = 8.4 Hz, *J* = 7.1 Hz, H-9), 7.68 (1H, dd, *J* = 1.1 Hz, *J* = 8.4 Hz, H-10), 7.50 (1H, ddd, *J* = 1.1 Hz, *J* = 7.1 Hz, *J* = 8.0 Hz, H-8), 7.47–7.30 (5H, m, Ar–H), 5.48 (1H, q, *J* = 7.1 Hz, H-4), 5.00 (1H, q, *J* = 7.1 Hz, H-1), 1.85 (3H, d, *J* = 7.1 Hz, $CH_3$-4), 1.73 (3H, d, *J* = 7.1 Hz, $CH_3$-1); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.8, 160.5, 151.8, 147,5, 138.9, 135.0, 129.9, 128.4, 127.6, 127.3, 127.0, 126.9, 120.4, 60.8, 52.7, 22.1, 19.5. $C_{19}H_{17}O_3N_2$ requires: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.28; H, 5.34; N, 12.82%.

**4.7.4.2. (+)-(1*S*,4*S*)-1-Allyl-4-methyl-2-phenyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 17b.** Mp: 122–124 °C (ethyl ether); yield 50%; $[\alpha]_D^{25} = +47.1$ (*c* 0.23, $CHCl_3$); $\nu_{max}$ (KBr) 3249, 2923, 1682, 1606 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.34 (1H, dd, *J* = 8.0 and 1.5 Hz, H-7), 7.80 (1H, ddd, *J* = 8.2, 7.0 and 1.5 Hz, H-9), 7.67 (1H, dd, *J* = 8.2 and 1.0 Hz, H-10), 7.53 (1H, ddd, *J* = 8.0, 7.0 and 1.0 Hz, H-8), 7.48-7.32 (5H, m, Ar–H), 5.73 (1H, ddt, *J* = 14.4, 9.8 and 7.3 Hz, H-2″), 5.45 (1H, q, *J* = 7.1 Hz, H-4), 5.09 (3H, m, 2H-3′, H-1), 2.95 (1H, m, H-1″), 2.75 (1H, m, H-1″), 1.92 (3H, d, *J* = 7.1 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.6, 160.4, 149.9, 147.0, 138.9, 134.8, 132.0, 129.6, 128.2, 127.5, 127.2, 127.0, 126.8, 120.3, 119.7, 64.4, 52.7, 40,2, 19.8. $C_{21}H_{19}N_3O_2$ requires: C, 73.03; H, 5.54; N, 12.17. Found: C, 72.98; H, 5.34; N, 12.22%.

**4.7.4.3. (+)-(1*R*,4*S*)-1-Allyl-4-methyl-2-phenyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18b.** Mp: 136–138 °C (ethyl ether); yield 7%; $[\alpha]_D^{25} = +32.2$ (*c* 0.65, $CHCl_3$); $\nu_{max}$ (KBr) 1683 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.32 (1H, dd, *J* = 8.0 and 1.5 Hz, H-7), 7.77 (1H, ddd, *J* = 8.4, 7.1 and 1.5 Hz, H-9), 7.69 (1H, dd, *J* = 8.4 and 1.2 Hz, H-10), 7.53 (1H, ddd, *J* = 8.0, 7.1 and 1.2 Hz, H-8), 7.52–7.30 (5H, m, Ar–H), 5.63 (1H, ddt, *J* = 17.1, 10.3 and 7.0 Hz, H-2″), 5.53 (1H, q, *J* = 7.0 Hz, H-4), 5.22 (1H, t, *J* = 4.1 Hz, H-1), 5.01 (1H, dd, *J* = 10.3 and 1.5 Hz, H-3″), 4.87 (1H, ddd, *J* = 17.1, 2.5 and 1.5 Hz, H-3″), 2.98 (1H, m, H-1″), 2.70 (1H, m, H-1″), 1.74 (3H, d, *J* = 7.0 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.8, 160.4, 149.5, 147.0, 137.8, 134.8, 131.2, 129.3, 128.3, 128.1, 127.3, 126.8, 120.4, 120.3, 60.3, 52.3, 36.1, 19.2. $C_{21}H_{19}N_3O_2$ requires: C, 73.03; H, 5.54; N, 12.17. Found: C, 72.79; H, 5.43; N, 12.02%.

**4.7.4.4. (+)-(1*S*,4*S*)-1-Benzyl-4-methyl-2-phenyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 17c.** Mp: 146–148 °C (ethyl ether); yield 57%; $[\alpha]_D^{25} = +79.5$ (*c* 0.15, $CHCl_3$); $\nu_{max}$ (KBr) 2923, 1679, 1600 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.29 (1H, dd, *J* = 1.5 Hz, *J* = 8.0 Hz, H-7), 7.79 (1H, ddd, *J* = 1.5 Hz, *J* = 7.2 Hz, *J* = 8.5 Hz, H-9), 7.62 (1H, dd, *J* = 1.1 and 8.5 Hz, H-10), 7.51 (1H, dd, *J* = 1,1 and 7.2 Hz, *J* = 8.0 Hz, H-8), 7.42 (2H, m, Ar–H), 7.34 (3H, m, Ar–H), 7.16 (3H, m, Ar–H), 5.42 (1H, t, *J* = 5.7 Hz, H-1), 5.26 (1H, q, *J* = 7.1 Hz, H-4), 3.49 (1H, dd, *J* = 5.8 and 13.9 Hz, $CH_2$–Ar), 3.71 (1H, dd, *J* = 5.6 and 13.9 Hz, $CH_2$–Ar), 1.18 (3H, d, *J* = 7.1 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.3, 160.2, 149.9, 147.0, 138.8, 135.0, 134.7, 129.8, 129.4, 128.7, 127.8, 127.5, 127.1, 127.0, 126.9, 126.7, 120.2, 65.6, 52.7, 41.0, 18.5. $C_{25}H_{21}N_3O_2$ requires: C, 75.93; H, 5.35; N, 10.63. Found: 75.68; H, 5.20; N, 10.45%.

**4.7.4.5. (+)-(1*R*,4*S*)-1-Benzyl-4-methyl-2-phenyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18c.** Mp: 128–130 °C (ethyl ether); yield 1%; $[\alpha]_D^{25} = -38.2$ (*c* 0.12, $CHCl_3$); $\nu_{max}$ (KBr) 2923, 1679, 1600 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.24 (1H, dd, *J* = 8.0 and 1.3 Hz, H-7), 7.77 (1H, ddd, *J* = 8.3, 7.0 and 1.3 Hz, H-9), 7.69 (1H, dd, *J* = 8.3 and 1.0 Hz, H-10), 7.44 (6H, m, Ar–H), 7.17 (3H, m, Ar–H), 6.85 (2H, m, Ar–H), 5.48 (1H, t, *J* = 4,3 Hz, H-1), 4.69 (1H, q, *J* = 6.9 Hz, H-4), 3.42 (1H, dd, *J* = 14.3 Hz, *J* = 4.3 Hz, $CH_2$–Ar), 3.27 (1H, dd, *J* = 14.3 Hz, *J* = 4.3 Hz, $CH_2$–Ar), 1.65 (3H, d, *J* = 6.9 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.7, 160.7, 150.3, 147.1, 138.6, 135.4, 134.2, 129.8, 129.7, 129.0, 128.5, 128.2, 127.8, 127.6, 127.5, 127.3, 121.0, 63.0, 52.9, 39.4, 19.7. $C_{25}H_{21}N_3O_2$ requires: C, 75.93; H, 5.35; N, 10.63. Found: C, 75.86; H, 5.28; N, 10.65%.

**4.7.4.6. (+)-(1*S*,4*S*)-4-Methyl-2-phenyl-1-(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 17d.** Mp: 100–101 °C (ethyl ether); yield 51%; $[\alpha]_D^{25} = +62.2$ (*c* 0.50, $CHCl_3$); $\nu_{max}$ (KBr) 1677, 1596 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.32 (1H, dd, *J* = 8.0 and 1.5 Hz, H-7), 7.82 (1H, ddd, *J* = 8.3, 7.2 Hz and 1.5 Hz, H-9), 7.66 (1H, dd, *J* = 8.3 and 1.0 Hz, H-10), 7.57–7.35 (6H, m, ArH), 6,97 (2H, d, *J* = 7,9 Hz, H-3″, H-5″), 6,84 (2H, d, *J* = 7,9 Hz, H-2″, H-6″), 5,42 (1H, t, *J* = 5.5 Hz, H-1), 5.28 (1H, q, *J* = 7.2 Hz, H-4), 3.48 (1H, dd, *J* = 14,0 and 5.5 Hz, $CH_2$–Ar), 3.20 (1H, dd, *J* = 14.0 and 5.5 Hz, $CH_2$–Ar), 2.26 (3H, s, $CH_3$), 1.23 (3H, d, *J* = 7.2 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 166.4, 160.3, 150.1, 147.0, 138.9, 134.8, 131.9, 129.8, 129.5, 129.4, 127.8, 127.2, 127.1, 126.9, 126.8, 120.3, 65.7, 52.8, 40.5, 21.0, 18.5. $C_{26}H_{23}O_2N_3$ requires: C, 76.26; H, 5.66; N, 10.26. Found: 76.22; H, 5.55; N, 9.81%.

**4.7.4.7. (−)-(1*R*,4*S*)-4-Methyl-2-phenyl-1-(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18d.** Mp: 70–72 °C (ethyl ether); yield 8%; $[\alpha]_D^{25} = -15.4$ (*c* 0.30, $CHCl_3$); $\nu_{max}$ (KBr) 1681, 1596 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.27 (1H, dd, *J* = 8.0 and 1.5 Hz, H-7), 7.81 (1H, ddd, *J* = 8.3, 7.1 and 1.5 Hz, H-9), 7.71 (1H, dd, *J* = 8.3 and 1.1 Hz, H-10), 7.52–7.38 (6H, m, Ar–H), 6.95 (2H, d, *J* = 7.8 Hz, H-3″,H-5″), 6.71 (2H, d, *J* = 7.8 Hz, H-2″, H-6″), 5.45 (1H, 't', *J* = 4.2 Hz, H-1), 4.64 (1H, 'q', *J* = 6.8 Hz, H-4), 3.32 (1H, dd, *J* = 14.2 and 4.3 Hz, $CH_2$–Ar), 3.22 (1H, dd, *J* = 14.2 and 4.3 Hz, $CH_2$–Ar), 2.28 (3H, s, $CH_3$), 1.64 (3H, d, *J* = 6.8 Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.2, 160.3, 150.0, 146.7, 138.3, 137.2, 134.7, 131.5, 129.4, 129.3, 129.2, 128.0, 127.7, 127.2, 127.0, 126.8, 120.6, 62.8, 52.5, 38.9, 21.0, 19.4 Found: C, 75.97; H, 5,81; N, 10,02, $C_{26}H_{23}O_2N_3$ requires: C, 76.26; H, 5,66; N, 10,26%.

**4.7.4.8. (+)-(1*S*,4*S*)-1(*p*-Fluorobenzyl)-4-methyl-2-phenyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 17e.** Mp: 77–78 °C (ethyl ether); yield 56%; $[\alpha]_D^{25} = +52.8$ ($c$ 0.50, $CHCl_3$); $\nu_{max}$ (KBr) 1680, 1601 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J = 8.1$ and $J = 1.5$ Hz, H-7), 7.76 (1H, ddd, $J = 8.4$, 7.2 and 1.5 Hz, H-9), 7.59 (1H, dd, $J = 8.4$ and 1.0 Hz, H-10), 7.51 (1H, ddd, $J = 8.1$, 7.2 and 1.0 Hz, H-8), 7.45–7.26 (6H, m, F–Ar–H), 6.85 (3H, m, Ar–H), 5.36 (1H, t, $J = 5.9$ Hz, H-1), 5.32 (1H, q, $J = 7.1$ Hz, H-4), 3.43 (1H, dd, $J = 14.0$ and 5.8 Hz, $CH_2$–Ar–F), 3.23 (1H, dd, $J = 14.0$ and $J = 5.9$ Hz, $CH_2$–Ar–F), 1.38 (3H, d, $J = 7.1$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.2, 161.8 (d, $J = 24{,}5$ Hz, C-4″), 161.1, 150.6, 147.8, 139.7, 135.7, 132.2 (d, $J = 8{,}0$ Hz, C-2″, C-6′), 127.7, 131.9 (d, $J = 3.5$ Hz, C-1″), 130.5, 128.7, 128.1, 127.9, 127.7, 121.0, 116.5 (d, $J = 21.4$ Hz, C-3″,C-5″), 66.0, 53.1, 40,9, 19,3. $C_{25}H_{20}$ $FN_3O_2$ requires: C, 72.63; H, 4.60; N, 10.16. Found: C, 72.29; H, 4.57; N, 10.39%.

**4.7.5. Alkylation of 3 and 4.** To a cold (−78 °C), magnetically stirred solution of **3** or **4** ($c$ 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 after 10 min by a solution of the appropriate halide (0.5 mmol dissolved in THF (5 mL)). The reaction mixture was stirred at −78 °C for 10 min and 30 min at 0 °C (10 min for methyl iodide and 45 min for **4**), quenched with ice and extracted 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, 8:2 unless otherwise mentioned) afforded the *anti*-1-alkyl and *syn*-1-alkyl derivatives.

**4.7.5.1. (+)-(1′*R*,1*S*,4*S*)-1,4-Dimethyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19a.** White oil,($CH_2Cl_2$/EtOAc, 95:5); yield 76%; $[\alpha]_D^{25} = +120$ ($c$ 0.30, $CHCl_3$); $\nu_{max}$ (NaCl) 1682, 1660 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.18 (1H, dd, $J = 8.0$ and 1.5 Hz, H-7), 7.68 (1H, ddd, $J = 8.4$, 6.9 and 1.5 Hz, H-9), 7.54 (1H, d, $J = 7.7$ Hz, H-10), 7.36 (6H, m, Ar–H and H-8), 6.05 (1H, q, $J = 7.1$ Hz, H-4), 5.34 (1H, q, $J = 7.2$ Hz, H-1), 4.61 (1H, q, $J = 7.0$ Hz, H-7), 1.69 (3H, d, $J = 7.1$ Hz, $CH_3$), 1.55 (3H, d, $J = 7.2$ Hz, $CH_3$), 0.92 (3H, d, $J = 7.0$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.2, 160.4, 152.7, 147.4, 139.4, 134.8, 128.9, 128.4, 128.2, 127.1, 126.9, 120.3, 53.1, 52.9, 51.3, 44.8, 23.3, 18.6, 16.2. $C_{21}H_{21}O_2N_3$ requires: C, 72.60; H, 6.09; N, 12.09. Found: C, 72.43; H, 6.21; N, 12.32%.

**4.7.5.2. (+)-(1′*R*,1*S*,4*S*)-1-Allyl-4-methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19b.** White oil, yield 36%; $[\alpha]_D^{25} = +109.4$ ($c$ 0.27, $CHCl_3$); $\nu_{max}$ (NaCl) 1682, 1662 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.23 (1H, dd, $J = 7.7$ and 1.4 Hz, H-7), 7.73 (1H, ddd, $J = 8.3$, 6.8 and 1.4 Hz, H-9), 7.63 (1H, d, $J = 8.3$ Hz, H-10), 7.42 (6H, m, Ar–H and H-8), 6.04 (1H, q, $J = 7.1$ Hz, H-1′), 5.47 (1H, m, H-2″), 5.34 (1H, q, $J = 7.0$ Hz, H-4), 4.83 (1H, ddd, $J = 10.2$, 2.7 and 1.5 Hz, H-3′), 4.53 (1H, ddd, $J = 17.2$, 2.7 and 1.5 Hz, H-3′), 4.48 (1H, dd, $J = 10.2$ and 4.1 Hz, H-1), 1.77 (3H, d, $J = 7.1$ Hz, $CH_3$), 1.72 (2H, m, $CH_2$), 1.59 (3H, d, $J = 7.1$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.4, 160.7, 150.3, 147.0, 139.1, 134.7, 132.2, 129.0, 128.6, 128.5, 128.3, 128.0, 127.0, 126.7, 120.4, 118.5, 57.4, 52.9, 53.2, 51.9, 41.4, 18.9, 16.4. $C_{23}H_{23}O_2N_3$ requires: C, 73.97; H, 6.21; N, 11.25. Found: C, 73.78; H, 6.41; N, 11.45%.

**4.7.5.3. (+)-(1′*R*,1*R*,4*S*)-1-Allyl-4-methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 20b.** White oil, yield 5%; $[\alpha]_D^{25} = +102$ ($c$ 0.16, $CHCl_3$); $\nu_{max}$ (NaCl) 1682, 1662 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.21 (1H, dd, $J = 8.0$ and 1.5 Hz, H-7), 7.71 (1H, ddd, $J = 8.4$, 6.9 and 1.5 Hz, H-9), 7.52 (1H, d,d, $J = 8.4$ and 1.2 Hz, H-10), 7.44 (1H, ddd, $J = 8.0$, 6.9 and 1.2, H-8), 7.37 (5H, m, Ar–H), 5.76 (1H, q, $J = 7.2$ Hz, H-1′), 5.52 (1H, ddd, $J = 17.0$, 10.2 and 7.9 Hz, H-2″), 5.11 (1H, q, $J = 6.6$ Hz, H-4), 5.01 (1H, ddd, $J = 10.2$, 2.5 and 1.4 Hz, H-3″), 4.83 (1H, ddd, $J = 17.0$, 2.5 and 1.4 Hz, H-3″), 4.46 (1H, dd, $J = 4.9$ and 3.1 Hz, H-1), 2.76 (1H, ddd, $J = 14.3$, 6.0 and 4.9 Hz, H-1″), 2.64 (1H, ddd, $J = 14.3$, 7.9 and 3.1 Hz, H-2″), 1.80 (3H, d, $J = 7.2$ Hz, $CH_3$), 1.73 (3H, d, $J = 6.6$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.8, 160.5, 150.7, 146.8, 138.5, 134.8, 129.8, 128.9, 128.2, 127.6, 126.9, 126.8, 126.6, 121.8, 120.4, 54.3, 53.1, 41.5, 21.0, 17.9. $C_{21}H_{21}O_2N_3$ requires: C, 73.97; H, 6.21; N, 11.25. Found: C, 73.69; H, 6.10; N, 11.30%.

**4.7.5.4. (+)-(1′*R*,1*S*,4*S*)-1-Benzyl-4-methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19c.** White oil, yield 43%; $[\alpha]_D^{25} = +120$ ($c$ 0.27, $CHCl_3$); $\nu_{max}$ (NaCl) 1684, 1661 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.23 (1H, dd, $J = 8.0$ and 1.2 Hz, H-7), 7.66 (1H, ddd, $J = 8.4$, 6.9 and 1.5 Hz, H-9), 7.58 (1H, d, $J = 8.4$ Hz, H-10), 7.40 (6H, m, Ar–H and H-8), 7.10 (3H, m, H-2″, H-4″, H-6″), 6,50 (2H, dd, $J = 7.4$ and 1.2 Hz, H-2″, H-5″), 6.02 (1H, q, $J = 7.0$ Hz, H-1′), 5.32 (1H, q, $J = 7.2$ Hz, H-4), 4.65 (1H, dd, $J = 9.4$ and 4.5 Hz, H-1), 2.68 (1H, dd, $J = 13.5$ and 9.4 Hz, $CH_2$), 2.48 (1H, dd, $J = 13.5$ and 4.5 Hz, $CH_2$), 1.64 (3H, d, $J = 7.0$ Hz, $CH_3$), 1.62 (3H, d, $J = 7.2$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.5, 160.7, 149.7, 146.8, 139.2, 135.5, 134.7, 129.2, 129.0, 128.5, 128.2, 127.8, 126.9, 126.8, 126.4, 120.3, 59.3, 53.4, 52.7, 43.0, 18.5, 16.7. $C_{27}H_{25}O_2N_3$ requires: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.68; H, 6.22; N, 10.21%.

**4.7.5.5. (+)-(1′*R*,1*R*,4*S*)-1-Benzyl-4-methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 20c.** White oil, yield 14%; $[\alpha]_D^{25} = +127$ ($c$ 0.20, $CHCl_3$); $\nu_{max}$ (NaCl) 1684, 1660 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.14 (1H, dd, $J = 8.0$ and 1.5 Hz, H-7), 7.73 (1H, ddd, $J = 8.4$, 6.9 and 1.5 Hz, H-9), 7.55 (1H, d, $J = 8.4$ Hz, H-10), 7.44 (1H, ddd, $J = 8.0$, 6,9 and 1.1 Hz, H-8), 7.38 (4H, m, Ar–H), 7.20 (2H, m, ArH), 7.10 (2H, m, ArH), 6,65 (2H, m, ArH), 5.90 (1H, q, $J = 7.2$ Hz, H-1′), 4.71 (1H, t, $J = 3.7$ Hz, H-1), 3.67 (1H, q, $J = 6{,}6$ Hz, H-4), 3.31 (1H, dd, $J = 13.6$ and 3.8 Hz, $CH_2$), 3.16 (1H, dd, $J = 13.6$ and 3.6 Hz, $CH_2$), 1.97 (3H, d, $J = 7.2$ Hz, $CH_3$), 1.51 (3H, d, $J = 6.6$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.3.4, 160.4, 150.4, 146.6, 139.5, 134.6, 133.6, 129.8, 129.0, 128.5, 128.2, 127.9, 127.4, 126.7, 126.6, 126.4, 120.7, 58.1, 54.3, 52.9, 44.0, 20.4, 18.7. $C_{27}H_{25}O_2N_3$ requires: C, 76.57; H, 5.95; N, 9.92%. Found: C, 76.46; H, 5.78; N, 10.13%.

**4.7.5.6. (+)-(1′*R*,1*S*,4*S*)-1-*p*-Fluorophenylmethyl-4-methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione 19d.** White oil, (ethyl ether/hexane 8:2); yield 72%; $[\alpha]_D^{25} = +123.7$ (*c* 0.27, $CHCl_3$); $\nu_{max}$ (NaCl) 1684, 1661 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.24 (1H, dd, $J = 8.0$ and 1.4 Hz, H-7), 7.67 (1H, ddd, $J = 8.6$, 7.0 and 1.4 Hz, H-9), 7.58 (1H, d, $J = 8.6$ Hz, H-10), 7.46 (6, m, Ar–H and H-8), 6.72 (2H, t, $J = 8.6$ Hz, H-3″, H-5″), 6.41 (2H, dd, $J = 8.6$ and 5.3 Hz, H-2″, H-6″), 6.08 (1H, q, $J = 7.1$ Hz, H-1′), 5.34 (1H, q, $J = 7.2$ Hz, H-4), 4.57 (1H, dd, $J = 9.9$ and 4.2 Hz, H-1), 2.65 (1H, dd, $J = 13.7$ and 9.9 Hz, $CH_2$), 2.39 (1H, dd, $J = 13.7$ and 4.2 Hz, $CH_2$), 1.71 (3H, d, $J = 7.2$ Hz, $CH_3$), 1.61 (3H, d, $J = 7.1$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.5, 165.2, 160.7, 149.3, 146.7, 139.1, 134.8, 131.3, 130.9, 129.1, 128.8, 128.1, 127.2, 127.0, 126.7, 120.1, 115.2, 59.0, 53.3, 52.3, 42.2, 18.7, 16.6. $C_{27}H_{24}O_2N_3F$ requires: C, 73.45; H, 5,48; N, 9,52. Found: C, 73.71; H, 5.71; N, 9.77%.

**4.7.5.7. (+)-(1′*R*,1*R*,4*S*)-1-*p*-Fluorophenylmethyl-4-methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione 20d.** White solid, (ethyl ether/hexane, 8:2); mp: 118–120 °C; yield 9%; $[\alpha]_D^{25} = +92$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (KBr) 1671, 1658 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.15 (1H, dd, $J = 8.0$ and 1.4 Hz, H-7), 7.73 (1H, ddd, $J = 8.4$, 6.9 and 1.4 Hz, H-9), 7.54 (1H, d, $J = 8.4$ Hz, H-10), 7.44 (1H, ddd, $J = 8.0$, 6.9 and 1.1 Hz, H-8), 7.38 (5H, m, Ar–H), 6.80 (2H, t, $J = 8.6$ Hz, H-3″, H-5″), 6.61 (2H, dd, $J = 8.6$ and 5.3 Hz, H-2″, H-6″), 5.87 (1H, q, $J = 7.2$ Hz, H-1′), 4.69 (1H, t, $J = 3.8$ Hz, H-3′), 3.86 (1H, q, $J = 6.6$ Hz, H-4), 3.27 (1H, dd, $J = 13.8$ and 4.0 Hz, $CH_2$), 3.15 (1H, dd, $J = 13.8$ and 3.6 Hz, $CH_2$), 1.95 (3H, d, $J = 7.2$ Hz, $CH_3$), 1.54 (3H, d, $J = 6.6$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 168.2, 162.4, 160.3, 150.1, 146.6, 139.4, 134.7, 131.5, 129.2, 128.4, 127.6, 127.0, 126.8, 126.7, 120.6, 115.8, 58.3, 54.5, 52.9, 43.0, 20.5, 18.7. $C_{27}H_{24}O_2N_3F$ requires: C, 73.45; H, 5.48; N, 9.52. Found: C, 73.62; H, 5.63; N, 9.68%.

**4.7.5.8. (+)-(1′*S*,1*S*,4*S*)-1-Benzyl-4-methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 21.** White oil, yield 46%; $[\alpha]_D^{25} = +27.3$ (*c* 0.33, $CHCl_3$); $\nu_{max}$ (NaCl) 1682, 1659 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.23 (1H, dd, $J = 8.2$ and 1.3 Hz, H-7), 7.65 (1H, ddd, $J = 8.2$, 7.1 and 1.3 Hz, H-9), 7.43 (1H, ddd, $J = 8.1$, 7.1 and 1.1 Hz, H-8), 7.35 (1H, d, $J = 8.1$ Hz, H-10), 7.26 (5H, m, Ar–H), 7.18 (3H, m, ArH), 6.98 (2H, m, ArH), 5.91 (1H, q, $J = 7.2$ Hz, H-1′), 5.32 (1H, q, $J = 7.2$ Hz, H-4), 4.54 (1H, dd, $J = 7.7$ and 4.8 Hz, H-1), 3.38 (1H, dd, $J = 14.0$ and 4.8 Hz, $CH_2$), 3.24 (1H, dd, $J = 14.0$ and 7.7 Hz, $CH_2$), 1.75 (3H, d, $J = 7.2$ Hz, $CH_3$), 1.53 (3H, d, $J = 7.2$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.9, 160.6, 150.1, 147.0, 138.8, 135.8, 134.6, 129.6, 129.1, 128.8, 128.4, 128.3, 127.6, 127.0, 125.4, 120.3, 59.5, 53.6, 53.0, 44.1, 18.5, 18.3. $C_{27}H_{25}O_2N_3$ requires: C, 76.50; H, 5.90; N, 9.91. Found: C, 76.71; H, 6.14; N, 10.19%.

**4.7.5.9. (−)-(1′*S*,1*R*,4*S*)-1-Benzyl-4-methyl-2-(1′-phenylethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 22.** White oil, yield 14%; $[\alpha]_D^{25} = -42.4$ (*c* 0.25, $CHCl_3$); $\nu_{max}$ (NaCl) 1686, 1657, 1599 cm$^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 8.15 (1H, dd, $J = 8.0$ and 1.2 Hz, H-7), 7.76 (1H, ddd, $J = 8.3$, 7.1 and 1.5 Hz, H-9), 7.62 (1H, d, $J = 7.7$ Hz, H-10), 7.43 (6H, m, Ar–H and H-8), 7.15 (4H, m, Ar–H), 7.03 (2H, m, ArH), 6.42 (2H, m, ArH), 6.08 (1H, q, $J = 7.1$ Hz, H-1′), 4.98 (1H, t, $J = 3.8$ Hz, H-1), 3.55 (1H, q, $J = 6.6$ Hz, H-4), 2.73 (1H, dd, $J = 13.6$ and 3.6 Hz, $CH_2$), 2,24 (1H, dd, $J = 13.6$ and 4.0 Hz, $CH_2$), 1.73 (3H, d, $J = 7.1$ Hz, $CH_3$), 1.49 (3H, d, $J = 6.6$ Hz, $CH_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 167.8, 160.5, 150.6, 146.6, 139.2, 134.7, 133.6, 129.9, 129.1, 128.9, 128.5, 128.3, 127.9, 126.9, 126.8, 126.6, 120.8, 57.7, 53.2, 53.1, 42.7, 20.1, 17.7. $C_{27}H_{25}O_2N_3$ requires: C, 76.50; H, 5.90; N, 9.91. Found: C, 76.15; H, 6.11; N, 10.01%.

### 4.8. General procedure for cyclization to de-‘prenyl’-ardeemin

The corresponding 1-(3-indolylmethyl) derivative **12g** or **14g** (0.21 mmol) was added in one portion to TFA (5 mL). The solution was stirred for 20 min (compound **12g**) or 2.30 h (compound **14g**) and was poured onto an externally ice cooled, vigorously stirred, two phase system of $CH_2Cl_2$ (20 mL) and 20% aqueous $K_2CO_3$ (20 mL). The pH of the aqueous layer was adjusted to 7 and was extracted with $CHCl_3$. The organic layers were dried over $Na_2SO_4$ and evaporated. The residue was purified by chromatography (ethyl acetate/petroleum ether, (8:2 for **12g** and 6:4 for **14g**)).

**4.8.1. (+)-(5a*R*,8*S*,15b*R*,16a*R*)-8-Methyl-5,5a,8,15b,16,16a-hexahydro-indolo[3″,2″-4′,5′]pyrrolo[2′,1′-3,4]pyrazino[2,1-*b*]quinazoline-7,10-dione 16a.** Solid, yield 72%; mp: 193–195 °C; $[\alpha]_D^{25} = +203.9$ (*c* 0.17, $CHCl_3$); IR (NaCl) 3336, 1676, 1605, 1469 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.25 (1H, dd, $J = 1.3$ and 8.1 Hz, H-11), 7.75 (1H, ddd, $J = 1.3$, 7.1 and 8.3 Hz, H-13), 7.64 (1H, dd, $J = 1.2$ and 8.3 Hz, H-14), 7.48 (1H, ddd, $J = 1.2$, 7.1 and 8.1 Hz, H-12), 7.22 (1H, d, $J = 7.7$ Hz, H-1), 7.11 (1H, dt, $J = 0.8$ and 7.7 Hz, H-3), 6.80 (1H, dt, $J = 0.8$ and 7.7 Hz, H-2), 6.65 (1H, d, $J = 7.7$ Hz, H-4), 5.79 (1H, d, $J = 6.8$ Hz, H-5a), 5.46 (1H, q, $J = 7.2$ Hz, H-8), 5.19 (1H, br s, N–H$^i$), 4.61 (1H, dd, $J = 6.3$ and 10.5 Hz, H-15b), 4.13 (1H, t, $J = 7.0$ Hz, H-16a), 3.08 (1H, dd, $J = 6.3$ and 13.2 Hz, H-16), 2.75 (1H, ddd, $J = 7.2$, 10.5 and 13.2 Hz, H-16), 1.51 (3H, d, $J = 7.2$ Hz, $CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.7, 159.9, 150.7, 149.0, 147.0, 134.6, 128.7, 127.3, 127.2, 127.1, 126.8, 124.2, 120.4, 119.4, 109.3, 75.9, 57.2, 53.3, 44.5, 35.8, 16.7. $C_{21}H_{18}N_4O_2$ requires: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.12; H, 5.13; N, 15.16%.

**4.8.2. (+)-(5a*R*,8*S*,15b*R*,16a*R*)-8-*iso*-Propyl-5,5a,8,15b,16,16a-hexahydro-indolo[3″,2″-4′,5′]pyrrolo[2′,1′-3,4]-pyrazino[2,1-*b*]quinazoline-7,10-dione 16b.** Solid, yield 48%; mp: 124–126 °C; $[\alpha]_D^{25} = +135.4$ (*c* 0.07, $CHCl_3$); IR (NaCl) 3346, 1715, 1682, 1605, 1467 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.25 (1H, dd, $J = 1.5$ and 8.1 Hz, H-11), 7.75 (1H, ddd, $J = 1.5$, 7.1 and 8.3 Hz, H-13), 7.65 (1H, dd, $J = 1.3$ and 8.3 Hz, H-14), 7.48 (1H, ddd, $J = 1.3$, 7.1 and 8.1 Hz, H-12), 7.21 (1H, d, $J = 7.6$ Hz, H-1), 7.10 (1H, dt, $J = 0.9$ and 7.6 Hz, H-3), 6.80 (1H, dt, $J = 0.9$ and 7.6 Hz, H-2), 6.66 (1H, d, $J = 7.6$ Hz, H-4), 5.78 (1H, d, $J = 6.8$ Hz, H-5a), 5.29 (1H, d, $J = 7.9$ Hz, H-8), 4.65 (1H, dd, $J = 6.3$ and 10.4 Hz, H-15b), 4.09 (1H, t, $J = 7.0$ Hz, H-16a), 3.07 (1H, dd, $J = 6.3$ and 13.2 Hz, H-16), 2.68 (1H, ddd, $J = 7.2$, 10.4 and 13.1 Hz, H-16), 2.68 (1H, m, $CH(CH_3)_2$), 0.99 (3H, d, $J = 6.9$ Hz, $CH_3$), 0.99 (3H, d, $J = 6.9$ Hz, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 165.4, 160.6, 151.6, 149.1, 146.9, 134.7, 128.8, 127.4, 127.3, 127.2, 127.1, 124.2, 120.4, 119.5, 109.2, 75.8, 62.1, 57.8, 44.5, 36.0, 31.8, 19.9, 18.8. $C_{23}H_{22}N_4O_2$ requires: C, 71.48; H, 5.73; N, 14.49. Found: C, 71.22; H, 5.43; N, 14.26%.

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