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TETRAHEDRON: *ASYMMETRY*

1-Alkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones as glycine templates. Synthesis of Fiscalin B

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Abstract—An excess of base allows the regio- and diastereoselective alkylation at C(4) of the glycine templates 1-methyl(isopropyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones **9a** and **9b** without the need for *N*(2)-protecting groups. While the alkylation of **9a** gave exclusively the 1,4-*anti*-isomers, the isopropyl derivative **9b** required much longer reaction times and occurred with lower diastereoselectivity. Fiscalin B **3** was obtained by alkylation of **9b** with *N*-Boc-3-indolylmethyl bromide followed by indole deprotection.

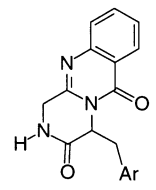
1. Introduction

Several fungal metabolites like compounds **1**–**5**[1–7] are 4-alkyl or 1,4-dialkyl derivatives of the pyrazino[2,1-*b*]quinazoline-3,6-dione system. They display significant biological activities, the more complex *N*-acetyl ardeemin **5** being an MDR-reversal agent which inhibits the membrane transport glycoprotein Gp-170.

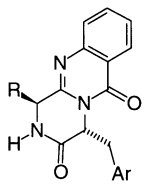
Up to now, metabolites **1**–**4** have been synthesised from tripeptides containing D- or L-tryptophan, L-alanine or L-valine or glycine and anthranilic acid, through initial cyclodehydration to 4-imino-4*H*-3,1-benzoxazines[8–12] or piperazine-2,5-dione for **1**.[13] Related *N*-substituted compounds are usually prepared from enantiomerically pure 1,3-dialkylpiperazine-2,5-diones[14–17] via imino ethers by condensation with anthranilic acid, or alternatively from 1,6-dialkyl-,[18] and 1,3,6-trialkylpiperazine-2,5-diones[19,20] through *N*-acylation with *o*-azidobenzoyl chloride followed by an intramolecular Staudinger reaction. We have also shown that *N*-unsubstituted 3-arylmethyl-(6-alkyl)-piperazine-2,5-diones can be regioselectively *N*-acylated to give 2,4-dihydro-4-arylmethyl-(1-alkyl)-pirazino[2,1-*b*]quinazoline-3,6-diones.[21]

In this context, we have previously studied the alkylation of anions derived from 2,4-dialkyl[15–17] and 1,2-dialkyl-pyrazino[2,1-*b*]quinazoline-3,6-diones,[18] demonstrating the behaviour of the starting *N*-substituted tricyclic system as glycine template. Interestingly, some of these alkyl derivatives retained most of the MDR reversal activity showed by *N*-acetyl ardeemin.[22]

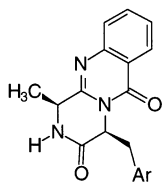
Approaches to *N*-unsubstituted compounds such as **2**–**4** through this chemistry, would require the *N*,*C*-dianions of 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones and have not been reported to date. Herein, we study the alkylation of these anions using their (1*S*)-1-methyl and (1*S*)-1-isopropyl derivatives **9a** and **9b** as starting materials.



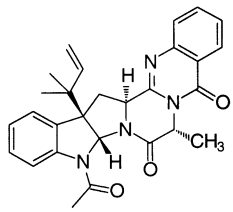
1 Glyantrypine
Ar = 3-indolyl



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



4 Fumiquinazoline G
Ar = 3-indolyl



5 *N*-Acetylardeemin

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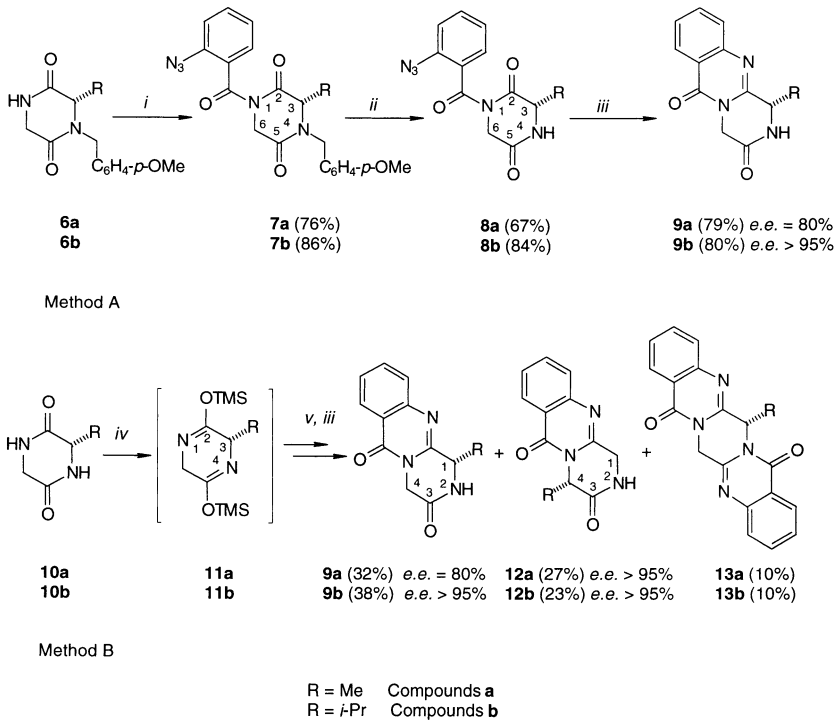
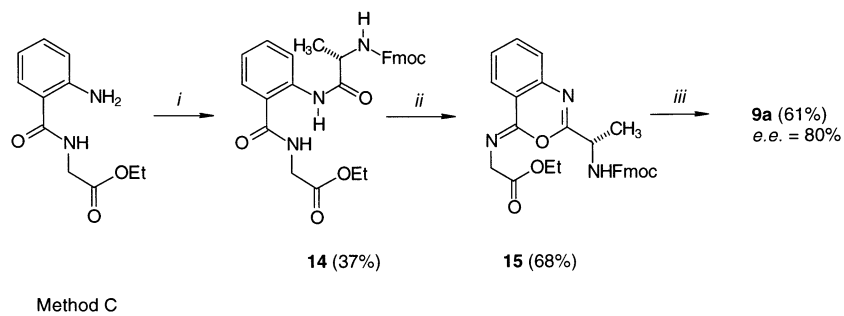
2. Results and discussion

Compounds **9a** and **9b** were prepared by two routes (Scheme 1): firstly, oxidative debenzylation of (3*S*)-3-methyl(isopropyl)-4-*p*-methoxybenzyl-1-*o*-azidobenzoyl-piperazine-2,5-dione **7a**, **7b** with CAN[23–26] followed by intramolecular Staudinger reaction (method A), or secondly, by acylation with *o*-azidobenzoyl chloride of (3*S*)-3-methyl(isopropyl)-2,5-bis(trimethylsilyloxy)-3,6-dihydropyrazine **11a**, **11b** followed by treatment with tributylphosphine (method B),[27] which was less satisfactory. Both methods gave the 1-methyl derivative **9a** with an e.e. of 80% which could not be optimised, although both enantiomers were easily separated by analytical chiral HPLC. This value is similar to that found in the synthesis of 1-methyl-2-benzyl-pyrazino[2,1-*b*]quinolizinedione.[18] However, the 1-isopropyl derivative **9b** always had a satisfactory enantiomeric purity (e.e. >95%). Attempting the synthesis of **9a** with greater e.e. we followed Ganesan's strategy[8,10] by starting from ethyl *N*-Fmoc-l-alanylanthranylglycinate (method C), but we obtained the same e.e. (80%, Scheme 2). Since the enantiomeric purity of **9a** could not be optimised, we concluded that epimerization of the C(1)-methyl derivatives in such tricyclic systems is easier than epimerization of the previously studied C(4)-methyl analogues.[15,16,18,28]

Several alkylation assays allowed us to establish good reaction conditions for the use of **9a** as a glycine template. Thus, with THF as solvent, 10 equiv. of lithium hexamethyldisilazide as base, 2 equiv. of the alkyl halide, at low temperatures (–78°C), and with long reaction times (16 h) we obtained the 1,4-*anti* isomers regioselectively and with good diastereoselectivity (compounds **16a**–**16g**, Table 1). In contrast to the

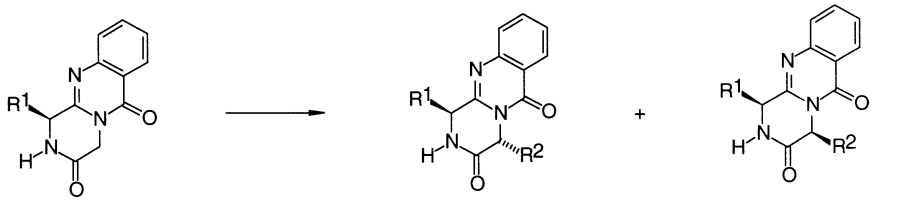


Scheme 1. *Reagents and conditions*: (i) 2 equiv. DMI, 1.5 equiv. KHMDS, 10 min, –78°C; 3 equiv. *o*-$N_3C_6H_4COCl$, –78°C (15 min), 0°C (16 h); (ii) 4 equiv. CAN, H_2O/MeCN 2:5, 0.5–1 h, rt; (iii) 1.1 equiv. Bu_3P, dry toluene, rt, 16 h; (iv) 2 equiv. TMSCl, 2 equiv. Et_3N, CH_2Cl_2, rt, 2.5 h; (v) 1 equiv. *o*-$N_3C_6H_4COCl$, rt, 16 h.



Scheme 2. *Reagents and conditions*: (i) 1.2 equiv. Fmoc-D-Ala-Cl, CH_2Cl_2/aq. Na_2CO_3, rt, 1 h; (ii) 5 equiv. Ph_3P, 4.9 equiv. I_2, 10.1 equiv. $EtN(i\text{-}Pr)_2$, rt, 3 h; (iii) 20% piperidine in CH_2Cl_2, rt, 3 h.

Table 1. Alkylation of compounds **9a** and **9b**[a]



9a, R^1 = Me
9b, R^1 = *i*-Pr

16a - 16g, R^1 = Me
18a - 18g, R^1 = *i*-Pr

17c, R^1 = Me
19a - 19f, R^1 = *i*-Pr

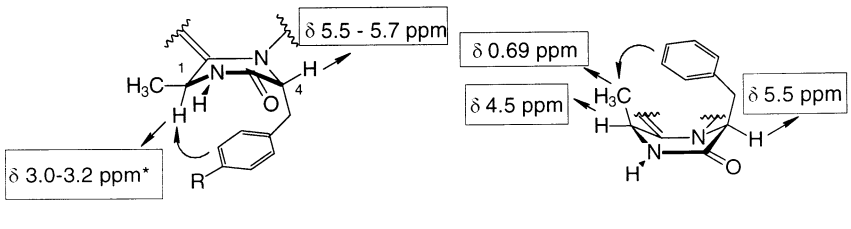
Entry	R^1	R^2	% *anti* compounds **a**	% *syn* compounds **b**	d.e.[b] (%)
1	CH_3	CH_3	57 (**16a**)	Traces	>95
2	CH_3	$CH_2CH=CH_2$	28 (**16b**)	Traces	>95
3	CH_3	$CH_2C_6H_5$	68 (**16c**)	Traces (**17c**)	>95
4	CH_3	$CH_2C_6H_4$-*p*-CH_3	64 (**16d**)	Traces	>95
5	CH_3	$CH_2C_6H_4$-*p*-F	68 (**16e**)	Traces	>95
6	CH_3	$CH_2C_6H_4$-*m*-Cl	59 (**16f**)	Traces	>95
7	CH_3	2-Naphthylmethyl	66 (**16g**)	Traces	>95
8	$CH(CH_3)_2$	CH_3	24 (**18a**)	41 (**19a**)	36[c]
9	$CH(CH_3)_2$	$CH_2CH=CH_2$	23 (**18b**)	12 (**19b**)	32
10	$CH(CH_3)_2$	$CH_2C_6H_5$	63 (**18c**)	15 (**19c**)	62
11	$CH(CH_3)_2$	$CH_2C_6H_4$-*p*-CH_3	57 (**18d**)	10 (**19d**)	70
12	$CH(CH_3)_2$	$CH_2C_6H_4$-*p*-F	48 (**18e**)	8 (**19e**)	72
13	$CH(CH_3)_2$	*N*-Boc-3-indolylmethyl	31 (**18f**)	46 (**19f**)	19[c]

[a] General reaction conditions: THF as solvent, 10 equiv. LHMDS and 2 equiv. of alkyl halide, 16 h (entries 1–7), 3.5 days (entry 8) or 5 days (entries 9–13) at −78°C.
[b] The ratios given are of the isolated products.
[c] Indicates a *syn*/*anti* ratio.

previously studied 1-methyl-2-benzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione,[18] even at higher temperatures, only traces of the 1,4-*syn*-isomers were formed and no dialkylation was observed. In this context it was also notable that alkylation with iodomethane (entry 1) afforded the 1,4-*anti* isomer and only traces of the 1,4-*syn*-isomer, while in the 1-methyl-2-benzyl derivative the observed *syn*/*anti* ratio was 3/1. Since the enantiomeric excess values of these compounds were similar to that of the starting compound **9a** (about 80%), we concluded that the alkylation reaction does not affect the stereogenic centre at C(1). The low epimerization rates and the lack of alkylation at C(1) can be explained by taking into account that under these reaction conditions the negative charge of the amide anion makes the neighbouring C(1) position virtually inert to the base.

NOESY experiments and ^{1}H NMR chemical shifts of significant protons were conclusive about the relative configuration of both stereogenic centres and the boat conformation of the piperazine ring in compounds **16a**–**16g** (Fig. 1). The C(4) substituent always adopts a pseudoaxial disposition while the C(4) proton is shifted to $\delta = 5.6$ ppm in all compounds, showing the characteristic anisotropic effect of the coplanar carbonyl group at C(6) on the quasi-equatorial proton.[15] As well as the observed NOEs between the axial substituent at C(4) and the C(1) proton in the *anti*-isomers, the chemical shift at $\delta = 3.0$–3.2 ppm for C(1)H in compounds **16c**–**16g** indicates folding of the C(4)-benzyl substituent over the piperazine ring. In accordance, the *syn*-isomer **17c**, which could be purified, showed the shielding effect of the phenyl group on the C(1) methyl group ($\delta = 0.69$ ppm).

When alkylation of **9b** was performed with benzyl bromide under reaction conditions similar to those used for **9a**, only 8% of the *anti*-isomer **18c** was isolated. Longer reaction times (5 days) improved the yields considerably,



16c - **16g** (*anti*)

17c (*syn*)

* δ 4.7 ppm for **16a** and **16b**

Figure 1. Significant NOEs and chemical shifts for compounds **16a**–**16g** and **17c**.

but also favoured epimerization at C(4) giving the 1,4-dialkyl derivatives with a diastereomeric excess between 60 and 70% in favour of the *anti*-isomers (Table 1, entries 9–12) or in favour of the *syn*-isomers (Table 1, entry 8).[29]

Since **9b** is a suitable starting material for the synthesis of Fiscalin B, its alkylation with *N*-Boc-3-indolylmethyl bromide[30,31] was performed using the above conditions, the *syn*-isomer **19f** being the predominant product (entry 13, Table 1). Subsequent deprotection of **18f** with boron tribromide[32] gave Fiscalin B in 88% yield.

The boat conformation of the piperazine ring and the axial disposition of the C(4) substituent in compounds **18** and **19** were also determined from NOESY experiments and were supported by ^{1}H NMR data: chemical shift values of $\delta = 5.3$–5.6 ppm for C(4)H in all compounds and differences between the *anti* and *syn* isomers for C(1)H. The *anti*-isomers showed different C(1)H chemical shifts: $\delta \sim 4.6$ ppm in **18a** and **18b** and $\delta \sim 2.7$–3.2 ppm in compounds **18c**–**18f** (shielding by the aromatic ring). In the *syn*-isomers the C(1) proton resonated at $\delta = 4.0$–4.3 ppm and the CH isopropyl proton shifts differed between **19a**, **19b** ($\delta = 2.4$ ppm) and compounds **19c**–**19f** ($\delta = 1.2$–1.5 ppm) where an aromatic ring shielding effect is present (see Fig. 2).

3. Conclusion

We conclude that the 1-methyl(isopropyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones **9a** and **9b** allow regio- and diastereoselective alkylation at C(4) without the need for *N*(2)-protecting groups showing variations in the diastereoselectivity when compared with the *N*(2)-alkylated systems.

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 using 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; 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. (6*S*)-6-Alkylpiperazine-2,5-diones 6a and 6b

To a stirred solution of of *N*-Cbz-glycine (4.5 g, 21.4 mmol) and DCC (4.8 g, 23 mmol) in dry CH_2Cl_2 (150 mL) freshly distilled ethyl *N*-(*p*-methoxybenzyl)-L-alaninate[33] (23 mmol) for **6a** or ethyl *N*-(*p*-methoxybenzyl)-L-valinate[33] for **6b** was added, and stirring was continued at room temperature for 12 h. The reaction mixture was filtered, washed successively with aqueous HCl (1N), aqueous $NaHCO_3$ (1N) 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 g) in ethanol (120 mL), filtered (Celite) and evaporated. The residue was heated under reflux in toluene (50 mL) for 12 h affording **6a** or **6b**, respectively.

4.2.1. (6*S*)-6-Methyl-1-*p*-methoxybenzylpiperazine-2,5-dione 6a. Yield 73%; mp: 145–146°C; $[\alpha]_D^{25} = +11.0$ (*c* 0.25; $CHCl_3$); ν_{max} (KBr) 2931, 1692, 1655 cm^{-1}; δ_H

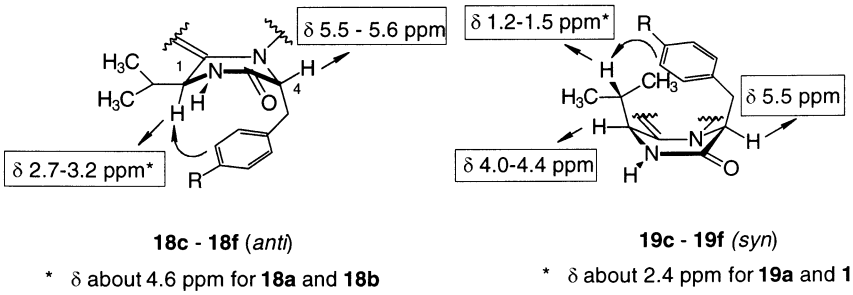


Figure 2. Significant NOEs and chemical shifts for compounds **18** and **19**.

(250 MHz, $CDCl_3$) 7.16 (d, 2H, $J=8.6$ Hz, H-2′ and H-6′), 6.83 (d, 2H, $J=8.6$ Hz, H-3′ and H-5′), 6.53 (s, 1H, *N*-H), 5.11 (d, 1H, $J=14.7$ Hz, *N*-CH_2–Ar), 4.07 (d, 1H, $J=17.2$ Hz, H-3), 3.98 (d, 1H, $J=14.7$ Hz, *N*-CH_2–Ar), 3.96 (d, 1H, $J=17.2$ Hz, H-3), 3.81 (q, 1H, $J=7.1$ Hz, H-6), 3.77 (s, 3H, OCH_3), 1.40 (d, 3H, $J=7.1$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 169.9, 163.9, 159.5, 129.8, 127.6, 114.4, 55.4, 54.8, 46.8, 45.0, 17.5. $C_{13}H_{16}N_2O_3$ requires: C, 62.83; H, 6.44; N, 11.27. Found: C, 62.57; H, 6.69; N, 11.10%.

4.2.2. (6*S*)-6-Isopropyl-1-*p*-methoxybenzylpiperazine-2,5-dione 6b. Compound **6b** was obtained as a syrup; yield 76%; $[\alpha]_D^{25}=-9.0$ (*c* 0.24; $CHCl_3$); ν_{max} (NaCl) 2963, 2932, 1654, 1245 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.13 (d, 2H, $J=8.6$ Hz, H-2′ and H-6′), 6.82 (d, 2H, $J=8.6$ Hz, H-3′ and H-5′), 6.61 (s, 1H, *N*-H), 5.34 (d, 1H, $J=14.7$ Hz, *N*-CH_2–Ar), 4.10 (d, 1H, $J=17.4$ Hz, H-3), 3.98 (d, 1H, $J=14.7$ Hz, *N*-CH_2–Ar), 3.96 (d, 1H, $J=17.4$ Hz, H-3), 3.77 (s, 3H, OCH_3), 3.63 (d, 1H, $J=4.9$ Hz, H-6), 2.22 (m, 1H, $J=4.9$ and 6.9 Hz, $CH(CH_3)_2$), 1.08 (d, 3H, $J=6.9$ Hz, CH_3), 1.40 (d, 3H, $J=6.9$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 167.7, 164.5, 159.4, 129.7, 127.5, 114.4, 64.3, 55.4, 47.8, 45.4, 31.9, 19.9, 17.7. $C_{15}H_{20}N_2O_3$ requires: C, 65.13; H, 7.23; N, 10.13. Found: C, 64.90; H, 7.34; N, 10.34%.

4.3. (3*S*)-3-Alkyl-1-(*o*-azidobenzoyl)-4-*p*-methoxybenzylpiperazine-2,5-diones 7a and 7b

To a magnetically stirred solution of compound **6a** or **6b** (4.7 mmol) in dry THF (90 mL) at −78°C under argon was added dropwise via syringe DMI (0.95 mL, 9.5 mmol) and a solution of potassium hexamethyldisilazide in dry toluene (0.5 M, 14 mL), followed 10 min later by addition of *o*-azidobenzoyl chloride (2 g, 14.1 mmol) in THF (5 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 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 2:3 for **7a** and petroleum ether:EtOAc, 1:1 for **7b**).

4.3.1. (3*S*)-1-(*o*-Azidobenzoyl)-4-*p*-methoxybenzyl-3-methylpiperazine-2,5-dione 7a. Compound **7a** was obtained as an oily product; yield 76%; $[\alpha]_D^{25}=-78.0$ (*c* 0.25; $CHCl_3$); ν_{max} (NaCl) 2128, 1725, 1675 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.41 (ddd, 1H, $J=1.6$, 7.6 and 8.0 Hz, H-4″), 7.35 (dd, 1H, $J=1.3$ and 8.1 Hz, H-6″), 7.18 (d, 2H, $J=8.6$ Hz, H-2′ and H-6′), 7.14 (ddd, 1H, $J=0.9$, 7.6 and 8.0 Hz, H-5″), 7.03 (d, 1H, $J=8.0$ Hz, H-3″), 6.84 (d, 2H, $J=8.6$ Hz, H-3′ and H-5′), 5.21 (d, 1H, $J=14.7$ Hz, *N*-CH_2–Ar), 4.90 (d, 1H, $J=17.4$ Hz, H-6), 4.15 (d, 1H, $J=17.4$ Hz, H-6), 3.92 (q, 1H, $J=7.2$ Hz, H-3), 3.90 (d, 1H, $J=14.7$ Hz, *N*-CH_2–Ar), 3.74 (s, 3H, OCH_3), 1.38 (d, 3H, $J=7.2$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.9, 167.7, 163.7, 159.3, 136.5, 131.9, 129.3, 129.2, 127.6, 127.1, 124.9, 117.9, 114.3, 55.7, 55.1, 46.1, 45.9, 16.9. $C_{20}H_{19}N_5O_4$ requires: C, 61.06; H, 4.86; N, 17.80. Found: C, 60.89; H, 4.77; N, 18.10%.

4.3.2. (3*S*)-1-(*o*-Azidobenzoyl)-4-*p*-methoxybenzyl-3-isopropylpiperazine-2,5-dione 7b. Compound **7b** was obtained as an oily product; yield 86%; $[\alpha]_D^{25}=-123.0$ (*c* 0.27; $CHCl_3$); ν_{max} (NaCl) 2129, 1718, 1675, 1249 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.43 (ddd, 1H, $J=1.5$, 6.5 and 8.0 Hz, H-4″), 7.34 (dd, 1H, $J=1.5$ and 7.7 Hz, H-6″), 7.17 (d, 2H, $J=8.9$ Hz, H-3′ and H-5′), 7.16 (ddd, 1H, $J=0.9$, 6.5 and 7.7 Hz, H-5″), 7.05 (dd, 1H, $J=0.9$ and 8.0 Hz, H-3″), 6.85 (d, 2H, $J=8.7$ Hz, H-2′ and H-6′), 5.51 (d, 1H, $J=14.7$ Hz, *N*-CH_2–Ar), 4.86 (d, 1H, $J=17.8$ Hz, H-6), 4.24 (d, 1H, $J=17.8$ Hz, H-6), 3.90 (d, 1H, $J=14.7$ Hz, *N*-CH_2–Ar), 3.76 (s, 3H, OCH_3), 3.69 (d, 1H, $J=6.0$ Hz, H-3), 2.25 (m, 1H, $CH(CH_3)_2$), 1.06 (d, 3H, $J=6.8$ Hz, CH_3), 1.01 (d, 3H, $J=6.8$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.2, 167.3, 164.4, 159.6, 136.6, 131.9, 129.6, 129.2, 128.3, 127.2, 125.2, 118.0, 114.5, 65.4, 55.3, 47.8, 46.8, 32.4, 20.0, 18.6. $C_{22}H_{23}N_5O_4$ requires: C, 62.64; H, 5.45; N, 16.60. Found: C, 62.59; H, 5.28; N, 16.25%.

4.4. (3*S*)-3-Alkyl-1-(*o*-azidobenzoyl)piperazine-2,5-diones 8a and 8b

A solution of **7a** or **7b** (3.8 mmol) in acetonitrile:water (5:2, 50 mL) and CAN (8.4 g, 15.3 mmol) was stirred for 80 min (**8a**) or 35 min (**8b**) at room temperature. The reaction mixture was extracted with $CHCl_3$, dried (Na_2SO_4) and evaporated. Column chromatography (EtOAc:petroleum ether, 1:1) afforded **8a** or **8b**, respectively.

4.4.1. (3*S*)-1-(*o*-Azidobenzoyl)-3-methylpiperazine-2,5-dione 8a. Yield: 67%; mp: 155–157°C; $[\alpha]_D^{25}=-4.0$ (*c* 0.25; $CHCl_3$); ν_{max} (NaCl) 3424, 2133, 1692 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.48 (ddd, 1H, $J=1.6$, 6.4 and 7.9 Hz, H-4′), 7.37 (dd, 1H, $J=1.6$ and 7.7 Hz, H-6′), 7.33 (s, 1H, *N*-H), 7.20 (ddd, 1H, $J=1.0$, 6.4 and 7.7 Hz, H-3′), 7.15 (dd, 1H, $J=1.6$ and 7.9 Hz, H-5′), 4.64 (d, 1H, $J=17.7$ Hz, H-6), 4.38 (d, 1H, $J=17.7$ Hz, H-6), 4.20 (dq, 1H, $J=1.4$ and 6.9 Hz, H-3), 1.50 (d, 3H, $J=6.9$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.6, 168.1, 166.8, 136.5, 131.7, 128.8, 128.0, 124.9, 118.1, 51.7, 46.6, 17.9. $C_{12}H_{11}N_5O_3$ requires: C, 52.74; H, 4.02; N, 25.64. Found: C, 52.59; H, 4.17; N, 25.29%.

4.4.2. (3*S*)-1-(*o*-Azidobenzoyl)-3-isopropylpiperazine-2,5-dione 8b. Yield: 84%; mp: 115–117°C; $[\alpha]_D^{25}=-86.4$ (*c* 0.25; $CHCl_3$); ν_{max} (NaCl) 2966, 2129, 1686 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.42 (d, 1H, $J=4.3$ Hz, *N*-H), 7.32 (ddd, 1H, $J=1.5$, 7.0 and 8.3 Hz, H-4′), 7.22 (dd, 1H, $J=1.5$ and 7.8 Hz, H-6′), 7.04 (ddd, 1H, $J=0.9$, 7.0 and 7.8 Hz, H-5′), 7.01 (dd, 1H, $J=0.9$ and 8.3 Hz, H-3′), 4.42 (d, 1H, $J=17.9$ Hz, H-6), 4.24 (d, 1H, $J=17.9$ Hz, H-6), 3.80 (dd, 1H, $J=4.3$ and 6.8 Hz, H-3), 2.20 (m, 1H, $J=4.3$ and 6.8 Hz, $CH(CH_3)_2$), 0.93 (d, 3H, $J=6.8$ Hz, CH_3), 0.85 (d, 3H, $J=6.8$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.4, 168.0, 167.4, 136.5, 131.6, 128.6, 124.9, 118.2, 61.7, 46.2, 32.4, 20.9, 18.7. $C_{14}H_{15}N_5O_3$ requires: C, 55.75; H, 4.97; N, 23.23. Found: C, 55.46; H, 4.95; N, 23.08%.

4.5. Synthesis of compounds 9 (method A)

To a stirred solution of **8a** or **8b** (3 mmol) in dry toluene (10 mL) tributylphosphine (3.3 mmol) was added via 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 (ethyl acetate).

4.5.1. (1*S*)-1-Methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione 9a. Yield: 79%; mp: 240–243°C; ν_{max} (KBr) 3261, 2924, 1684, 1607 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.27 (dd, 1H, J=1.4 and 8.1 Hz, H-7), 7.77 (ddd, 1H, J=1.4, 7.1 and 8.3 Hz, H-9), 7.66 (dd, 1H, J=1.3 and 8.3 Hz, H-10), 7.49 (ddd, 1H, J=1.3, 7.1 and 8.1 Hz, H-8), 7.00 (s, 1H, *N*-H), 4.74 (m, 2H, H-4), 4.68 (dq, 1H, J=2.4 and 6.9 Hz, H-1), 1.71 (d, 3H, J=6.9 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 178.7, 166.4, 148.9, 147.0, 134.7, 127.3, 127.2, 126.7, 119.9, 51.4, 44.5, 20.3. $C_{12}H_{11}N_3O_2$ requires: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.56; H, 4.88; N, 17.98%.

4.5.2. (1*S*)-1-Isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione 9b. Yield: 80%; mp: 171°C; $[\alpha]_D^{25}$=−26.0 (*c* 0.28; DMSO); ν_{max} (KBr) 1667, 1604 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.45 (s, 1H, *N*-H), 8.20 (dd, 1H, J=1.2 and 8.0 Hz, H-7), 7.72 (ddd, 1H, J=1.2, 7.0 and 8.3 Hz, H-9), 7.62 (dd, 1H, J=1.2 and 8.3 Hz, H-10), 7.43 (ddd, 1H, J=1.2, 7.0 and 8.0 Hz, H-8), 4.93 (d, 1H, J=18.9 Hz, H-4), 4.39 (t, 1H, J=4.4 Hz, H-1), 4.31 (d, 1H, J=18.9 Hz, H-4), 2.39 (m, 1H, J=8.8 Hz, $CH(CH_3)_2$), 1.07 (d, 3H, J=6.8 Hz, CH_3), 0.94 (d, 3H, J=6.8 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 166.6, 160.5, 150.1, 146.7, 134.8, 127.2, 126.9, 126.6, 119.6, 61.5, 44.6, 35.1, 19.1, 16.9. $C_{14}H_{15}N_3O_2$ requires: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.21; H, 5.83; N, 16.42%.

4.6. Synthesis of compounds 9, 12 and 13 (method B)

To a suspension of the suitable piperazinedione **10a**[34,35] or **10b**[36,37] (7.7 mmol) in dry CH_2Cl_2 (50 mL) were added trimethylsilyl chloride (2 mL, 15.4 mmol) and NEt_3 (1.0 mL, 7.7 mmol). The suspension was vigorously stirred under argon at room temperature until complete disolution. Then, a solution of *o*-azidobenzoyl chloride (1.48 g, 7.7 mmol) in CH_2Cl_2 (10 mL) was added and the reaction was stirred for a further 16 h at room temperature. The mixture was washed with brine (3×25 mL). The organic layer together with the CH_2Cl_2 layers coming from the extraction of the brine with CH_2Cl_2 (3×10 mL), were dried (Na_2SO_4), filtered, evaporated and dried. The solid residue, which was a mixture of both *N*-acyl piperazinediones plus *N*,*N*-diacyl derivative was used without further purification in the next step. The acyl derivatives and Bu_3P (2 mL, 8 mmol) in dry toluene (8 mL) were stirred at room temperature under argon for 16 h. After evaporation, the residue was purified by column chromatography (EtOAc:MeOH, 9:1) yielding **13a** (10%), **9a** (32%) and **12a** (27%); or **13b** (10%); **9b** (38%) and **12b** (23%).

4.6.1. (6*S*)-6-Methyl-6,14-dihydroquinazolino[2′,3′:5,4]-pyrazino[2,1-*b*]quinazoline-8,16-dione 13a. Compound **13a** was obtained as an oily product; $[\alpha]_D^{25}$=−90.5 (*c* 0.61; $CHCl_3$); ν_{max} (NaCl) 2932, 2859, 1683, 1610, 1470, 1320 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.30 (dd, 2H, J=1.4 and 8.1 Hz, H-1 and H-9), 7.79 (ddd, 2H, J=1.4, 7.1 and 8.3 Hz, H-3 and H-11), 7.69 (dd, 2H, J=1.3 and 8.3 Hz, H-4 and H-12), 7.52 (ddd, 2H, J=1.3, 7.1 and 8.1 Hz, H-2 and H-10), 6.21 (q, 1H, J=7.2 Hz, H-6), 6.06 (d, 1H, J=17.6 Hz, H-14), 4.76 (d, 1H, J=17.6 Hz, H-14), 1.77 (d, 3H, J=7.2 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 160.2, 159.8, 151.1, 147.3, 147.2, 147.1, 134.9, 127.5, 127.4, 127.3, 126.9, 120.5, 120.1, 52.1, 43.9, 18.6. $C_{19}H_{14}N_4O_2$ requires: C, 69.08; H, 4.27; N, 16.96. Found: C, 69.13; H, 4.28; N, 16.94%.

4.6.2. (4*S*)-4-Methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione 12a. Compound **12a** was obtained as a solid; mp: 216–218°C; $[\alpha]_D^{25}$=+146.9 (*c* 0.28; DMSO); ν_{max} (KBr) 3199, 3067, 2927, 1671, 1602 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.21 (dd, 1H, J=1.5 and 8.1 Hz, H-7), 8.18 (s, 1H, *N*-H), 7.71 (ddd, 1H, J=1.5, 7.1 and 8.2 Hz, H-9), 7.57 (dd, 1H, J=1.2 and 8.2 Hz, H-10), 7.44 (ddd, 1H, J=1.2, 7.1 and 8.1 Hz, H-8), 5.38 (q, 1H, J=7.2 Hz, H-4), 4.64 (d, 1H, J=16.9 Hz, H-1), 4.48 (dd, 1H, J=4.7 and 16.9 Hz, H-1), 1.61 (d, 3H, J=7.2 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 170.6, 160.3, 147.7, 147.2, 135.0, 127.4, 127.1, 127.0, 120.5, 51.9, 45.1, 17.0. $C_{12}H_{11}N_3O_2$ requires: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.74; H, 4.68; N, 18.34%.

4.6.3. (6*S*)-6-Isopropyl-6,14-dihydroquinazolino[2′,3′-5,4]pyrazino[2,1-*b*]quinazoline-8,16-dione 13b. Compound **13b** was obtained as an oily product; $[\alpha]_D^{25}$=−155.6 (*c* 0.32; $CHCl_3$); ν_{max} (NaCl) 2970, 1684, 1608, 1568 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.30 (m, 2H, H-1 and H-9), 7.75 (m, 4H, H-3, H-4, H-11 and H-12), 7.51 (ddd, 2H, J=1.5, 6.9 and 8.1 Hz, H-2 and H-10), 6.00 (d, 1H, J=17.7 Hz, H-14), 5.90 (d, 1H, J=10.1 Hz, H-6), 4.80 (d, 1H, J=17.7 Hz, H-14), 2.30 (m, 1H, J=6.7 and 10.1 Hz, $CH(CH_3)_2$), 1.14 (d, 3H, J=6.7 Hz, CH_3), 1.06 (d, 3H, J=6.7 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 160.5, 160.4, 149.6, 147.7, 146.9, 146.8, 134.9, 134.8, 127.6, 127.55, 127.5, 127.2, 127.1, 126.8, 120.4, 120.1, 61.0, 44.5, 32.3, 19.7, 19.6. $C_{21}H_{18}N_4O_2$ requires: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.21; H, 4.98; N, 15.92%.

4.6.4. (4*S*)-4-Isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione 12b. Compound **12b** was obtained as a solid; mp: 203–204°C; $[\alpha]_D^{25}$=+132.0 (*c* 0.22; $CHCl_3$); ν_{max} (NaCl) 3214, 2969, 1685, 1606, 1469 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (dd, 1H, J=1.5 and 8.0 Hz, H-7), 7.75 (ddd, 1H, J=1.5, 7.0 and 8.4 Hz, H-9), 7.60 (dd, 1H, J=1.1 and 8.4 Hz, H-10), 7.48 (ddd, 1H, J=1.1, 7.0 and 8.0 Hz, H-8), 7.20 (s, 1H, *N*-H), 5.24 (d, 1H, J=7.9 Hz, H-4), 4.69 (d, 1H, J=17.2 Hz, H-1), 4.42 (dd, 1H, J=5.2 and 17.2 Hz, H-1), 2.27 (m, 1H, J=7.0 Hz, $CH(CH_3)_2$), 1.14 (d, 3H, J=6.8 Hz, CH_3), 1.06 (d, 3H, J=6.8 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.7, 160.8, 148.4, 147.0,

134.9, 127.3, 127.2, 126.9, 120.3, 60.8, 45.5, 31.8, 19.9, 18.9. $C_{14}H_{15}N_3O_2$ requires: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.21; H, 5.98; N, 16.12%.

4.7. Ethyl *N*-(2-aminobenzoyl)-glycinate

To a solution of glycine ethyl ester hydrochloride (1.0 g, 7.16 mmol) in dry CH_2Cl_2 (30 mL) was added Et_3N (1 mL, 7.2 mmol). To the filtered organic phase EDC (1.5 g, 7.88 mmol) was added followed by anthranilic acid (2 g, 14.32 mmol) in 10 portions over 1.5 h at room temperature with stirring. After being stirred for an additional 1.5 h, the organic phase was washed with diluted ammonium hydroxide, dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography (EtOAc:CH_2Cl_2, 0.5:9.5) to yield 1.15 g (72%) of *N*-(2-aminobenzoyl)glycinate ethyl ester as a white solid. Mp: 54–55°C; ν_{max} (NaCl) 3359, 2983, 1733, 1644, 1585, 1531 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.34 (dd, 1H, $J=1.5$ and 8.1 Hz, H-6), 7.10 (ddd, 1H, $J=1.5$, 7.4 and 8.4 Hz, H-4), 6.89 (t, 1H, $J=5.3$ Hz, CO-*N*H), 6.58 (dd, 1H, $J=1.0$ and 8.4 Hz, H-3), 6.53 (ddd, 1H, $J=1.0$, 7.4 and 8.1 Hz, H-5), 5.66 (s, 2H, NH_2), 4.13 (q, 2H, $J=7.1$ Hz, *O*-CH_2–CH_3), 4.06 (d, 2H, $J=5.3$ Hz, *N*H-CH_2-CO), 1.20 (t, 3H, $J=7.1$ Hz, *O*-CH_2–CH_3); δ_C (62.5 MHz, $CDCl_3$) 170.2, 169.4, 148.7, 132.4, 127.5, 117.1, 116.4, 115.0, 61.4, 41.4, 14.0. $C_{11}H_{14}N_2O_3$ requires: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.18; H, 6.18; N, 12.52%.

4.8. Ethyl-*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-D-alanyl-2-aminobenzoylglycinate 14

To a solution of ethyl *N*-(2-aminobenzoyl)glycinate (1.15 g, 5.18 mmol) and DMAP (0.63 g, 5.18 mmol) in dry CH_2Cl_2 (30 mL) was added Fmoc-L-Ala-Cl[38] (5.7 mmol). The mixture was stirred for 1 h at room temperature, followed by addition of aqueous Na_2CO_3 solution (1 M, 30 mL). After stirring the reaction for a total of 2 h, the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography (EtOAc:hexane, 6:4) to give **14** as a white solid (0.98 g, 86%). Mp: 184–185°C; ν_{max} (NaCl) 3326, 2922, 2855, 1725, 1643, 1590, 1522, 1446 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 11.47 (s, 1H, *N*H-CO), 8.59 (d, 1H, $J=7.8$ Hz, H-3), 7.74 (d, 2H, $J=7.3$ Hz, H-4′ and H-5′), 7.63 (t, 1H, $J=8.3$ Hz, H-4), 7.54 (d, 2H, $J=7.3$ Hz, H-1′ and H-8′), 7.48 (t, 1H, $J=8.3$ Hz, H-6), 7.31 (m, 4H, Ar), 7.12 (t, 1H, $J=7.0$ Hz, H-5), 6.72 (s, 1H, *N*H(Gly)), 5.52 (d, 1H, $J=7.0$ Hz, *N*H(Ala)), 4.42 (qui, 1H, $J=7.0$ Hz, CH-CH_3), 4.33 (t, 1H, $J=7.2$ Hz, H-9′), 4.26 (m, 2H, *O*-CH_2–Ar), 4.21 (q, 2H, $J=7.2$ Hz, *O*-CH_2–CH_3), 4.09 (m, 2H, CO–CH_2–*N*), 1.52 (d, 3H, $J=7.0$ Hz, CH_3), 1.27 (t, 3H, $J=7.2$ Hz, *O*-CH_2–CH_3); δ_C (62.5 MHz, $CDCl_3$):171.0, 169.6, 168.5, 156.4, 143.7, 141.1, 139.1, 133.0, 127.6, 126.9, 126.7, 125.2, 123.2, 121.4, 119.8, 119.6, 67.1, 61.8, 48.3, 47.1, 41.6, 19.1, 14.0. $C_{29}H_{29}N_3O_6$ requires: C, 67.56; H, 5.67; N, 8.15. Found: C, 67.61; H, 5.64; N, 8.19%.

4.9. Ethyl-*N*-{2-[(*S*)-1-*N*-[(9*H*-fluoren-9-ylmethoxy)-carbonyl]aminoethyl]-4*H*-3,1-benzoxazin-4-ylidene}-glycinate 15

To a solution of **14** (0.98 g, 1.9 mmol) in dry CH_2Cl_2 (30 mL) was added Ph_3P (2.49 g, 9.5 mmol), I_2 (2.38 g, 9.4 mmol) and *N*,*N*-diisopropylethylamine (3.5 mL, 19.9 mmol). The reaction mixture was stirred at room temperature for 3 h, quenched with aqueous Na_2CO_3 (20 mL), then extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography (EtOAc:hexane: Et_3N, 5:5:0.2) to give **15** (0.64 g, 68%). Mp: 100–101°C; ν_{max} (NaCl) 3339, 2927, 1681, 1605, 1523, 1450 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.15 (dd, 1H, $J=1.3$ and 7.9 Hz, H-5), 7.74 (d, 2H, $J=7.4$ Hz, H-4′ and H-5′), 7.61 (t, 2H, $J=7.4$ Hz, H-2′ and H-7′), 7.55 (dt, 1H, $J=1.5$ and 8.1 Hz, H-7), 7.32 (m, 6H, H-6, H-8, H-1′, H-3′, H-6′ and H-8′), 5.73 (d, 1H, $J=7.7$ Hz, *N*H-COO), 4.64 (qui, 1H, $J=7.2$ Hz, CH-CH_3), 4.41 (m, 3H, H-9′ and *O*-CH_2–Ar), 4.28 (s, 2H, *N*-CH_2-COO), 4.20 (q, 2H, $J=7.2$ Hz, *O*-CH_2–CH_3), 1.52 (d, 3H, $J=7.2$ Hz, CH_3), 1.29 (t, 3H, $J=7.1$ Hz, *O*-CH_2–CH_3); δ_C (62.5 MHz, $CDCl_3$) 170.2, 159.4, 155.5, 148.6, 143.7, 141.2, 140.8, 133.4, 128.4, 127.6, 126.9, 126.2, 125.0, 124.9, 119.9, 119.0, 66.9, 61.0, 48.8, 48.2, 47.1, 19.1, 14.1. $C_{29}H_{27}N_3O_5$ requires: C, 70.01; H, 5.47; N, 8.45. Found: C, 69.91; H, 5.44; N, 8.52%.

4.10. Synthesis of compound 9a from 15

The oxazine **15** (638 mg, 1.3 mmol) in CH_2Cl_2 (30 mL) was treated with piperidine (8 mL) at room temperature under argon for 3 h. The reaction mixture was evaporated and purified by column chromatography (EtOAc/MeOH, 9.5:0.5) to give **9a** (176 mg, 61%).

4.11. General alkylation procedures

4.11.1. Alkylation of 9a. To a cold (−78°C), magnetically stirred solution of **9a** (0.5 mmol) in dry THF (10 mL) was added, under argon, dropwise via syringe a solution of lithium hexamethyldisilazide in THF (1 M, 5.0 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, 2:3 unless otherwise mentioned) afforded the *anti*-4-alkyl compounds **16a**–**16g** followed by traces of the *syn*-compounds **17**.

4.11.1.1. (1*S*,4*R*)-1,4-Dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 16a. Compound **16a** was obtained (EtOAc) as a solid; mp: 165°C; yield 57%; ν_{max} (NaCl) 3239, 2931, 1688, 1607 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (dd, 1H, $J=1.5$ and 8.1 Hz, H-7), 7.75 (ddd, 1H, $J=1.5$, 7.0 and 8.2 Hz,

H-9), 7.67 (dd, 1H, $J=1.4$ and 8.2 Hz, H-10), 7.48 (ddd, 1H, $J=1.4$, 7.0 and 8.1 Hz, H-8), 7.36 (s, 1H, *N*-H), 5.47 (dq, 1H, $J=1.0$ and 7.2 Hz, H-4), 4.71 (q, 1H, $J=6.6$ Hz, H-1), 1.79 (d, 3H, $J=6.6$ Hz, C(1)-CH_3), 1.63 (d, 3H, $J=7.2$ Hz, C(4)-CH_3); δ_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. $C_{13}H_{13}N_3O_2$ requires: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.98; H, 5.34; N, 17.22%.

4.11.1.2. (1*S*,4*R*)-4-Allyl-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 16b. Compound **16b** was obtained (EtOAc) as a solid; mp: 102–103°C; yield 31%; ν_{max} (NaCl) 3249, 2923, 1682, 1606 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (dd, 1H, $J=1.5$ and 8.0 Hz, H-7), 7.75 (ddd, 1H, $J=1.5$, 7.0 and 8.4 Hz, H-9), 7.66 (dd, 1H, $J=1.3$ and 8.4 Hz, H-10), 7.48 (ddd, 1H, $J=1.3$, 7.0 and 8.0 Hz, H-8), 7.36 (s, 1H, *N*-H), 5.85 (ddt, 1H, $J=7.5$, 10.4 and 17.8 Hz, H-2′), 5.45 (t, 1H, $J=6.3$ Hz, H-4), 5.08 (d, 1H, $J=10.4$ H-3′), 5.03 (dd, 1H, $J=1.3$ and 17.8 Hz, H-3′), 4.76 (q, 1H, $J=6.6$ Hz, H-1), 2.85 (ddd, 1H, $J=7.1$, 7.5 and 14.1 Hz, H-1′), 2.80 (ddd, 1H, $J=7.1$, 7.5 and 14.1 Hz, H-1′), 1.75 (d, 3H, $J=6.6$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 169.0, 160.4, 151.0, 146.8, 134.6, 131.3, 127.4, 127.2, 126.8, 120.2, 120.1, 55.9, 49.5, 39.5, 18.1. $C_{15}H_{15}N_3O_2$ requires: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.71; H, 5.64; N, 15.52%.

4.11.1.3. (1*S*,4*R*)-4-Benzyl-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 16c. Mp: 194–195°C; yield 68%; ν_{max} (NaCl) 2923, 1684, 1600 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.31 (dd, 1H, $J=1.3$ and 8.0 Hz, H-7), 7.76 (ddd, 1H, $J=1.3$, 7.1 and 8.3 Hz, H-9), 7.63 (dd, 1H, $J=1.1$ and 8.3 Hz, H-10), 7.50 (ddd, 1H, $J=1.1$, 7.1 and 8.0 Hz, H-8), 7.21 (m, 3H, Ph), 6.93 (m, 2H, Ph), 6.55 (s, 1H, *N*-H), 5.63 (t, 1H, $J=4.6$ Hz, H-4), 3.48 (dd, 1H, $J=5.1$ and 14.0 Hz, CH_2-Ph), 3.42 (dd, 1H, $J=3.9$ and 14.0 Hz, CH_2-Ph), 3.00 (q, 1H, $J=6.6$ Hz, H-1), 1.46 (d, 3H, $J=6.6$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.8, 160.7, 151.5, 147.0, 135.0, 134.8, 129.8, 128.9, 127.9, 127.5, 127.3, 126.9, 120.1, 57.7, 49.0, 37.0, 18.9. $C_{19}H_{17}N_3O_2$ requires: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.61; H, 5.34; N, 13.22%.

4.11.1.4. (1*S*,4*S*)-4-Benzyl-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 17c. Traces of **17c** were obtained as an oil; ν_{max} (NaCl) 2923, 1684, 1600 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.34 (dd, 1H, $J=1.4$ and 8.0 Hz, H-7), 7.79 (ddd, 1H, $J=1.4$, 7.1 and 8.4 Hz, H-9), 7.62 (dd, 1H, $J=1.1$ and 8.4 Hz, H-10), 7.52 (ddd, 1H, $J=1.1$, 7.1 and 8.0 Hz, H-8), 7.18 (m, 3H, Ph), 6.93 (m, 2H, Ph), 6.11 (s, 1H, *N*-H), 5.52 (dd, 1H, $J=3.6$ and 5.4 Hz, H-4), 4.52 (dq, 1H, $J=3.2$ and 7.2 Hz, H-1), 3.60 (dd, 1H, $J=5.4$ and 14.0 Hz, CH_2-Ph), 3.47 (dd, 1H, $J=3.6$ and 14.0 Hz, CH_2–Ph), 0.69 (d, 3H, $J=7.2$ Hz, CH_3).

4.11.1.5. (1*S*,4*R*)-1-Methyl-4-(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 16d. Mp: 146–147°C; yield 64%; ν_{max} (NaCl) 3253, 2926, 1686, 1599 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.33 (dd, 1H, $J=1.3$ and 8.0 Hz, H-7), 7.78 (ddd, 1H, $J=1.3$, 7.0 and 8.4 Hz, H-9), 7.63 (dd, 1H, $J=1.2$ and 8.4 Hz, H-10), 7.52 (ddd, 1H, $J=1.2$, 7.0 and 8.0 Hz, H-8), 7.42 (s, 1H, *N*-H), 6.97 (d, 2H, $J=7.0$ Hz, Ar), 6.83 (d, 2H, $J=7.0$ Hz, Ar) 5.60 (‘t′, 1H, $J=4.3$ Hz, H-4), 3.43 (dd, 1H, $J=4.3$ and 15.0 Hz, CH_2–Ar), 3.36 (dd, 1H, $J=4.3$ and 15.0 Hz, CH_2–Ar), 3.04 (q, 1H, $J=6.6$ Hz, H-1), 2.26 (s, 3H, Ar-CH_3), 1.47 (d, 3H, $J=6.6$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 169.0, 160.5, 151.5, 146.9, 137.4, 134.6, 131.7, 129.5, 129.4, 127.3, 127.0, 126.8, 120.0, 57.6, 48.8, 36.4, 21.0, 18.8. $C_{20}H_{19}N_3O_2$ requires: C, 72.04; H, 5.75; N, 12.61. Found: C, 71.91; H, 5.73; N, 11.87%.

4.11.1.6. (1*S*,4*R*)-4-(*p*-Fluorobenzyl)-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 16e. Mp: 161°C; yield 68%; ν_{max} (NaCl) 3230, 2923, 1684, 1601 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.28 (dd, 1H, $J=1.5$ and 8.0 Hz, H-7), 7.76 (ddd, 1H, $J=1.5$, 7.1 and 8.3 Hz, H-9), 7.64 (s, 1H, *N*-H), 7.63 (dd, 1H, $J=1.2$ and 8.3 Hz, H-10), 7.50 (ddd, 1H, $J=1.2$, 7.1 and 8.0 Hz, H-8), 6.90 (m, 4H, Ar), 5.59 (dd, 1H, $J=4.2$ and 5.5 Hz, H-4), 3.42 (dd, 1H, $J=5.5$ and 14.2 Hz, CH_2–Ar), 3.36 (dd, 1H, $J=4.2$ and 14.2 Hz, CH_2–Ar), 3.24 (q, 1H, $J=6.6$ Hz, H-1), 1.52 (d, 3H, $J=6.6$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.7, 162.2 (d, $J=247.2$ Hz), 160.5, 151.1, 146.9, 134.7, 131.1 (d, $J=7.9$ Hz), 130.7 (d, $J=3.4$ Hz), 127.4, 127.2, 126.7, 119.9, 115.7 (d, $J=21.2$ Hz), 57.4, 48.9, 36.0, 18.6. $C_{19}H_{16}FN_3O_2$ requires: C, 67.65; H, 4.78; N, 12.46. Found: C, 67.41; H, 4.65; N, 12.64%.

4.11.1.7. (1*S*,4*R*)-4-(*m*-Chlorobenzyl)-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 16f. Mp: 85–86°C; yield 59%; ν_{max} (NaCl) 3253, 2926, 1686, 1599 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.29 (dd, 1H, $J=1.5$ and 8.0 Hz, H-7), 7.77 (ddd, 1H, $J=1.5$, 7.1 and 8.4 Hz, H-9), 7.64 (dd, 1H, $J=1.2$ and 8.4 Hz, H-10), 7.51 (ddd, 1H, $J=1.2$, 7.1 and 8.0 Hz, H-8), 7.35 (s, 1H, *N*-H), 7.21 (ddd, 1H, $J=1.1$, 1.6 and 7.8 Hz, H-4′), 7.13 (t, 1H, $J=7.8$ Hz, H-5′), 7.03 (dd, 1H, $J=1.1$ and 1.6 Hz, H-2′), 6.84 (dd, 1H, $J=1.1$ and 7.5 Hz, H-6′), 5.61 (t, 1H, $J=4.8$ Hz, H-4), 3.40 (dd, 1H, $J=4.8$ and 14.3 Hz, CH_2–Ar), 3.39 (dq, 1H, $J=2.6$ and 6.6 Hz, H-1), 3.34 (dd, 1H, $J=4.8$ and 14.3 Hz, CH_2–Ar), 1.54 (d, 3H, $J=6.6$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.4, 160.5, 150.9, 146.9, 136.9, 134.8, 134.5, 130.0, 129.6, 127.9, 127.7, 127.4, 127.2, 126.7, 119.9, 57.4, 49.2, 36.7, 18.9. $C_{19}H_{16}ClN_3O_2$ requires: C, 64.50; H, 4.56; N, 11.88. Found: C, 64.41; H, 4.73; N, 11.87%.

4.11.1.8. (1*S*,4*R*)-1-Methyl-4-(2-naphthylmethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 16g. Mp: 63–65°C; yield 66%; ν_{max} (NaCl) 2923, 1684, 1600 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.34 (dd, 1H, $J=1.5$ and 8.0 Hz, H-7), 7.79 (ddd, 1H, $J=1.5$, 7.1 and 8.4 Hz, H-9), 7.75 (m, 1H, H-8′), 7.66 (d, 1H, $J=8.5$ Hz, H-4′), 7.62 (dd, 1H, $J=1.2$ and 8.4 Hz, H-10), 7.57 (m, 1H, H-5′), 7.53 (ddd, 1H, $J=1.2$, 7.1 and 8.0 Hz, H-8), 7.44 (t, 1H, $J=1.7$ Hz, H-1′), 7.40 (m, 2H, H-6′ and H-7′), 7.09 (dd, 1H, $J=1.7$ and 8.4 Hz, H-3′), 6.92 (s, 1H, *N*-H), 5.71 (t, 1H, $J=4.8$ Hz, H-4), 3.66 (dd, 1H, $J=4.8$ and 14.1 Hz, CH_2–Ar), 3.56 (dd, 1H, $J=4.8$ and 14.1 Hz, CH_2–Ar), 3.10 (q, 1H, $J=6.6$ Hz, H-1), 1.36

(d, 3H, $J=6.6$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.7, 160.8, 151.4, 147.1, 134.9, 133.4, 132.6, 132.5, 128.7, 128.6, 127.8, 127.7, 127.6, 127.5, 127.3, 127.0, 126.5, 126.2, 120.3, 57.8, 49.2, 37.3, 18.9. $C_{23}H_{19}N_3O_2$ requires: C, 74.78; H, 5.18; N, 11.37. Found: C, 74.69; H, 5.13; N, 11.37%.

4.11.2. Alkylation of 9b. To a magnetically stirred solution of **9b** (0.5 mmol) in dry THF (10 mL) at −78°C under argon, was added dropwise via syringe a solution of lithium hexamethyldisilazide in THF (1 M, 5 mL) followed by a solution of the appropriate halide (1 mmol) in THF (5 mL) 10 min later. The reaction mixture was stirred at −78°C for 5 days (3.5 days for **18a** and **19a**), quenched by the dropwise addition of glacial acetic acid followed by saturated aqueous ammonium chloride (10 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 the 4-alkyl derivatives **18** and **19**.

4.11.2.1. (1*S*,4*R*)-1-Isopropyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18a. Compound **18a** was obtained (EtOAc) as a solid; mp: 135–137°C; yield 25%; $[\alpha]_D^{25}=-124.7$ (*c* 0.09; $CHCl_3$); ν_{max} (NaCl) 3197, 2968, 2930, 1733, 1682, 1608, 1496 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.27 (dd, 1H, $J=1.4$ and 8.0 Hz, H-7), 7.75 (ddd, 1H, $J=1.4$, 7.1 and 8.2 Hz, H-9), 7.65 (dd, 1H, $J=1.3$ and 8.2 Hz, H-10), 7.49 (ddd, 1H, $J=1.3$, 7.1 and 8.0 Hz, H-8), 6.37 (s, 1H, *N*-H), 5.46 (q, 1H, $J=7.2$ Hz, H-4), 4.52 (d, 1H, $J=2.3$ Hz, H-1), 3.16 (m, 1H, $J=2.3$ and 7.1 Hz, $CH(CH_3)_2$), 1.62 (d, 3H, $J=7.2$ Hz, C(4)-CH_3), 1.21 (d, 3H, $J=7.4$ Hz, CH_3), 0.94 (d, 3H, $J=6.8$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 170.2, 160.6, 149.2, 147.1, 134.7, 127.5, 127.4, 126.9, 120.4, 58.4, 52.0, 29.0, 19.5, 15.3, 14.2. $C_{15}H_{17}N_3O_2$ requires: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.29; H, 6.13; N, 15.37%.

4.11.2.2. (1*S*,4*S*)-1-Isopropyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19a. Compound **19a** was obtained (EtOAc) as an oily product; yield 41%; $[\alpha]_D^{25}=+25.5$ (*c* 0.17; $CHCl_3$); ν_{max} (NaCl) 3176, 3062, 2925, 1682, 1594, 1568, 1472 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.27 (dd, 1H, $J=1.4$ and 8.1 Hz, H-7), 7.76 (ddd, 1H, $J=1.4$, 7.1 and 8.4 Hz, H-9), 7.64 (dd, 1H, $J=1.2$ and 8.4 Hz, H-10), 7.48 (ddd, 1H, $J=1.2$, 7.1 and 8.1 Hz, H-8), 6.96 (d, 1H, $J=3.9$ Hz, *N*-H), 5.25 (q, 1H, $J=7.1$ Hz, H-4), 4.29 (dd, 1H, $J=3.9$ and 7.0 Hz, H-1), 2.36 (m, 1H, $J=7.1$ Hz, $CH(CH_3)_2$), 1.74 (d, 3H, $J=7.1$ Hz, C(4)-CH_3), 1.13 (d, 3H, $J=7.0$ Hz, CH_3), 1.07 (d, 3H, $J=7.0$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 169.3, 160.6, 149.4, 146.8, 134.6, 127.0, 126.9, 126.6, 120.1, 62.1, 51.9, 35.6, 19.5, 19.2, 18.4. $C_{15}H_{17}N_3O_2$ requires: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.38; H, 6.28; N, 15.41%.

4.11.2.3. (1*S*,4*R*)-4-Allyl-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18b. Mp: 158–159°C; yield 23%; $[\alpha]_D^{25}=-285.0$ (*c* 0.30; $CHCl_3$); ν_{max} (NaCl) 2923, 2355, 2329, 1684, 1602 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.27 (dd, 1H, $J=1.4$ and 8.1 Hz, H-7), 7.76 (ddd, 1H, $J=1.4$, 7.2 and 8.3 Hz, H-9), 7.65 (dd, 1H, $J=1.3$ and 8.3 Hz, H-10), 7.49 (ddd, 1H, $J=1.3$, 7.2 and 8.1 Hz, H-8), 6.41 (s, 1H, *N*-H), 5.78 (ddt, 1H, $J=7.5$, 10.1 and 17.5 Hz, H-2′), 5.47 (t, 1H, $J=5.6$ Hz, H-4), 5.04 (dd, 1H, $J=1.4$ and 10.1 Hz, H-3′), 4.99 (dd, 1H, $J=1.4$ and 17.5 Hz, H-3′), 4.58 (d, 1H, $J=2.4$ Hz, H-1), 3.10 (m, 1H, $J=2.4$ and 7.0 Hz, $CH(CH_3)_2$), 2.91 (ddd, 1H, $J=6.2$, 7.5 and 12.4 Hz, H-1′), 2.79 (ddd, 1H, $J=5.2$, 7.5 and 12.4 Hz, H-1′), 1.17 (d, 3H, $J=7.0$ Hz, CH_3), 0.86 (d, 3H, $J=7.0$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.2, 160.4, 149.6, 146.6, 134.6, 130.9, 127.0, 126.7, 120.5, 119.9, 58.6, 55.3, 36.1, 30.0, 19.1, 14.9. $C_{17}H_{19}N_3O_2$ requires: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.06; H, 6.64; N, 13.77%.

4.11.2.4. (1*S*,4*S*)-4-Allyl-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19b. Compound **19b** was obtained as an oily product; yield 12%; $[\alpha]_D^{25}=+134.4$ (*c* 0.09; $CHCl_3$); ν_{max} (NaCl) 3257, 3215, 2962, 2934, 1684, 1608, 1472 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (dd, 1H, $J=1.3$ and 8.1 Hz, H-7), 7.79 (ddd, 1H, $J=1.3$, 7.1 and 8.4 Hz, H-9), 7.68 (dd, 1H, $J=1.3$ and 8.4 Hz, H-10), 7.52 (ddd, 1H, $J=1.3$, 7.1 and 8.1 Hz, H-8), 6.64 (s, 1H, *N*-H), 5.24 (ddt, 1H, $J=7.3$, 9.6 and 17.2 Hz, H-2′), 5.24 (dd, 1H, $J=5.4$ and 8.1 Hz, H-4), 5.10 (dd, 1H, $J=1.4$ and 17.2 Hz, H-3′), 5.10 (dd, 1H, $J=1.4$ and 9.6 Hz, H-3′), 4.45 (m, 1H, H-1), 2.83 (m, 2H, H-1′), 2.43 (m, 1H, $J=6.7$ Hz, $CH(CH_3)_2$), 1.07 (d, 3H, $J=6.7$ Hz, CH_3), 1.05 (d, 3H, $J=6.7$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 165.6, 160.4, 152.1, 145.7, 134.9, 132.3, 127.1, 126.9, 120.4, 118.3, 58.6, 56.4, 38.0, 30.9, 18.3, 16.5. $C_{17}H_{19}N_3O_2$ requires: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.43; H, 6.19; N, 13.91%.

4.11.2.5. (1*S*,4*R*)-4-Benzyl-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18c. Mp: 78–80°C; yield 63%; $[\alpha]_D^{25}=-225.0$ (*c* 0.05; $CHCl_3$); ν_{max} (NaCl) 3210, 2918, 2847, 1723, 1683, 1599, 1470 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.33 (dd, 1H, $J=1.4$ and 8.0 Hz, H-7), 7.77 (ddd, 1H, $J=1.4$, 7.2 and 8.3 Hz, H-9), 7.60 (dd, 1H, $J=1.1$ and 8.3 Hz, H-10), 7.51 (ddd, 1H, $J=1.1$, 7.2 and 8.0 Hz, H-8), 7.20 (m, 3H, Ph), 6.90 (m, 2H, Ph), 6.03 (s, 1H, *N*-H), 5.64 (dd, 1H, $J=4.1$ and 4.3 Hz, H-4), 3.49 (dd, 1H, $J=4.3$ and 14.5 Hz, CH_2-Ph), 3.43 (dd, 1H, $J=4.1$ and 14.5 Hz, CH_2-Ph), 2.75 (m, 1H, $J=2.2$ and 6.9 Hz, $CH(CH_3)_2$), 2.69 (d, 1H, $J=2.2$ Hz, H-1), 0.86 (d, 3H, $J=6.9$ Hz, CH_3), 0.69 (d, 3H, $J=6.9$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.5, 160.9, 150.0, 147.1, 135.0, 134.9, 130.0, 128.9, 128.0, 127.5, 127.3, 127.0, 120.1, 58.0, 57.2, 37.3, 29.5, 19.1, 15.0. $C_{21}H_{21}N_3O_2$ requires: C, 72.60; H, 6.09; N, 12.09. Found: C, 72.54; H, 6.34; N, 12.27%.

4.11.2.6. (1*S*,4*S*)-4-Benzyl-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19c. Compound **19c** was isolated as an oily product; yield 15%; $[\alpha]_D^{25}=+154.4$ (*c* 0.48; $CHCl_3$); ν_{max} (NaCl) 3196, 3063, 2968, 1683, 1596, 1570, 1473 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.30 (dd, 1H, $J=1.3$ and 8.0 Hz, H-7), 7.77 (ddd, 1H, $J=1.3$, 7.1 and 8.3 Hz, H-9), 7.63 (dd, 1H, $J=1.2$ and 8.3 Hz, H-10), 7.57 (d, 1H, $J=3.5$ Hz, *N*-H), 7.50 (ddd, 1H, $J=1.2$, 7.1 and 8.0 Hz, H-8), 7.18

(m, 5H, Ph), 5.41 (t, 1H, $J=5.6$ Hz, H-4), 4.02 (dd, 1H, $J=3.5$ and 8.5 Hz, H-1), 3.45 (2dd, 2H, $J=5.6$ and 13.5 Hz, CH_2–Ph), 1.16 (m, 1H, $J=6.7$ and 8.5 Hz, $CH(CH_3)_2$), 0.94 (d, 3H, $J=6.7$ Hz, CH_3), 0.84 (d, 3H, $J=6.7$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 167.7, 161.1, 149.3, 146.8, 136.0, 134.8, 129.9, 128.7, 127.3, 127.1, 126.7, 120.1, 61.9, 57.5, 38.1, 35.1, 20.0, 19.0. $C_{21}H_{21}N_3O_2$ requires: C, 72.60; H, 6.09; N, 12.09. Found: C, 72.73; H, 6.04; N, 12.10%.

4.11.2.7. (1*S*,4*R*)-1-Isopropyl-4-(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18d. Mp: 75–77°C; yield 57%; $[\alpha]_D^{25}=-340.0$ (*c* 0.11; $CHCl_3$); ν_{max} (NaCl) 3199, 3076, 2961, 2926, 1730, 1683, 1599, 1570 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.33 (dd, 1H, $J=1.4$ and 8.1 Hz, H-7), 7.77 (ddd, 1H, $J=1.4$, 7.1 and 8.4 Hz, H-9), 7.61 (dd, 1H, $J=1.1$ and 8.4 Hz, H-10), 7.51 (ddd, 1H, $J=1.1$, 7.1 and 8.1 Hz, H-8), 6.96 (d, 2H, $J=7.9$ Hz, H-3′ and H-5′), 6.78 (d, 2H, $J=7.9$ Hz, H-2′ and H-6′), 5.99 (s, 1H, *N*-H), 5.61 (t, 1H, $J=4.2$ Hz, H-4), 3.42 (dd, 1H, $J=4.2$ and 13.7 Hz, CH_2–Ar), 3.40 (dd, 1H, $J=4.3$ and 13.7 Hz, CH_2–Ar), 2.76 (m, 1H, $J=2.4$ and 7.0 Hz, $CH(CH_3)_2$), 2.72 (d, 1H, $J=2.4$ Hz, H-1), 2.27 (s, 3H, $ArCH_3$), 0.86 (d, 3H, $J=7.0$ Hz, CH_3), 0.69 (d, 3H, $J=7.0$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.6, 160.9, 150.1, 147.1, 137.4, 134.9, 131.8, 129.8, 129.5, 127.4, 127.2, 127.0, 120.1, 58.0, 57.3, 36.9, 29.6, 21.2, 19.1, 15.0. $C_{22}H_{23}N_3O_2$ requires: C, 73.11; H, 6.41; N, 11.63. Found: C, 72.84; H, 6.34; N, 11.57%.

4.11.2.8. (1*S*,4*S*)-1-Isopropyl-4-(*p*-methylbenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19d. Compound **19d** was isolated as an oil; yield 10%; $[\alpha]_D^{25}=+161.7$ (*c* 0.06; $CHCl_3$); ν_{max} (NaCl) 3208, 3064, 2958, 2928, 1682, 1597, 1472 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.31 (dd, 1H, $J=1.4$ and 8.1 Hz, H-7), 7.77 (ddd, 1H, $J=1.4$, 7.1 and 8.4 Hz, H-9), 7.63 (dd, 1H, $J=1.2$ and 8.4 Hz, H-10), 7.51 (ddd, 1H, $J=1.2$, 7.1 and 8.1 Hz, H-8), 7.03 (m, 4H, Ar), 6.88 (d, 1H, $J=3.8$ Hz, *N*-H), 5.34 (dd, 1H, $J=4.9$ and 6.3 Hz, H-4), 4.03 (dd, 1H, $J=3.8$ and 8.5 Hz, H-1), 3.45 (dd, H, $J=4.9$ and 14.0 Hz, CH_2–Ar), 3.38 (dd, H, $J=6.3$ and 14.0 Hz, CH_2–Ar), 2.26 (s, 3H, $ArCH_3$), 1.23 (m, 1H, $J=6.6$ Hz, $CH(CH_3)_2$), 0.94 (d, 3H, $J=6.6$ Hz, CH_3), 0.83 (d, 3H, $J=6.6$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 167.2, 161.0, 149.2, 146.7, 136.9, 134.7, 132.8, 129.6, 129.2, 127.0, 126.7, 120.1, 61.9, 57.6, 37.6, 34.8, 21.0, 19.8, 18.8. $C_{22}H_{23}N_3O_2$ requires: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.04; H, 6.39; N, 11.47%.

4.11.2.9. (1*S*,4*R*)-4-(*p*-Fluorobenzyl)-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18e. Mp: 188–190°C; yield 48%; $[\alpha]_D^{25}=-478.3$ (*c* 0.06; $CHCl_3$); ν_{max} (NaCl) 3200, 2967, 2921, 2857, 1684, 1601, 1508 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.31 (dd, 1H, $J=1.3$ and 8.1 Hz, H-7), 7.78 (ddd, 1H, $J=1.3$, 7.1 and 8.3 Hz, H-9), 7.61 (dd, 1H, $J=1.1$ and 8.3 Hz, H-10), 7.51 (ddd, 1H, $J=1.1$, 7.1 and 8.1 Hz, H-8), 6.85 (m, 4H, Ar), 6.33 (s, 1H, *N*-H), 5.61 (dd, 1H, $J=4.3$ and 4.6 Hz, H-4), 3.45 (dd, 1H, $J=4.6$ and 14.6 Hz, CH_2–Ar), 3.39 (dd, 1H, $J=4.3$ and 14.6 Hz, CH_2–Ar), 2.96 (d, 1H, $J=2.3$ Hz, H-1), 2.81 (m, 1H, $J=2.3$ and 7.0 Hz, $CH(CH_3)_2$), 0.93 (d, 3H, $J=7.0$ Hz, CH_3), 0.71 (d, 3H, $J=7.0$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.2, 162.4 (d, $J=247$ Hz), 160.6, 149.6, 146.8, 134.8, 131.2 (d, $J=8.0$ Hz), 130.5 (d, $J=3.3$ Hz), 127.3, 127.1, 126.8, 119.9, 115.6 (d, $J=21.3$ Hz), 58.1, 56.8, 36.3, 29.7, 18.9, 14.8. $C_{21}H_{20}FN_3O_2$ requires: C, 69.03; H, 5.52; N, 11.50. Found: C, 68.98; H, 5.78; N, 11.35%.

4.11.2.10. (1*S*,4*S*)-4-(*p*-Fluorobenzyl)-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19e. Compound **19e** was obtained as an oil; yield 8%; δ_H (250 MHz, $CDCl_3$) 8.30 (dd, 1H, $J=1.4$ and 8.0 Hz, H-7), 7.79 (ddd, 1H, $J=1.4$, 7.2 and 8.4 Hz, H-9), 7.65 (dd, 1H, $J=1.1$ and 8.4 Hz, H-10), 7.52 (ddd, 1H, $J=1.1$, 7.2 and 8.0 Hz, H-8), 7.17 (m, 2H, Ar), 6.93 (m, 2H, Ar), 6.73 (d, 1H, $J=3.7$ Hz, *N*-H), 5.37 (dd, 1H, $J=4.5$ and 6.9 Hz, H-4), 4.11 (dd, 1H, $J=3.7$ and 8.1 Hz, H-1), 3.44 (dd, 1H, $J=4.5$ and 13.9 Hz, CH_2–Ar), 3.36 (dd, 1H, $J=6.9$ and 13.9 Hz, CH_2–Ar), 1.54 (m, 1H, $J=6.8$ and 8.1 Hz, $CH(CH_3)_2$), 1.01 (d, 3H, $J=6.8$ Hz, CH_3), 0.87 (d, 3H, $J=6.8$ Hz, CH_3).

4.11.2.11. (1*S*,4*R*)-4-(*N*-Boc-3-indolylmethyl)-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18f. Compound **18f** was isolated (EtOAc:toluene, 1:1) as an oil; yield 31%; $[\alpha]_D^{25}=-241.4$ (*c* 0.62; methanol); ν_{max} (NaCl) 1734, 1685, 1601 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.36 (dd, 1H, $J=1.5$ and 8.0 Hz, H-7), 8.07 (dd, 1H, $J=0.8$ and 8.3 Hz, H-7′), 7.78 (ddd, 1H, $J=1.5$, 7.1 and 8.4 Hz, H-9), 7.57 (dd, 1H, $J=1.0$ and 8.4 Hz, H-10), 7.54 (ddd, 1H, $J=1.0$, 7.1 and 8.0 Hz, H-8), 7.41 (dd, 1H, $J=0.8$ and 8.0 Hz, H-4′), 7.24 (dt, 1H, $J=0.8$ and 8.0 Hz, H-6′), 7.01 (dt, 1H, $J=0.8$ and 8.0 Hz, H-5′), 6.96 (s, 1H, H-2′), 6.19 (s, 1H, *N*-H), 5.67 ('t', 1H, $J=5.4$ Hz, H-4), 3.63 (dd, 1H, $J=5.4$ and 14.9 Hz, CH_2–Ar), 3.57 (dd, 1H, $J=5.4$ and 14.9 Hz, CH_2–Ar), 3.20 (d, 1H, $J=2.2$ Hz, H-1), 2.73 (m, 1H, $J=2.2$ and 6.9 Hz, $CH(CH_3)_2$), 1.49 (s, 9H, $3CH_3$), 0.79 (d, 3H, $J=7.2$ Hz, CH_3), 0.69 (d, 3H, $J=6.7$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.8, 160.8, 149.7, 149.1, 146.9, 135.2, 134.6, 129.7, 127.1, 127.0, 126.7, 124.9, 124.7, 122.7, 120.0, 118.7, 115.0, 113.8, 86.3, 58.3, 56.0, 29.9, 27.9, 26.8, 18.8, 14.7. $C_{28}H_{30}N_4O_4$ requires: C, 69.05; H, 6.16; N, 11.50. Found: C, 69.45; H, 6.02; N, 11.24%.

4.11.2.12. (1*S*,4*S*)-4-(*N*-Boc-3-indolylmethyl)-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19f. Compound **19f** was isolated (EtOAc:toluene, 1:1) as an oil; yield 46%; $[\alpha]_D^{25}=+173.5$ (*c* 0.62; methanol); ν_{max} (NaCl) 3344 1735, 1684, 1595 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.33 (dd, 1H, $J=1.5$ and 8.0 Hz, H-7), 8.05 (dd, 1H, $J=0.8$ and 8.2 Hz, H-7′), 7.78 (ddd, 1H, $J=1.5$, 7.2 and 8.4 Hz, H-9), 7.62 (dd, 1H, $J=1.1$ and 8.4 Hz, H-10), 7.60 (d, 1H, $J=3.7$ Hz, *N*-H), 7.51 (ddd, 1H, $J=1.1$, 7.2 and 8.0 Hz, H-8), 7.30 (s, 1H, H-2′), 7.23 (dt, 1H, $J=0.8$ and 8.0 Hz, H6′), 7.12 (dt, 1H, $J=0.8$ and 8.2 Hz, H-5′), 5.50 (dd, 1H, $J=4.2$ and 7.4 Hz, H-4), 4.02 (dd, 1H, $J=3.7$ and 8.3 Hz, H-1), 3.61 (dd, 1H, $J=4.2$ and 14.5 Hz, CH_2–Ar), 3.51 (dd, 1H, $J=4.2$ and 14.5 Hz, CH_2–Ar), 1.55 (s, 9H, $3CH_3$), 1.45 (m, 1H, $J=6.7$ and 8.3 Hz, $CH(CH_3)_2$), 0.89 (d, 3H, $J=6.7$ Hz, CH_3), 0.68 (d, 3H, $J=6.7$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 167.6, 161.1, 149.3, 149.1, 146.7, 135.1, 134.7, 130.4, 127.0, 126.6, 124.5, 122.7, 120.0,

119.1, 115.0, 114.9, 83.5, 61.7, 56.2, 35.2, 28.0, 27.7, 19.4, 18.1. $C_{28}H_{30}N_4O_4$ requires: C, 69.05; H, 6.16; N, 11.50. Found: C, 68.68; H, 6.26; N, 11.45%.

4.12. Deprotection of 18f and 19f

To a cold (−78°C) magnetically stirred solution of **18f** or **19f** (0.1 mmol) in dry CH_2Cl_2 (3 mL), boron tribromide (0.5 mmol) was added and stirring was continued for 40 min. The reaction mixture was extracted with ethyl acetate (9 mL) and the organic layers were dried over anhydrous Na_2SO_4, filtered, evaporated, and purified by column chromatography (EtOAc:MeOH, 3:2).

4.12.1. Fiscalin B 3. Yield 88%; ^1H and ^{13}C NMR spectra were identical to those previously reported.[10,21] The enantiomeric purity was measured by chiral HPLC.

4.12.2. (1*S*,4*S*)-4-(3-Indolylmethyl)-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 20. Compound **20** was isolated as an oil; yield 44%; $[\alpha]_D^{25}=+255.0$ (*c* 0.02; methanol); ν_{max} (NaCl) 3283, 2925, 1679, 1594, 1472, 1332, 1219 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.35 (dd, 1H, $J=1.5$ and 8.0 Hz, H-7), 8.10 (s, 1H, *N*-H^i), 7.77 (ddd, 1H, $J=1.5$, 7.2 and 8.4 Hz, H-9), 7.61 (dd, 1H, $J=1.1$ and 8.4 Hz, H-10), 7.52 (ddd, 1H, $J=1.1$ 7.2 and 8.0 Hz, H-8), 7.48 (dd, 1H, $J=0.9$ and 8.0 Hz, H-4′), 7.23 (dd, 1H, $J=0.9$ and 8.0 Hz, H-7′), 7.13 (dt, 1H, $J=0.9$ and 8.0 Hz, H-6′), 6.97 (s, 1H, *N*-H), 6.90 (dt, 1H, $J=0.9$ and 8.0 Hz, H-5′), 6.88 (d, 1H, $J=2.0$ Hz, H-2′), 5.49 (dd, 1H, $J=4.1$ and 6.0 Hz, H-4), 3.93 (dd, 1H, $J=3.4$ and 8.4 Hz, H-1), 3.76 (dd, 1H, $J=6.0$ and 14.8 Hz, CH_2–Ar), 3.68 (dd, 1H, $J=4.1$ and 14.8 Hz, CH_2–Ar), 0.97 (m, 1H, $CH(CH_3)_2$), 0.73 (d, 3H, $J=6.7$ Hz, CH_3), 0.47 (d, 3H, $J=6.7$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 167.9, 161.2, 149.4, 146.6, 135.9, 134.8, 127.1, 126.9, 126.8, 123.5, 122.2, 120.2, 119.8, 118.9, 110.9, 110.1, 61.7, 57.4, 34.9, 27.5, 19.5, 18.1. $C_{23}H_{22}N_4O_2$ requires: C, 71.47; H, 5.74; N, 14.50. Found: C, 71.54; H, 5.48; N, 14.17%.

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