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A new stereocontrolled approach to fused polycyclic compounds containing a diketopiperazine ring

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Abstract—Representative (1*S*)- and (4*S*)-alkyl-1,4-dihydropyrazino[2,1-*b*]quinazoline-3,6-dione lactim ethers were regio- and diastereoselectively alkylated after metallation to give the corresponding 1,4-*trans*-isomers with retention of the stereocentres. The results were compared with the previously studied lactams. The (1*R*,4*S*)-dialkyl derivatives obtained by C(1)-alkyation with bifunctional reagents were lately cyclized to complex polycyclic compounds through a second N(2)-alkylation promoted by sodium iodide.

1. Introduction

In our work directed towards the synthesis of analogues of the multi-drug resistance reversal agent to antitumour drugs *N*-acetylardeemin,[1,2] we focussed our attention on the synthesis and reactivity of the 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione system **1**,[3] which constitutes the pharmacophoric moiety of this natural product (Fig. 1). This system is also the core of other natural compounds such as glyantripine,[4] fiscalins,[5] fumiquinazolines,[6] alantrypinone[7] and spiroquinazoline.[8] Part of this work showed that monosubstituted compounds **1**, where R^1 or R^4 are alkyl groups and R^2 are hydrogen, alkyl or aryl substituents, behave as nucleophilic glycine templates. In this way, we have developed useful approaches to these products by regio- and diastereoselective alkylation of metallated derivatives generated by the elimination of either the C(1)- or C(4)-protons in compounds **1**.[9–16] On the other hand, bis-lactim ethers derived from chiral piperazine-2,5-diones, which are known as Schöllkopf auxiliaries, have been extensively used in the asymmetric synthesis of acyclic or cyclic amino acids in a process that implies their regioselective metallation followed by a diastereoselective nucleophilic displacement and a final acid hydrolysis,[17,18] but lactim ethers of fused diketopiperazines have rarely been used.[19] On this basis, we herein report the alkylation of (1*S*)- and (4*S*)-pyrazino[2,1-*b*]quinazoline-3,6-dione lactim ethers **2**–**4**.

2. Results and discussion

Compounds **2**–**4** were quantitatively obtained from the corresponding starting materials **1** ($R^2 = H$) after treatment with Meerwein's reagent.[20] When compounds **2**

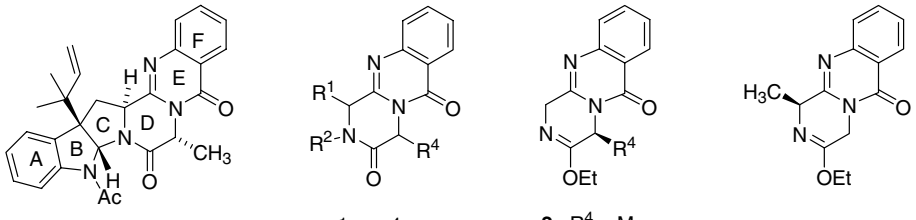

Figure 1.

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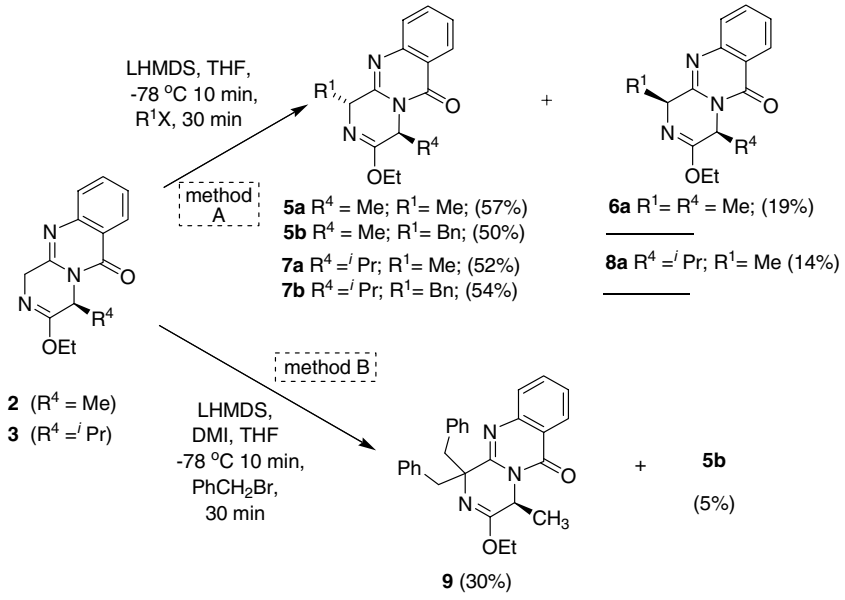


Scheme 1.

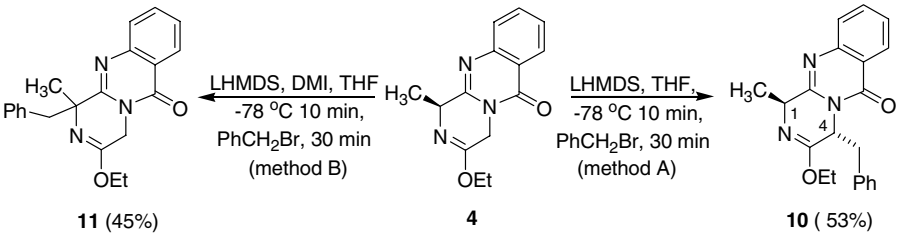
and **3** were metallated with lithium hexamethyldisilazide and the corresponding intermediates were trapped with methyl iodide or benzyl bromide, the reactions gave regio- and diastereoselectively the enantiomerically pure 1,4-*trans*-isomers **5** and **7** (method A, Scheme 1). The yields obtained were similar to those reported for other fused diketopiperazine lactim ethers,[19] and could not be further optimized either with longer reaction times or with the addition of DMI as a cosolvent (method B). This last alternative promoted instead the 1,1-dialkylation (see compound **9**). The 1,4-*trans*-diastereoselectivity was especially important for benzyl halides (de > 98%), being in general the asymmetric *trans*-induction of compounds **2** and **3** almost similar to and better than in their precursor-lactams **1**.[16] During the reaction, the alkylated lactims **5** and **7** obtained were less prone to epimerize, via enamine tautomers, to the 1,4-*cis*-isomers than the previously studied lactams **1**.[9–16] However, more care was needed during the chromatographic work-up to avoid epimerization on contact with silica gel.

As expected, the alkylation of the metallated 1-methyllactim ether **4** with benzyl bromide (method A) conduced regio- and diastereoselectively (de >98%) to the 1,4-*trans* isomer **10**. Attempts to improve the yields by using DMI (method B) gave exclusively, in this case, the C(1) alkylation product **11** instead of **10** (Scheme 2).

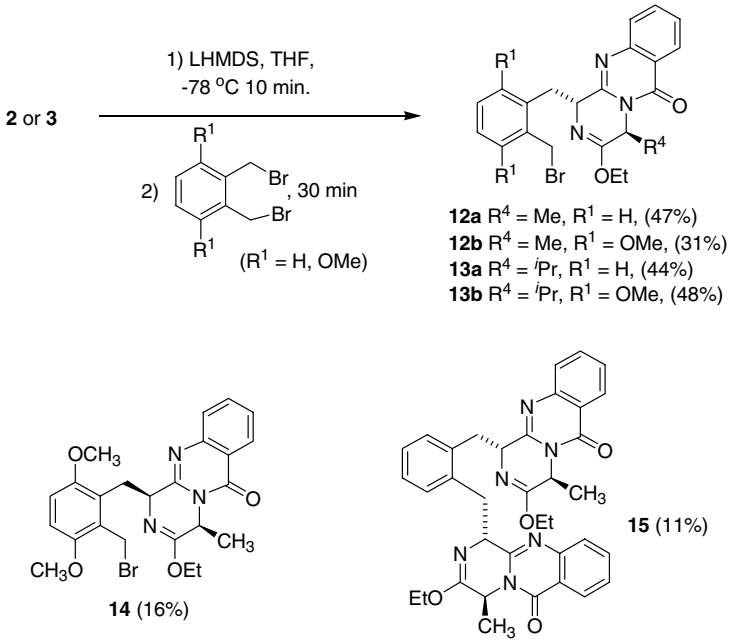
To prove that a double alkylation on C(1) and N(2) in compounds **2** and **3** using bifunctional reagents would lead to fused polycycles, we performed the reaction of metallated **2** and **3** with bis-1,2-phenylenemethyl bromides. Here the main products isolated were 1,4-*trans* isomers **12** and **13**. Only compound **2** gave small amounts of 1,4-*cis*-isomer **14** and dimer **15** (Scheme 3).

According to ^{1}H NMR experiments, in all 1,4-disubstituted compounds **5**–**15**, the piperazine ring adopts a boat conformation, with the alkyl chain at C(4) in an axial disposition. The important NOEs observed in these compounds between the H(1) and the C(4) alkyl protons corroborate this conformation. In compound **10**, an additional shielding effect was observed on H(1), which is produced by the C(4) phenyl ring (Fig. 2). The boat conformation contrasts with the flat boat conformation previously described for the alkylated lactam isomers of **1**.[9–16] This conformational difference explains the greater integrity of the C(1)-stereogenic centre in the 1,4-*trans*-dialkyllactim ethers in comparison to 1,4-*trans*-lactams **1**, where the mobile proton H(1) is nearly coplanar to the whole ring system.[9–16]

Cyclization of compounds **12** and **13** through a subsequent N(2)-alkylation to give stereoselectively the pentacyclic compounds **16** and **17**, required the assistance of sodium iodide, to promote a Finkelstein reaction. Only



Scheme 2.



Scheme 3.

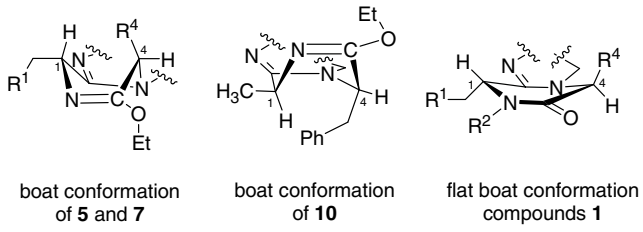
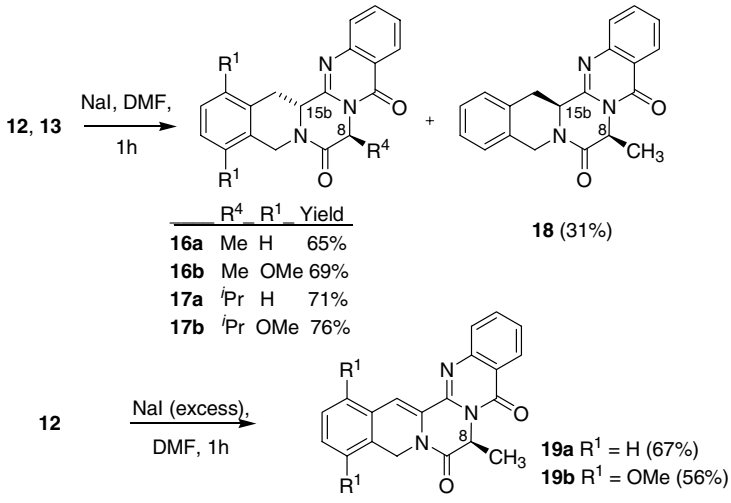


Figure 2. Conformation of the piperazine ring in 1,4-dialkyl *anti*- and *syn*-isomers.

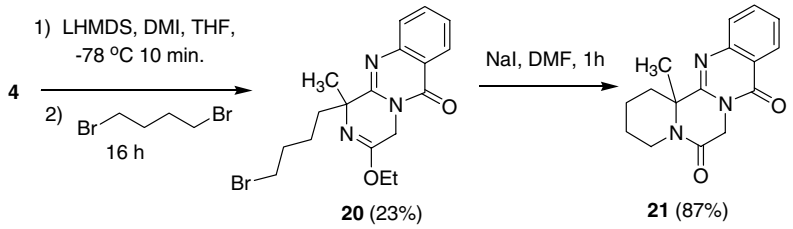
in **16a** was the stereocentre C(15b), which was partially epimerized, giving in part **18** during work-up (Scheme 4). This type of cyclization has previously been observed by Davies et al. on a similar allylic system in diketopiperazine bis-lactim ethers.[21] The exclusive formation of the didehydroderivatives **19** when compounds **12** were treated with an excess of NaI is also noticeable. According to our experiences with related systems,[22,23] compounds **19** are probably formed through a radical iodination of compounds **16** at the 15b-captodative position followed by subsequent dehydrohalogenation. The stereochemistry of the pentacyclic compounds **16** and **17** was confirmed by NOESY experiments [NOE between H(15b)-proton and the methyl or isopropyl substituent at C(8) confirms their *syn* relationship] and their enantiomeric purity was measured by chiral HPLC.

In a similar protocol, 1-substituted lactim ether **4** was dialkylated with tetramethylene bromide to give first,



	R4	R1	Yield
16a	Me	H	65%
16b	Me	OMe	69%
17a	iPr	H	71%
17b	iPr	OMe	76%

Scheme 4.



Scheme 5.

with DMI as a cosolvent, compound **20** and, finally, the fused tetracycle **21** (Scheme 5).

3. Conclusion

Herein, we have reported a simple method for the diastereocontrolled synthesis of different fused polycyclic systems containing a diketopiperazine ring by starting from the so far unexplored lactim ethers.

4. Experimental

4.1. General methods

All reagents were of commercial quality and 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 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 microanalyzer.

4.2. (1*S*)-3-Ethoxy-1-(or 4-)alkyl-1,4-dihydropyrazino-[2,1-*b*]quinazolin-6-ones 2–4: general procedure

The mixture of the corresponding 1- or 4-alkyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-3,6-dione **1** (1.0 mmol; vacuum dried),[14,16] triethyloxonium tetrafluoroborate (0.57 g, 2.3 mmol) and anhydrous Na_2CO_3 (0.52 g, 4.5 mmol) in 10 mL dry CH_2Cl_2 was stirred for 24 h at room temperature and then ice water was added. The product was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated, yielding 95%, 93% and 95% of **2**, **3** and **4**, respectively, as oily products.

4.2.1. (+)-(4*S*)-3-Ethoxy-4-methyl-1,4-dihydropyrazino-[2,1-*b*]quinazolin-6-one 2. $[\alpha]_D^{25} = +143.1$ (*c* 0.16, $CHCl_3$); ν_{max} (NaCl) 2981, 1679, 1604 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.25 (1H, dd, $J = 1.4$ and $J = 8.0$ Hz, H-7), 7.74 (1H, ddd, $J = 1.4$, 7.0 and 8.4 Hz, H-9), 7.63 (1H, dd, $J = 1.2$ and 8.4 Hz, H-10), 7.45 (1H, ddd, $J = 1.2$, 7.0 and 8.0 Hz, H-8), 5.29 (1H, dq, $J = 1.1$ and 7.0 Hz, H-4), 4.80 (1H, d, $J = 19.6$ Hz, H-1), 4.65 (1H, dd, $J = 1.1$ and 19.6 Hz, H-1), 4.19 (2H, q, $J = 7.1$ Hz, O–*CH*$_2$–CH$_3$), 1.53 (3H, d, $J = 7.0$ Hz, O–CH$_2$–*CH*$_3$), 1.32 (3H, t, $J = 7.1$ Hz, *CH*$_3$); δ_C (62.5 MHz, $CDCl_3$) 164.1 (C-3), 160.3 (C-6), 150.7 (C-11a), 147.4 (C-10a), 134.6 (C-9), 126.7 (C-10), 126.6 (C-7), 126.5 (C-8), 120.1 (C-6a), 62.1 (O–*CH*$_2$–CH$_3$), 50.6 (C-1), 47.7 (C-4), 16.5 (*CH*$_3$), 14.0 (O–CH$_2$–*CH*$_3$). $C_{14}H_{15}O_2N_3$ requires: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.46; H, 5.83; N, 15.57.

4.2.2. (+)-(4*S*)-3-Ethoxy-4-isopropyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 3. $[\alpha]_D^{25} = +187.3$ (*c* 0.15, $CHCl_3$); ν_{max} (NaCl) 2927, 1678, 1600, 1472, 1328, 1028 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.25 (1H, dd, $J = 1.4$ and 8.1 Hz, H-7), 7.74 (1H, ddd, $J = 1.4$, 7.1 and 8.3 Hz, H-9), 7.63 (1H, dd, $J = 1.2$ and 8.3 Hz, H-10), 7.45 (1H, ddd, $J = 1.2$, 7.1 and 8.1 Hz, H-8), 5.20 (1H, d, $J = 6.3$ Hz, H-4), 4.77 (1H, d, $J = 20.4$ Hz, H-1), 4.68 (1H, d, $J = 20.4$ Hz, H-1), 4.20 (2H, m, O–*CH*$_2$–CH$_3$), 2.28 (1H, m, $J = 6.8$ Hz, CH$_3$–*CH*–CH$_3$), 1.33 (3H, t, $J = 7.1$ Hz, O–CH$_2$–*CH*$_3$), 1.08 (3H, d, $J = 6.8$ Hz, *CH*$_3$–CH–CH$_3$), 0.97 (3H, d, $J = 6.8$ Hz, CH$_3$–CH–*CH*$_3$); δ_C (62.5 MHz, $CDCl_3$) 163.2 (C-3), 161.0 (C-6), 151.7 (C-11a), 147.5 (C-10a), 134.8 (C-9), 127.0 (C-10), 126.9 (C-7), 126.7 (C-8), 120.3 (C-6a), 62.0 (O–*CH*$_2$–CH$_3$), 57.0 (C-4), 51.7 (C-1), 32.5 (CH$_3$–*CH*–CH$_3$), 21.2 (*CH*$_3$–CH–CH$_3$), 19.6 (CH$_3$–CH–*CH*$_3$), 14.4 (O–CH$_2$–*CH*$_3$). $C_{16}H_{19}O_2N_3$ requires: C,

67.35; H, 6.71; N, 14.73. Found: C, 67.27; H, 6.63; N, 14.54.

4.2.3. (+)-(1*S*)-3-Ethoxy-1-methyl-1,4-dihydropyrazino[2,1-*b*]-quinazolin-6-one 4. Since the starting piperazine-2,5-dione **1** could only be obtained with an ee = 80%,[14] no specific rotation could be determined for **4** and its derivatives; ν_{max} (NaCl) 2981, 1679, 1604 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.19 (1H, dd, $J = 1.5$ and 8.0 Hz, H-7), 7.70 (1H, ddd, $J = 1.5$, 7.0 and 8.4 Hz, H-9), 7.60 (1H, dd, $J = 1.2$ and 8.4 Hz, H-10), 7.40 (1H, ddd, $J = 1.2$, 7.0 and 8.0 Hz, H-8), 4.76 (1H, dq, $J = 1,1$ and 7.1 Hz, H-1), 4.71 (1H, dd, $J = 1.1$ and 17.5 Hz, H-4), 4.31 (1H, d, $J = 17.5$ Hz, H-4), 4.18 (2H, q, $J = 7.1$ Hz, O–*CH_2*–CH_3), 1.54 (3H, d, $J = 7.1$ Hz, *CH_3*), 1.29 (3H, t, $J = 7.1$ Hz, O–CH_2–*CH_3*); δ_C (62.5 MHz, $CDCl_3$) 161.1, 159.2, 154.2, 147.6, 134.7, 127.1, 126.7, 126.6, 119.8, 62.2, 56.7, 40.5, 21.9, 14.2. $C_{14}H_{15}O_2N_3$ requires: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.09; H, 5.75; N, 16.48.

4.3. General alkylation procedures

4.3.1. Alkylation of 2–4. To a cold (−78 °C) magnetically stirred solution of **2** (257 mg, 1.0 mmol) in dry THF (10 mL) was added, under argon, a solution of lithium hexamethyldisilazide in THF (1 M, 1.1 mL) dropwise via syringe, followed by a solution of the appropriate halide [1.0 mmol dissolved in THF (5 mL)] after 10 min. The reaction mixture was stirred at −78 °C for 30 min for **2**, 1 h for **3** or 16 h for **4**, quenched with ice and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography to furnish compounds **5**–**8** and **10** as white syrups.

4.3.1.1. (+)-(1*R*,4*S*)-1,4-Dimethyl-3-ethoxy-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 5a. Column chromatography (ethyl acetate/CH_2Cl_2/triethylamine, 1:1:0.02) afforded **5a** (yield 57%) followed by **6a** (yield 19%). $[\alpha]_D^{25} = +253.5$ (*c* 0.17, $CHCl_3$); ν_{max} (NaCl) 2983, 2938, 1684, 1595, 1569 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.22 (1H, ddd, $J = 0.8$, 1.4 and 8.1 Hz, H-7), 7.69 (1H, ddd, $J = 1.4$, 6.7 and 8.2 Hz, H-9), 7.62 (1H, dd, $J = 1.6$ and 8.2 Hz, H-10), 7.41 (1H, ddd, $J = 1.6$, 6.7 and 8.1 Hz, H-8), 5.30 (1H, dq, $J = 0.8$ and 7.0 Hz, H-4), 4.55 (1H, dq, $J = 0.8$ and 6.9 Hz, H-1), 4.18 (2H, q, $J = 7.2$ Hz, O–*CH_2*–CH_3), 1.78 (3H, d, $J =$ 6.9 Hz, *CH_3*-1), 1.50 (3H, d, $J = 7.0$ Hz, *CH_3*-4), 1.28 (3H, t, $J = 7.2$ Hz, O–CH_2–*CH_3*); δ_C (62.5 MHz, $CDCl_3$) 163.2 (C-3), 160.6 (C-6), 153.9 (C-11a), 147.4 (C-10a), 134.3 (C-9), 127.4 (C-10), 126.5 (C-8), 126.4 (C-7), 120.1 (C-6a), 61.9 (O–*CH_2*–CH_3), 53.4 (C-1), 48.5 (C-4), 20.3 (*CH_3*-1), 15.8 (*CH_3*-4), 14.1 (O–CH_2–*CH_3*). $C_{15}H_{17}O_2N_3$ requires: C, 66.39; H, 6.32; N, 15.49. Found: C, 66.26; H, 6.29; N, 15.38.

4.3.1.2. (−)-(1*S*,4*S*)-1,4-Dimethyl-3-ethoxy-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 6a. $[\alpha]_D^{25} = -13.7$ (*c* 0.26, $CHCl_3$); ν_{max} (NaCl) 2979, 2933, 1683, 1654, 1595 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.25 (1H, ddd, $J = 0.8$, 1.5 and 8.0 Hz, H-7), 7.74 (1H, ddd, $J = 1.5$, 7.1 and 8.3 Hz, H-9), 7.63 (1H, dd, $J = 1.0$ and 8.3 Hz, H-10), 7.43 (1H, ddd, $J = 1.0$, 7.1 and 8.0 Hz, H-8), 5.11 (1H, q, $J = 6.9$ Hz, H-4), 4.86 (1H, q, $J = 7.3$ Hz, H-1), 4.15 (2H, m, $J = 7.1$ and 10.6 Hz, O–*CH_2*–CH_3), 1.59 (6H, d, $J = 7.1$ Hz, *CH_3*-1 and *CH_3*-4), 1.28 (3H, t, $J = 7.1$ Hz, O–CH_2–*CH_3*); δ_C (62.5 MHz, $CDCl_3$) 162.0 (C-3), 160.8 (C-6), 154.7 (C-11a), 147.8 (C-10a), 134.7 (C-9), 126.9 (C-10), 126.7 (C-7), 126.5 (C-8), 120.2 (C-6a), 61.9 (O–*CH_2*–CH_3), 57.0 (C-1), 47.9 (C-4), 24.4* (*CH_3*-1), 19.5* (*CH_3*-4), 14.2 (O–CH_2–*CH_3*). $C_{15}H_{17}O_2N_3$ requires: C, 66.39; H, 6.32; N, 15.49. Found: C, 66.13; H, 5.99; N, 15.29.

4.3.1.3. (+)-(1*R*,4*S*)-1-Benzyl-3-ethoxy-4-methyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 5b. Column chromatography (CH_2Cl_2/triethylamine, 100:2) afforded **5b** (yield 50%). Long chromatography times induce epimerization to the *cis*-isomer **6b**. $[\alpha]_D^{25} = +159.3$ (*c* 0.15, $CHCl_3$); ν_{max} (NaCl) 2979, 2930, 1678, 1598 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.24 (1H, dd, $J = 1.5$ and 8.1 Hz, H-7), 7.77 (1H, dd, $J = 1.1$ and 8.2 Hz, H-10), 7.76 (1H, ddd, $J = 1.5$, 5.3 and 8.1 Hz, H-9), 7.45 (1H, ddd, $J = 1.1$, 7.0 and 8.2 Hz, H-8), 7.38 (2H, m, Ar–H′), 7.21 (3H, m, Ar–H′), 5.16 (1H, dq, $J = 1.2$ and 7.0 Hz, H-4), 4.73 (1H, dd, $J = 3.9$ and 7.9 Hz, H-1), 4.18 (2H, m, O–*CH_2*–CH_3), 3.83 (1H, dd, $J = 3.9$ and 13.5 Hz, *CH_2*–Ar–H′), 3.32 (1H, dd, $J = 7.9$ and 13.5 Hz, *CH_2*–Ar–H′), 1.47 (3H, d, $J = 7.0$ Hz, *CH_3*), 1.28 (3H, t, $J = 7.1$ Hz, O–CH_2–*CH_3*); δ_C (62.5 MHz, $CDCl_3$) 162.4 (C-3), 160.6 (C-6), 152.4 (C-11a), 147.0 (C-10a), 138.8 (C-1′), 134.4 (C-9), 130.5 (C-2′ and 6′), 127.7 (C-3′ and 5′), 127.2 (C-4′), 126.6 (C-10), 126.5 (C-7), 126.1 (C-8), 120.1 (C-6a), 61.8 (O–*CH_2*–CH_3), 58.7 (C-1), 48.0 (C-4), 39.4 (*CH_2*–Ar–H′), 16.4 (*CH_3*), 14.0 (O–CH_2–*CH_3*). $C_{21}H_{21}O_2N_3$ requires: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.29; H, 5.76; N, 11.69.

4.3.1.4. (+)-(1*S*,4*S*)-1-Benzyl-3-ethoxy-4-methyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 6b. $[\alpha]_D^{25} = +5.2$ (*c* 0.16 $CHCl_3$); ν_{max} (NaCl) 2920, 2849, 1680, 1606, 1592 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.23 (1H, dd, $J = 1.4$ and 8.2 Hz, H-7), 7.77 (1H, ddd, $J = 1.4$, 6.9 and 8.4 Hz, H-9), 7.69 (1H, dd, $J = 1.4$ and 8.4 Hz, H-10), 7.45 (1H, ddd, $J = 1.4$, 6.9 and 8.2 Hz, H-8), 7.17 (3H, m, Ar–H′), 7.05 (2H, m, Ar–H′), 5.13 (1H, ddd, $J = 1.4$, 4.7 and 6.2 Hz, H-1), 4.88 (1H, dq, $J = 1.4$ and 6.9 Hz, H-4), 4.19 (2H, m, O–*CH_2*–CH_3), 3.47 (1H, dd, $J = 6.2$ and 13.2 Hz, *CH_2*–Ar–H′), 3.36 (1H, dd, $J = 4.7$ and 13.2 Hz, *CH_2*–Ar–H′), 1.31 (3H, t, $J = 7.1$ Hz, O–CH_2–*CH_3*), 0.79 (3H, d, $J = 6.9$ Hz, *CH_3*); δ_C (62.5 MHz, $CDCl_3$) 161.0 (C-3), 160.5 (C-6), 152.8 (C-11a), 147.4 (C-10a), 136.9 (C-1′), 134.5 (C-9), 130.0 (C-2′ and 6′), 128.2 (C-3′ and 5′), 126.8 (C-4′), 126.7 (C-10), 126.5 (C-7), 126.3 (C-8), 120.1 (C-6a), 61.9 (C-1), 61.5 (O–*CH_2*–CH_3), 47.5 (C-4), 43.0 (*CH_2*–Ar–H′), 17.8 (*CH_3*), 14.2 (O–CH_2–*CH_3*). $C_{21}H_{21}O_2N_3$ requires: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.37; H, 5.81; N, 11.75.

4.3.1.5. (+)-(1*R*,4*S*)-3-Ethoxy-4-isopropyl-1-methyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 7a. Column chromatography (ethyl acetate/petroleum ether/triethylamine, 4:6:0.2) afforded **7a** (yield 52%) followed by **8a**

(yield 14%); $[\alpha]_D^{25} = +231.4$ (c 0.29, $CHCl_3$); ν_{max} (NaCl) 2974, 2936, 1684, 1654, 1595 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.25 (1H, ddd, $J = 0.6$, 1.5 and 8.0 Hz, H-7), 7.74 (1H, ddd, $J = 1.5$, 6.7 and 8.2 Hz, H-9), 7.68 (1H, dd, $J = 1.6$ and 8.2 Hz, H-10), 7.45 (1H, ddd, $J = 1.6$, 6.7 and 8.0 Hz, H-8), 5.24 (1H, d, $J = 7.1$ Hz, H-4), 4.64 (1H, q, $J = 6.9$ Hz, H-1), 4.21 (2H, m, O–CH_2–CH_3), 2.32 (1H, m, $J = 7.1$ Hz, CH_3–CH–CH_3), 1.78 (3H, d, $J = 6.9$ Hz, CH_3-1), 1.32 (3H, t, $J = 7.2$ Hz, O–CH_2–CH_3), 1.05 (3H, d, $J = 7.1$ Hz, CH_3–CH–CH_3), 1.02 (3H, d, $J = 7.1$ Hz, CH_3–CH–CH_3); δ_C (62.5 MHz, $CDCl_3$) 162.9 (C-3), 161.5 (C-6), 155.2 (C-11a), 147.7 (C-10a), 134.8 (C-9), 127.7 (C-10), 127.2 (C-7), 127.0 (C-8), 120.5 (C-6a), 62.2 (O–CH_2–CH_3), 58.1 (C-4), 54.5 (C-1), 32.0 (CH_3–CH–CH_3), 21.2 (CH_3-1), 20.7 (CH_3–CH–CH_3), 19.3 (CH_3–CH–CH_3), 14.6 (O–CH_2–CH_3). $C_{17}H_{21}O_2N_3$ requires: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.00; H, 7.09; N, 13.95.

4.3.1.6. (−)-(1*S*,4*S*)-3-Ethoxy-4-isopropyl-1-methyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 8a. $[\alpha]_D^{25} = -26.8$ (c 0.25, $CHCl_3$); ν_{max} (NaCl) 2977, 2937, 1681, 1594, 1568, 1473 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (1H, ddd, $J = 0.5$, 1.5 and 8.1 Hz, H-7), 7.76 (1H, ddd, $J = 1.5$, 7.0 and 8.3 Hz, H-9), 7.64 (1H, ddd, $J = 0.5$, 1.3 and 8.3 Hz, H-10), 7.45 (1H, ddd, $J = 1.3$, 7.0 and 8.1 Hz, H-8), 5.12 (1H, dd, $J = 1.1$ and 6.1 Hz, H-4), 4.91 (1H, dq, $J = 1.0$ and 7.4 Hz, H-1), 4.21 (2H, m, O–CH_2–CH_3), 2.17 (1H, m, $J = 6.9$ Hz, CH_3–CH–CH_3), 1.73 (3H, d, $J = 7.4$ Hz, CH_3-1), 1.35 (3H, t, $J = 7.1$ Hz, O–CH_2–CH_3), 1.10 (3H, d, $J = 6.9$ Hz, CH_3–CH–CH_3), 1.04 (3H, d, $J = 6.9$ Hz, CH_3–CH–CH_3); δ_C (62.5 MHz, $CDCl_3$) 161.6 (C-6), 160.8 (C-3), 155.4 (C-11a), 147.8 (C-10a), 135.0 (C-9), 127.2 (C-7), 127.0 (C-10), 126.7 (C-8), 120.4 (C-6a), 61.9 (O–CH_2–CH_3), 57.4 (C-1), 56.5 (C-4), 34.2 (CH_3–CH–CH_3), 23.7 (CH_3-1), 20.8 (CH_3–CH–CH_3), 19.7 (CH_3–CH–CH_3), 14.6 (O–CH_2–CH_3). $C_{17}H_{21}O_2N_3$ requires: C, 68.20; H, 7.07; N, 14.04. Found: C, 67.72; H, 7.00; N, 13.89.

4.3.1.7. (+)-(1*R*,4*S*)-1-Benzyl-3-ethoxy-4-isopropyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 7b. Column chromatography (CH_2Cl_2/hexane/triethylamine, 9:1:0.2) afforded **7b** (yield 54%). $[\alpha]_D^{25} = +178.1$ (c 0.11, $CHCl_3$); ν_{max} (NaCl) 2925, 2853, 1735, 1681, 1595, 1471 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.24 (1H, dd, $J = 1.5$ and 8.0 Hz, H-7), 7.76 (1H, m, H-9), 7.73 (1H, m, H-10), 7.45 (1H, ddd, $J = 2.3$, 5.9 and 8.1 Hz, H-8), 7.38 (2H, m, Ar–H′), 7.22 (3H, m, Ar–H′), 5.12 (1H, dd, $J = 0.9$ and 6.8 Hz, H-4), 4.76 (1H, dd, $J = 4.0$ and 7.9 Hz, H-1), 4.18 (2H, m, O–CH_2–CH_3), 3.80 (1H, dd, $J = 4.0$ and 13.5 Hz, CH_2–Ar–H′), 3.29 (1H, dd, $J = 7.9$ and 13.5 Hz, CH_2–Ar–H′), 2.21 (1H, m, $J = 6.9$ Hz, CH_3–CH–CH_3), 1.28 (3H, t, $J = 7.1$ Hz, O–CH_2–CH_3), 1.02 (3H, d, $J = 6.9$ Hz, CH_3–CH–CH_3), 0.92 (3H, d, $J = 6.9$ Hz, CH_3–CH–CH_3); δ_C (62.5 MHz, $CDCl_3$) 161.5 (C-3), 161.1 (C-6), 153.2 (C-11a), 147.0 (C-10a), 139.0 (C-1′), 134.4 (C-9), 130.5 (C-2′ and 6′), 127.6 (C-3′ and 5′), 127.2 (C-10), 126.7 (C-7), 126.5 (C-8), 126.0 (C-4′), 120.0 (C-6a), 61.6 (O–CH_2–CH_3), 59.3 (C-1), 57.0 (C-4), 39.8 (CH_2–Ar–H′), 31.8 (CH_3–CH–CH_3), 20.1 (CH_3–CH–CH_3), 18.6 (CH_3–CH–CH_3), 14.2 (O–CH_2–CH_3). $C_{23}H_{25}O_2N_3$ requires: C, 73.57; H, 6.71; N, 11.19. Found: C, 73.39; H, 6.68; N, 11.08.

4.3.1.8. (1*S*,4*R*)-4-Benzyl-3-ethoxy-1-methyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 10. Column chromatography [CH_2Cl_2/triethylamine (50:1)] afforded 187 mg (53%) of **10**. ν_{max} (NaCl) 2930, 1677, 1593, 1472, 1415 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.30 (1H, dd, $J = 1.6$ and 8.1 Hz, H-7), 7.75 (1H, ddd, $J = 1.6$, 7.1 and 8.3 Hz, H-9), 7.63 (1H, dd, $J = 1.2$ and 8.3 Hz, H-10), 7.47 (1H, ddd, $J = 1.2$, 7.1 and 8.1 Hz, H-8), 7.18 (3H, m, Ar–H′), 6.87 (2H, m, Ar–H′), 5.49 (1H, ddd, $J = 1.5$, 3.6 and 6,1 Hz, H-4), 4.16 (2H, dq, $J = 0.6$ and 7.1 Hz, O–CH_2–CH_3), 3.39 (1H, dd, $J = 6.1$ and 13.8 Hz, CH_2–Ar–H′), 3.27 (1H, dq, $J = 1.5$ and 7.0 Hz, H-1), 3.23 (1H, dd, $J = 3.6$ and 13.8 Hz, CH_2–Ar–H′), 1.52 (3H, d, $J = 7.0$ Hz, CH_3), 1.28 (3H, t, $J = 7.1$ Hz, O–CH_2–CH_3); δ_C (62.5 MHz, $CDCl_3$) 160.9 (C-3), 159.6 (C-6), 154.7 (C-11a), 147.4 (C-10a), 135.1 (C-1′), 134.5 (C-9), 129.6 (C-2′ and 6′), 128.6 (C-3′ and 5′), 127.5 (C-10), 127.4 (C-4′), 126.6 (C-8), 126.5 (C-7), 119.9 (C-6a), 61.6 (O–CH_2–CH_3), 53.8 (C-4), 53.5 (C-1), 36.4 (CH_2–Ar–H′), 21.4 (CH_3), 14.2 (O–CH_2–CH_3). $C_{21}H_{21}O_2N_3$ requires: C, 72.60; H, 6.09; N, 12.10. Found: C, 71.65; H, 6.26; N, 11.70.

4.3.2. Alkylations with DMI as cosolvent. To a cold (−78 °C) magnetically stirred solution of **2** or **4** (1.0 mmol) and 2 equiv of DMI in dry THF (10 mL) was added, under argon, a solution of lithium hexamethyldisilazide in THF (1 equiv) dropwise via syringe, followed by a solution of benzyl bromide or 1,4-dibromobutane (1.0 equiv dissolved in THF) after 10 min. The reaction mixture was stirred at −78 °C for 1.5 h for **2** or 16 h for **4**, quenched with ice and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography to furnish **9** or **11** as white syrups.

4.3.2.1. (+)-(4*S*)-1,1-Dibenzyl-3-ethoxy-4-methyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 9. Column chromatography [toluene/ethyl acetate (95:5)] afforded 142 mg (30%) of **9** and 17 mg (5%) of **5b**. $[\alpha]_D^{25} = +158.7$ (c 0.15, $CHCl_3$); ν_{max} (NaCl) 3062, 3029, 2929, 1681, 1585 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.16 (1H, dd, $J = 1.4$ and 8.1 Hz, H-7), 7.91 (1H, dd, $J = 1.5$ and 8.2 Hz, H-10), 7.84 (1H, ddd, $J = 1.4$, 6.8 and 8.2 Hz, H-9), 7.47 (1H, ddd, $J = 1.5$, 6.8 and 8.1 Hz, H-8), 6.98 (10H, m, Ar–H), 4.33 (3H, m, H-4 and O–CH_2–CH_3), 3.97 (1H, d, $J = 12.4$ Hz, CH_2–Ar–H′), 3.86 (1H, d, $J = 12.4$ Hz, CH_2–Ar–H″), 3.23 (1H, d, $J = 12.4$ Hz, CH_2–Ar–H″), 3.22 (1H, d, $J = 12.4$ Hz, CH_2–Ar–H′), 1.35 (3H, t, $J = 7.1$ Hz, O–CH_2–CH_3), 0.32 (3H, d, $J = 6.7$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 160.1 (C-6), 158.8 (C-3), 154.0 (C-11a), 146.7 (C-10a), 137.2 (C-1′), 136.6 (C-1″), 134.4 (C-9), 130.6 (C-2′ and 6′), 130.1 (C-2″ and 6″), 128.0 (C-3″ and 5″), 127.5 (C-3′ and 5′), 127.0 (C-4″), 126.6 (C-10), 126.5 (C-4′), 126.4 (C-7), 126.3 (C-8), 119.9 (C-6a), 68.5 (C-1), 60.9 (O–CH_2–CH_3), 50.4 (CH_2–Ar–H″), 48.4 (CH_2–Ar–H′), 46.9 (C-4), 17.7 (CH_3), 14.4 (O–CH_2–CH_3).

$C_{28}H_{27}O_2N_3$ requires: C, 76.86; H, 6.22; N, 9.60. Found: C, 76.33; H, 6.36; N, 9.90.

4.3.2.2. (±)-1-Benzyl-3-ethoxy-1-methyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 11. Column chromatography [CH_2Cl_2/petroleum ether (9:1)] afforded 45% of **11**. ν_{max} (NaCl) 2977, 2929, 1682, 1610, 1589, 1566 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.18 (1H, dd, $J = 2.0$ and 8.0 Hz, H-7), 7.76 (2H, m, H-9 and 10), 7.44 (1H, m, H-8), 7.08 (3H, m, Ar–H′), 6.79 (2H, m, Ar–H′), 4.26 (2H, q, $J = 7.1$ Hz, O–*CH_2*–CH_3), 4.18 (1H, d, $J = 18.6$ Hz, H-4), 3.46 (1H, d, $J = 12.7$ Hz, *CH_2*–Ar–H′), 3.04 (1H, d, $J = 12.7$ Hz, *CH_2*–Ar–H′), 2.78 (1H, d, $J = 18.6$ Hz, H-4), 1.86 (3H, s, *CH_3*), 1.32 (3H, t, $J = 7.1$ Hz, O–CH_2–*CH_3*); δ_C (62.5 MHz, $CDCl_3$) 160.7 (C-3), 156.5 (C-6), 155.2 (C-11a), 147.3 (C-10a), 136.6 (C-1′), 134.4 (C-9), 130.1 (C-2′ and 6′), 128.0 (C-3′ and 5′), 127.4 (C-10), 127.0 (C-4′), 126.5 (C-8), 126.4 (C-7), 119.4 (C-6a), 63.5 (C-1), 61.4 (O–*CH_2*–CH_3), 50.3 (*CH_2*–Ar–H′), 40.8 (C-4), 30.3 (*CH_3*), 14.3 (O–CH_2–*CH_3*). $C_{21}H_{21}O_2N_3$ requires: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.36; H, 6.60; N, 11.63.

4.3.2.3. (±)-1-(4-Bromobutyl)-3-ethoxy-1-methyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 20. Column chromatography [CH_2Cl_2/petroleum ether (8:2)] afforded 23% of **20**. ν_{max} (NaCl) 2934, 1680, 1611, 1591, 1567 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.23 (1H, ddd, $J = 0.5$, 1.5 and 8.0 Hz, H-7), 7.74 (1H, ddd, $J = 1.5$, 6.8 and 8.3 Hz, H-9), 7.66 (1H, ddd, $J = 0.5$, 1.4 and 8.3 Hz, H-10), 7.44 (1H, ddd, $J = 1.4$, 6.8 and 8.0 Hz, H-8), 4.61 (1H, d, $J = 18.6$ Hz, H-4), 4.38 (1H, d, $J = 18.6$ Hz, H-4), 4.24 (2H, m, O–*CH_2*–CH_3), 3.35 (2H, m, H-4′), 2.34 (1H, m, H-1′), 1.83 (3H, m, H-1′ and 3′), 1.54 (3H, s, *CH_3*), 1.33 (3H, t, $J = 7.1$ Hz, O–CH_2–*CH_3*), 1.25 (2H, m, H-2′); δ_C (62.5 MHz, $CDCl_3$) 161.3 (C-3), 156.4 (C-6), 155.4 (C-11a), 147.5 (C-10a), 134.5 (C-9), 127.4* (C-7), 126.5* (C-8), 126.4* (C-10), 119.5 (C-6a), 61.9 (C-1), 61.6 (O–*CH_2*–CH_3), 41.5* (C-4), 41.0* (C-3′), 33.6* (C-4′), 32.8* (C-1′), 29.5 (*CH_3*), 23.0 (C-2′), 14.2 (O–CH_2–*CH_3*). $C_{18}H_{22}O_2N_3Br$ requires: C, 55.10; H, 5.70; N, 10.70. Found: C, 55.26; H, 5.61; N, 10.59.

4.3.3. (+)-(1*R*,4*S*)-1-(2-Bromomethylbenzyl)- and 1-(2-bromomethyl-3,6-dimethoxybenzyl)-3-ethoxy-4-alkyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-ones 12 and 13: general procedure. To a cold (−78 °C) magnetically stirred solution of **2** or **3** (1.0 mmol) in dry THF (10 mL) was added, under argon, a solution of lithium hexamethyldisilazide in THF (1 M, 1.5 mL) dropwise via syringe. After 10 min, the basic cold solution was transferred with a double-tipped needle over a cold solution (−78 °C) of the corresponding 1,2-bisbromoxylene (1.0 mmol) in THF (25 mL). The reaction mixture was stirred at −78 °C for 16 h, quenched with ice and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography [petroleum ether/ethyl acetate (9:1) for **12** and petroleum ether/ethyl acetate/triethylamine (95:5:2) for **13**] to furnish compounds **12**–**15** as oily products.

4.3.3.1. (+)-(1*R*,4*S*)-1-(2-Bromomethylbenzyl)-3-ethoxy-4-methyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 12a. Yield 47% of **12a** and 11% of dimer **15**. $[\alpha]_D^{25} = +52.8$ (*c* 0.36, $CHCl_3$); ν_{max} (NaCl) 2980, 2928, 1676, 1597 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (1H, ddd, $J = 0.8$, 1.4 and 8.2 Hz, H-7), 7.77 (2H, m, H-9 and H-10), 7.47 (1H, ddd, $J = 1.2$, 7.0 and 8.2 Hz, H-8), 7.45 (1H, dd, $J = 1.4$ and 7.5 Hz, H-6′), 7.37 (1H, dd, $J = 1.4$ and 7.5 Hz, H-3′), 7.19 (2H, m, H-4′ and 5′), 5.28 (1H, dq, $J = 1.1$ and 7.1 Hz, H-4), 5.00 (1H, d, $J = 10.0$ Hz, Ar–*CH_2*–Br), 4.72 (1H, d, $J = 10.0$ Hz, Ar–*CH_2*–Br), 4.71 (1H, dd, $J = 3.5$ and 9.1 Hz, H-1), 4.10 (1H, dd, $J = 3.5$ and 14.1 Hz, C_1–*CH_2*–Ar–H′), 4.09 (2H, q, $J = 7.1$ Hz, O–*CH_2*–CH_3), 3.35 (1H, dd, $J = 9.1$ and 14.1 Hz, C_1–*CH_2*–Ar–H′), 1.46 (3H, d, $J = 7.1$ Hz, *CH_3*), 1.24 (3H, t, $J = 7.1$ Hz, O–CH_2–*CH_3*); δ_C (62.5 MHz, $CDCl_3$) 163.3 (C-3), 160.6 (C-6), 152.2 (C-11a), 147.1 (C-10a), 138.7 (C-2′), 137.2 (C-1′), 134.4 (C-9), 131.5 (C-6′), 130.3 (C-3′), 128.5 (C-5′), 127.4 (C-10), 126.9 (C-8), 126.7 (C-4′), 126.7 (C-7), 120.1 (C-6a), 61.9 (O–*CH_2*–CH_3), 58.9 (C-1), 48.2 (C-4), 35.3 (C_1–*CH_2*–Ar–H′), 33.0 (Ar–*CH_2*–Br), 15.8 (*CH_3*), 14.0 (O–CH_2–*CH_3*). $C_{22}H_{22}O_2N_3Br$ requires: C, 60.01; H, 5.04; N, 9.54. Found: C, 60.12; H, 4.91; N, 9.45.

4.3.3.2. (1*R*,4*S*)-1,2-Bis-[(3-ethoxy-4-methyl-6-oxo-1,4-dihydropyrazino[2,1-*b*]quinazolin-1-yl)methyl]benzene 15. δ_H (250 MHz, $CDCl_3$) 8.23 (2H, dd, $J = 1.5$ and 8.0 Hz, H-7), 7.70 (2H, ddd, $J = 1.5$, 6.9 and 8.3 Hz, H-9), 7.62 (2H, dd, $J = 1.4$ and 8.3 Hz, H-10), 7.43 (4H, m, H-8 and Ar–H′), 7.19 (2H, m, Ar–H′), 5.24 (2H, dq, $J = 1.1$ and 7.0 Hz, H-4), 4.69 (2H, dd, $J = 2.6$ and 9.8 Hz, H-1), 4,16 (4H, dq, $J = 7.1$ and 10.8 Hz, O–*CH_2*–CH_3), 4.12 (2H, dd, $J = 2.6$ and 14.0 Hz, C_1–*CH_2*–Ar–H′), 3.55 (2H, dd, $J = 9.8$ and 14.0 Hz, C_1–*CH_2*–Ar–H′), 1.46 (6H, d, $J = 7.0$ Hz, *CH_3*), 1.26 (6H, t, $J = 7.1$ Hz, O–CH_2–*CH_3*); δ_C (62.5 MHz, $CDCl_3$) 162.9 (C-3), 160.9 (C-6), 153.0 (C-11a), 147.4 (C-10a), 136.9 (C-1′ and 2′), 134.5 (C-9), 130.7 (C-3′ and 6′), 127.5* (C-10), 126.8* (C-8), 126.7* (C-4′ and 5′), 126.2* (C-7), 120.3 (C-6a), 62.1 (O–*CH_2*–CH_3), 59.8 (C-1), 48.4 (C-4), 36.5 (C_1–*CH_2*–Ar–H′), 16.2 (*CH_3*), 14.4 (O–CH_2–*CH_3*). $C_{36}H_{36}O_4N_6$ requires: C, 70.11; H, 5.88; N, 13.63. Found: C, 70.36 H, 5.79; N, 13.51.

4.3.3.3. (+)-(1*R*,4*S*)-1-(2-Bromomethyl-3,6-dimethoxybenzyl)-3-ethoxy-4-methyl-1,4-dihydropyrazino[2,1-*b*]-quinazolin-6-one 12b. Yield 31% of **12b** and 16% of **14**. $[\alpha]_D^{25} = +48.7$ (*c* 0.25, $CHCl_3$); ν_{max} (NaCl) 2937, 1681, 1599, 1568, 1468 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.25 (1H, td, $J = 1.0$ and 8.0 Hz, H-7), 7.77 (2H, m, H-9 and H-10), 7.45 (1H, m, H-8), 6.62 (1H, d, $J = 9.0$ Hz, H-5′), 6.76 (1H, d, $J = 9.0$ Hz, H-4′), 5.30 (1H, dq, $J = 1.0$ and 7.1 Hz, H-4), 4.98 (1H, d, $J = 9.4$ Hz, Ar–*CH_2*–Br), 4.89 (1H, d, $J = 9.4$ Hz, Ar–*CH_2*–Br), 4.70 (1H, dd, $J = 3.3$ and 10.8 Hz, H-1), 4.27 (1H, dd, $J = 3.3$ and 13.8 Hz, C_1–*CH_2*–Ar–H′), 3.99 (2H, m, O–*CH_2*–CH_3), 3.86 (3H, s, OCH_3-3), 3.77 (3H, s, OCH_3-6), 3.10 (1H, dd, $J = 10.8$ and 13.8 Hz, C_1–*CH_2*–Ar–H′), 1.46 (3H, d, $J = 7.1$ Hz, *CH_3*), 1.21 (3H, t, $J = 7.0$ Hz, O–CH_2–*CH_3*); δ_C (62.5 MHz, $CDCl_3$)

163.4 (C-3), 160.7 (C-6), 152.7 (C-11a), 151.9 (C-6′), 151.7 (C-3′), 147.4 (C-10a), 134.3 (C-9), 128.9 (C-2′), 127.8 (C-1′), 127.7 (C-10), 126.6 (C-8), 126.4 (C-7), 120.1 (C-6a), 110.8 (C-4′), 109.3 (C-5′), 61.7 (O–*CH*$_2$–CH$_3$), 56.8 (C-1), 56.1 (OCH$_3$), 55.7 (OCH$_3$), 48.5 (C-4), 29.9 (C$_1$–*CH*$_2$–Ar–H′), 27.3 (Ar–*CH*$_2$–Br), 15.4 (*CH*$_3$), 14.0 (O–CH$_2$–*CH*$_3$). $C_{24}H_{26}O_4N_3Br$ requires: C, 57.61; H, 5.24; N, 8.40. Found: C, 57.45; H, 5.21; N, 8.37.

4.3.3.4. (+)-(1*S*,4*S*)-1-(2-Bromomethyl-3,6-dimethoxybenzyl)-3-ethoxy-4-methyl-1,4-dihydropyazino[2,1-*b*]-quinazolin-6-one 14. $[\alpha]_D^{25} = +54.0$ (*c* 0.25, $CHCl_3$); ν_{max} (NaCl) 2935, 1678, 1595, 1587, 1483, 1261 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.23 (1H, dd, $J = 1.6$ and 8.4 Hz, H-7), 7.66 (1H, ddd, $J = 1.6$, 7.2 and 8.0 Hz, H-9), 7.40 (1H, ddd, $J = 1.3$, 7.2 and 8.4 Hz, H-8), 7.39 (1H, dd, $J = 1.3$ and 8.0 Hz, H-10), 6.69 (1H, d, $J = 9.0$ Hz, H-5′), 6.50 (1H, d, $J = 9.0$ Hz, H-4′), 5.10 (1H, q, $J = 7.0$ Hz, H-4), 4.88 (1H, dd, $J = 6.7$ and 8.5 Hz, H-1), 4.87 (1H, d, $J = 9.7$ Hz, Ar–*CH*$_2$–Br), 4.65 (1H, d, $J = 9.7$ Hz, Ar–*CH*$_2$–Br), 4.12 (2H, q, $J = 7.1$ Hz, O–*CH*$_2$–CH$_3$), 3.83 (3H, s, OCH$_3$-3), 3.42 (1H, dd, $J = 6.7$ and 13.5 Hz, C$_1$–*CH*$_2$–Ar–H′), 3.26 (1H, dd, $J = 8.5$ and 13.5 Hz, C$_1$–*CH*$_2$–Ar–H′), 3.16 (3H, s, OCH$_3$-6), 1.63 (3H, d, $J = 7.0$ Hz, *CH*$_3$), 1.30 (3H, t, $J = 7.1$ Hz, O–CH$_2$–*CH*$_3$); δ_C (62.5 MHz, $CDCl_3$) 162.6 (C-3), 160.8 (C-6), 152.6 (C-11a), 152.1 (C-6′), 151.7 (C-3′), 147.4 (C-10a), 134.3 (C-9), 126.8 (C-8), 126.3 (C-7), 126.2 (C-1′), 126.2 (C-10), 125.9 (C-2′), 120.1 (C-6a), 110.2 (C-4′), 109.8 (C-5′), 61.8 (O–*CH*$_2$–CH$_3$), 61.3 (C-1), 56.1 (OCH$_3$), 54.9 (OCH$_3$), 48.3 (C-4), 34.2 (C$_1$–*CH*$_2$–Ar–H′), 26.2 (Ar–*CH*$_2$–Br), 18.5 (*CH*$_3$), 14.2 (O–CH$_2$–*CH*$_3$). $C_{24}H_{26}O_4N_3Br$ requires: C, 57.61; H, 5.24; N, 8.40. Found: C, 57.70; H, 5.12; N, 8.29.

4.3.3.5. (+)-(1*R*,4*S*)-1-(2-Bromomethylbenzyl)-3-ethoxy-4-isopropyl-1,4-dihydropyrazino[2,1-*b*]quinazolin-6-one 13a. Yield 44%; $[\alpha]_D^{25} = +70.9$ (*c* 1.60, $CHCl_3$); ν_{max} (NaCl) 2969, 2361, 1678, 1598 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (1H, td, $J = 1.6$ and 7.4 Hz, H-7), 7.77 (1H, dt, $J = 1.6$ and 8.2 Hz, H-9), 7.74 (1H, dd, $J = 2.4$ and 7.7 Hz, H-10), 7.47 (1H, ddd, $J = 2.4$, 6.9 and 8.1 Hz, H-8), 7.38 (2H, m, H-3′ and 6′), 7.24 (1H, dt, $J = 2.2$ and 7.5 Hz, H-5′), 7.20 (1H, dt, $J = 2.4$ and 7.5 Hz, H-4′), 5.18 (1H, dd, $J = 0.9$ and 7.4 Hz, H-4), 4.99 (1H, d, $J = 10.0$ Hz, Ar–*CH*$_2$–Br), 4.77 (1H, dd, $J = 3.4$ and 9.1 Hz, H-1), 4.73 (1H, d, $J = 10.0$ Hz, Ar–*CH*$_2$–Br), 4.12 (2H, m, O–*CH*$_2$–CH$_3$), 4.07 (1H, dd, $J = 3.4$ and 14.1 Hz, C$_1$–*CH*$_2$–Ar–H′), 3.31 (1H, dd, $J = 9.1$ and 14.1 Hz, C$_1$–*CH*$_2$–Ar–H′), 2.21 (1H, m, $J = 6.9$ Hz, CH$_3$–*CH*–CH$_3$), 1.25 (3H, t, $J = 7.1$ Hz, O–CH$_2$–*CH*$_3$), 1.00 (3H, d, $J = 6.9$ Hz, *CH*$_3$–CH–CH$_3$), 0.94 (3H, d, $J = 6.9$ Hz, CH$_3$–CH–*CH*$_3$); δ_C (62.5 MHz, $CDCl_3$) 162.5 (C-3), 161.1 (C-6), 153.0 (C-11a), 147.0 (C-10a), 138.8 (C-2′), 137.1 (C-1′), 134.4 (C-9), 131.5 (C-6′), 130.3 (C-3′), 128.5 (C-5′), 127.3 (C-10), 126.8 (C-8), 126.7 (C-4′), 126.6 (C-7), 120.1 (C-6a), 61.8 (O–*CH*$_2$–CH$_3$), 59.4 (C-1), 57.2 (C-4), 35.8 (C$_1$–*CH*$_2$–Ar–H′), 33.0 (Ar–*CH*$_2$–Br), 31.4 (CH$_3$–*CH*–CH$_3$), 20.1 (*CH*$_3$–CH–CH$_3$), 18.8 (CH$_3$–CH–*CH*$_3$), 14.1 (O–CH$_2$–*CH*$_3$). $C_{24}H_{26}O_2N_3Br$ requires: C, 61.64; H, 5.60; N, 8.97. Found: C, 61.43; H, 5.29; N, 8.86.

4.3.3.6. (+)-(1*R*,4*S*)-1-(2-Bromomethyl-3,6-dimethoxybenzyl)-3-ethoxy-4-isopropyl-1,4-dihydropyrazino [2,1-*b*]-quinazolin-6-one 13b. Yield 48%; $[\alpha]_D^{25} = +30.0$ (*c* 0.05, $CHCl_3$); ν_{max} (NaCl) 2969, 2361, 1678, 1598 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.25 (1H, td, $J = 1.0$ and 8.0 Hz, H-7), 7.77 (1H, dt, $J = 1.4$ and 8.2 Hz, H-9), 7.74 (1H, dt, $J = 1.3$ and 8.2 Hz, H-10), 7.45 (1H, ddd, $J = 1.3$, 7.2 and 8.2 Hz, H-8), 6.85 (1H, d, $J = 9.0$ Hz, H-5′), 6.75 (1H, d, $J = 9.0$ Hz, H-4′), 5.20 (1H, d, $J = 7.5$ Hz, H-4), 4.98 (1H, d, $J = 9.4$ Hz, Ar–*CH*$_2$–Br), 4.89 (1H, d, $J = 9.4$ Hz, Ar–*CH*$_2$–Br), 4.70 (1H, dd, $J = 3.3$ and 10.8 Hz, H-1), 4.27 (1H, dd, $J = 3.3$ and 13.8 Hz, C$_1$–*CH*$_2$–Ar–H′), 3.99 (2H, m, O–*CH*$_2$–CH$_3$), 3.86 (3H, s, OCH$_3$-3), 3.77 (3H, s, OCH$_3$-6), 3.10 (1H, dd, $J = 10.8$ and 13.8 Hz, C$_1$–*CH*$_2$–Ar–H′), 2.16 (1H, m, CH$_3$–*CH*–CH$_3$), 1.21 (3H, t, $J = 7.0$ Hz, O–CH$_2$–*CH*$_3$), 0.95 (3H, d, $J = 7.1$ Hz, *CH*$_3$–CH–CH$_3$), 0.85 (3H, d, $J = 7.1$ Hz, CH$_3$–CH–*CH*$_3$). $C_{26}H_{30}O_4N_3Br$ requires: C, 59.09; H, 5.72; N, 7.95. Found: C, 61.43; H, 5.29; N, 8.86.

4.4. Synthesis of (8*S*,15b*R*(*S*))-8-alkyl-15b,16-dihydro-5*H*,8*H*-isoquinolino[2′,3′-4,3]pyrazino[2,1-*b*]quinazolin-7,10-diones 16–18

A solution of compound **12** or compound **13** (0.1 mmol) in 2 mL of dry dimethylformamide and 15 mg (0.1 mmol) of NaI were refluxed for 1 h. Toluene was added and the organic layer extracted with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate [6:4 for **16**, **18** and 7:3 for **17**]).

4.4.1. (+)-(8*S*,15b*R*)-8-Methyl-15b,16-dihydro-5*H*,8*H*-isoquinolino[2′,3′-4,3]pyrazino[2,1-*b*]quinazoline-7,10-dione 16a. Chromatography yielded 65% of **16a** and 34% of **18a**. Mp: 178–179 °C (petroleum ether/ethyl acetate); $[\alpha]_D^{25} = +24.0$ (*c* 0.08, $CHCl_3$); ν_{max} (NaCl) 2922, 1670, 1605 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J = 1.4$ and 8.1 Hz, H-11), 7.79 (1H, ddd, $J = 1.4$, 6.7 and 8.2 Hz, H-13), 7.73 (1H, dd, $J = 1.6$ and 8.2 Hz, H-14), 7.51 (1H, ddd, $J = 1.6$, 6.7 and 8.1 Hz, H-12), 7.35 (4H, m, H-1, 2, 3 and 4), 5.69 (1H, q, $J = 7.2$ Hz, H-8), 5.16 (1H, d, $J = 16.0$ Hz, H-5), 4.67 (1H, dd, $J = 4.1$ and 10.7 Hz, H-15b), 4.42 (1H, d, $J = 16.0$ Hz, H-5), 3.87 (1H, dd, $J = 4.1$ and 15.5 Hz, H-16), 3.34 (1H, dd, $J = 10.7$ and 15.5 Hz, H-16), 1.59 (3H, d, $J = 7.2$ Hz, *CH*$_3$); δ_C (62.5 MHz, $CDCl_3$) 167.3 (C-7), 160.1 (C-10), 149.9 (C-15a), 147.0 (C-14a), 134.6 (C-13), 134.1 (C-16a), 132.7 (C-4a), 127.9 (C-1), 127.7 (C-3), 127.5 (C-14), 127.4 (C-2), 127.3 (C-11), 126.8 (C-12), 126.4 (C-4), 120.5 (C-10a), 53.7 (C-8), 52.3 (C-15b), 44.0 (C-5), 31.8 (C-16), 16.1 (*CH*$_3$). $C_{20}H_{17}O_2N_3$ requires: C, 72.48; H, 5.17; N, 12.69. Found: C, 72.33; H, 5.06; N, 12.48.

4.4.2. (−)-(8*S*,15b*S*)-8-Methyl-15b,16-dihydro-5*H*,8*H*-isoquinolino[2′,3′-4,3]pyrazino[2,1-*b*]quinazoline-7,10-dione 18. Mp: 98–99 °C (petroleum ether/ethyl acetate); $[\alpha]_D^{25} = -40.0$ (*c* 0.04, $CHCl_3$); ν_{max} (NaCl) 2928, 1671, 1600, 1474 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.30 (1H, dd, $J = 1.3$ and 8.1 Hz, H-11), 7.79 (1H, ddd, $J = 1.3$, 7.2

and 8.4 Hz, H-13), 7.65 (1H, dd, $J = 1.2$ and 8.4 Hz, H-14), 7.51 (1H, ddd, $J = 1.2$, 7.2 and 8.1 Hz, H-12), 7.20 (4H, m, H-1, 2, 3 and 4), 5.70 (1H, d, $J = 16.7$ Hz, H-5), 5.40 (1H, q, $J = 7.0$ Hz, H-8), 4.93 (1H, dd, $J = 3.9$ and 12.7 Hz, H-15b), 4.24 (1H, d, $J = 16.7$ Hz, H-6), 3.54 (1H, dd, $J = 3.9$ and 16.0 Hz, H-16), 3.23 (1H, dd, $J = 12.7$ and 16.0 Hz, H-16), 1.67 (3H, d, $J = 7.0$ Hz, *CH*$_3$); δ_C (62.5 MHz, $CDCl_3$) 165.3 (C-7), 160.1 (C-10), 149.3 (C-15a), 147.2 (C-14a), 134.8 (C-13), 131.7 (C-16a), 131.6 (C-4a), 129.1 (C-11a), 128.1 (C-1), 127.1 (C-3), 127.0 (C-12), 126.8 (C-4), 126.5 (C-14), 125.2 (C-2), 120.3 (C-10a), 57.4 (C-8), 51.6 (C-15b), 44.1 (C-5), 36.0 (C-16), 20.1 (*CH*$_3$). $C_{20}H_{17}O_2N_3$ requires: C, 72.48; H, 5.17; N, 12.69. Found: C, 72.51; H, 5.11; N, 12.39.

4.4.3. (+)-(8*S*,15b*R*)-1,4-Dimethoxy-8-methyl-15b,16-dihydro-5*H*,8*H*-isoquinolino[2′,3′-4,3]pyrazino[2,1-*b*]-quinazoline-7,10-dione 16b. Yield 68%; $[\alpha]_D^{25} = +31.6$ (*c* 0.06; $CHCl_3$); ν_{max} (NaCl) 2925, 1683, 1608 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.30 (1H, dd, $J = 2.0$ and 8.0 Hz, H-11), 7.80 (1H, m, H-12), 7.78 (1H, m, H-11), 7.45 (1H, m, H-13), 6.82 (1H, d, $J = 9.0$ Hz, H-2), 6.76 (1H, d, $J = 9.0$ Hz, H-3), 5.59 (1H, q, $J = 7.1$ Hz, H-8), 5.29 (1H, d, $J = 17.1$ Hz, H-5), 4.62 (1H, dd, $J = 4.1$ and 11.1 Hz, H-15b), 4.34 (1H, d, $J = 17.1$ Hz, H-5), 4.26 (1H, dd, $J = 4.1$ and 15.9 Hz, H-16), 3.88 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.91 (1H, dd, $J = 11.1$ and 15.9 Hz, H-16), 1.53 (3H, d, $J = 7.1$ Hz, *CH*$_3$); δ_C (62.5 MHz, $CDCl_3$) 167.4 (C-7), 160.2 (C-10), 151.0 (C-1), 150.3 (C-15a), 149.7 (C-4), 147.2 (C-14a), 134.6 (C-13), 127.5 (C-12), 127.3 (C-14), 126.8 (C-11), 123.5 (C-16a), 122.3 (C-4a), 120.6 (C-10a), 109.3 (C-2), 108.7 (C-3), 56.0 (OCH_3), 55.7 (OCH_3), 53.5 (C-15b), 52.2 (C-8), 39.2 (C-5), 26.0 (C-16), 16.9 (*CH*$_3$). $C_{22}H_{21}O_4N_3$ requires: C, 67.50; H, 5.40; N, 10.70. Found: C, 67.38; H, 5.31; N, 10.59.

4.4.4. (+)-(8*S*,15b*R*)-8-Isopropyl-15b,16-dihydro-5*H*,8*H*-isoquinolino[2′,3′-4,3]pyrazino[2,1-*b*]quinazoline-7,10-dione 17a. Yield 71%; $[\alpha]_D^{25} = +55.1$ (*c* 0.10; $CHCl_3$); ν_{max} (NaCl) 2928, 1682, 1606, 1568 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J = 1.5$ and 8.1 Hz, H-11), 7.79 (1H, ddd, $J = 1.5$, 6.8 and 8.2 Hz, H-13), 7.72 (1H, dd, $J = 1.6$ and 8.2 Hz, H-14), 7.50 (1H, ddd, $J = 1.6$, 6.8 and 8.1 Hz, H-12), 7.34 (4H, m, H-1, 2, 3 and 4), 5.48 (1H, d, $J = 9.2$ Hz, H-8), 5.10 (1H, d, $J = 16.0$ Hz, H-5), 4.74 (1H, dd, $J = 4.2$ and 10.5 Hz, H-15b), 4.42 (1H, d, $J = 16.0$ Hz, H-5), 3.85 (1H, dd, $J = 4.2$ and 15.4 Hz, H-16), 3.28 (1H, dd, $J = 10.5$ and 15.4 Hz, H-16), 2.19 (1H, m, CH_3–*CH*–CH_3), 1.12 (3H, d, $J = 6.7$ Hz, *CH*$_3$–CH–CH_3), 0.98 (3H, d, $J = 6.7$ Hz, CH_3–CH–*CH*$_3$); δ_C (62.5 MHz, $CDCl_3$) 166.1 (C-7), 160.7 (C-10), 150.7 (C-15a), 146.9 (C-14a), 134.5 (C-13), 134.2 (C-16a), 132.9 (C-4a), 127.8 (C-1), 127.7* (C-3), 127.4* (C-14), 127.3 (C-2), 127.2 (C-11), 127.1 (C-12), 126.4 (C-4), 120.4 (C-10a), 61.2 (C-8), 54.0 (C-15b), 44.0 (C-5), 32.2 (C-16), 30.8 (CH_3–*CH*–CH_3), 19.8 (*CH*$_3$–CH–CH_3), 19.4 (CH_3–CH–*CH*$_3$). $C_{22}H_{21}O_2N_3$ requires: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.36; H, 5.78; N, 11.55.

4.4.5. (+)-(8*S*,15b*R*)-1,4-Dimethoxy-8-isopropyl-15b,16-dihydro-5*H*,8*H*-isoquinolino[2′,3′-4,3]pyrazino[2,1-*b*]quinazoline-7,10-dione 17b. Mp: 191–192 °C (petroleum ether/ethyl acetate); $[\alpha]_D^{25} = +61.5$ (*c* 0.07; $CHCl_3$); ν_{max} (NaCl) 2956, 2927, 2841, 1669, 1606 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J = 1.0$ and 8.0 Hz, H-11), 7.77 (1H, ddd, $J = 1.0$, 7.6 and 8.2 Hz, H-13), 7.76 (1H, dd, $J = 1.4$ and 8.2 Hz, H-14), 7.49 (1H, ddd, $J = 1.4$, 7.6 and 8.0 Hz, H-12), 6.79 (1H, d, $J = 9.0$ Hz, H-2), 6.74 (1H, d, $J = 9.0$ Hz, H-3), 5.38 (1H, d, $J = 7.9$ Hz, H-8), 5.17 (1H, d, $J = 17.4$ Hz, H-5), 4.66 (1H, dd, $J = 4.1$ and 11.1 Hz, H-15b), 4.36 (1H, d, $J = 17.4$ Hz, H-5), 4.23 (1H, dd, $J = 4.1$ and 16.1 Hz, H-16), 3.86 (3H, s, OCH_3-1), 3.80 (3H, s, OCH_3-4), 2.82 (1H, dd, $J = 11.1$ and 16.1 Hz, H-16), 2.22 (1H, m, $J = 6.8$ Hz, CH_3–*CH*–CH_3), 1.06 (3H, d, $J = 6.8$ Hz, *CH*$_3$–CH–CH_3), 1.03 (3H, d, $J = 6.8$ Hz, CH_3–CH–*CH*$_3$), δ_C (62.5 MHz, $CDCl_3$) 166.0 (C-7), 160.7 (C-10), 150.8 (C-15a), 150.1* (C-1), 149.6* (C-4), 147.0 (C-14a), 134.5 (C-13), 127.4 (C-14), 127.1 (C-11), 126.9 (C-12), 123.4* (C-4a), 122.2* (C-16a), 120.4 (C-10a), 109.1* (C-3), 108.4* (C-2), 60.8 (C-8), 55.9 (OCH_3), 55.5 (OCH_3), 53.7 (C-15b), 39.1 (C-5), 31.7 (CH_3–*CH*–CH_3), 26.3 (C-16), 19.8 (*CH*$_3$–CH–CH_3), 18.9 (CH_3–CH–*CH*$_3$). $C_{24}H_{25}O_4N_3$ requires: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.43; H, 5.92; N, 10.35.

4.5. Synthesis of (8*S*)-8-methyl-5*H*,8*H*-isoquinolino[2′,3′-4,3]pyrazino[2,1-*b*]quinazolin-7,10-diones 19

A solution of compound **12** (0.1 mmol) in 2 mL of dry dimethylformamide and a big excess of NaI was refluxed for 1 h. Toluene was added and the organic layer extracted with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography [petroleum ether/ethyl acetate (6:4)].

4.5.1. (−)-(8*S*)-8-Methyl-5*H*,8*H*-isoquinolino[2′,3′-4,3]-pyrazino[2,1-*b*]quinazoline-7,10-dione 19a. White syrup; yield 67%; $[\alpha]_D^{25} = -31.9$ (*c* 0.16, $CHCl_3$); ν_{max} (NaCl) 2928, 1684, 1629 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.28 (1H, dd, $J = 1.6$ and 8.2 Hz, H-11), 7.79 (1H, ddd, $J = 1.5$, 6.7 and 8.2 Hz, H-13), 7.74 (1H, dd, $J = 1.5$ and 8.2 Hz, H-14), 7.49 (1H, ddd, $J = 1.6$, 6.7 and 8.2 Hz, H-12), 7.46 (1H, s, H-16), 7.32–7.21 (4H, m, H-1, 2, 3 and 4), 5.72 (1H, d, $J = 15.9$ Hz, H-5), 5.62 (1H, q, $J = 7.0$ Hz, H-8), 4.42 (1H, d, $J = 15.9$ Hz, H-5), 1.55 (3H, d, $J = 7.0$ Hz, *CH*$_3$); δ_C (62.5 MHz, $CDCl_3$) 165.1 (C-7), 159.9 (C-10), 147.5 (C-14a), 144.0 (C-15a), 134.8 (C-13), 129.7 (C-16a), 129.5* (C-4), 128.3* (C-3), 128.1 (C-15b), 128.0 (C-4a), 127.4 (C-14), 127.1* (C-3 and 12), 126.8 (C-11), 126.0* (C-1), 120.2 (C-10a), 115.7 (C-16), 51.7 (C-8), 43.7 (C-5), 19.2 (*CH*$_3$). $C_{20}H_{15}O_2N_3$ requires: C, 72.92; H, 4.59; N, 12.76. Found: C, 72.86; H, 4.76; N, 12.65.

4.5.2. (−)-(8*S*)-1,4-Dimethoxy-8-methyl-5*H*,8*H*-isoquinolino[2′,3′-4,3]pyrazino[2,1-*b*]quinazoline-7,10-dione 19b. Mp: 108–109 °C (petroleum ether/ethyl acetate); yield 56%; $[\alpha]_D^{25} = -212.0$ (*c* 0.16; $CHCl_3$); ν_{max} (NaCl) 2928, 2851, 1725, 1684, 1634 cm^{-1}; δ_H (250 MHz, $CDCl_3$)

8.25 (1H, dd, $J = 1.4$ and 8.4 Hz, H-11), 7.76 (1H, m, H-14), 7.75 (1H, m, H-12), 7.73 (1H, s, H-16), 7.45 (1H, ddd, $J = 2.1$, 6.0 and 8.1 Hz, H-13), 6.79* (1H, d, $J = 9.0$ Hz, H-2), 6.72* (1H, d, $J = 9.0$ Hz, H-3), 5.93 (1H, d, $J = 16.7$ Hz, H-5), 5.60 (1H, q, $J = 7.0$ Hz, H-8), 4.14 (1H, d, $J = 16.7$ Hz, H-5), 3.85 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 1.53 (3H, d, $J = 7.0$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 165.3 (C-7), 160.2 (C-10), 149.9* (C-1), 149.3* (C-4), 147.8 (C-14a), 144.5 (C-15a), 134.8 (C-13), 127.7* (C-14), 127.5 (C-15b), 127.1* (C-12), 126.9* (C-11), 120.4 (C-10a), 119.9* (C-16a), 119.4 (C-4a), 112.3 (C-16), 111.0* (C-2), 110.1* (C-3), 56.1 (OCH_3), 55.9 (OCH_3), 51.9 (C-8), 39.4 (C-5), 19.2 (CH_3). $C_{22}H_{19}O_4N_3$ requires: C, 67.84; H, 4.92; N, 10.80. Found: C, 67.74; H, 4.86; N, 10.66.

4.6. (±)-14b-Methyl-1,2,3,4-tetrahydro-7*H*,14b*H*-pyrido[2′,1′-3,4]pyrazino[2,1-*b*]quinazoline-6,9-dione 21

A solution of compound **20** (67 mg, 0.17 mmol) in 2 mL of dry dimethylformamide and 26 mg (0.17 mmol) of NaI were refluxed for 1 h. Toluene was added and the organic layer extracted with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate (1:1)) affording 42 mg (87%) of **21**. ν_{max} (NaCl) 2935, 1665, 1594, 1568 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.27 (1H, ddd, $J = 0.5$, 1.4 and 8.0 Hz, H-10), 7.77 (1H, ddd, $J = 1.5$, 7.0 and 8.3 Hz, H-12), 7.65 (1H, ddd, $J = 0.5$, 1.2 and 8.2 Hz, H-13), 7.48 (1H, ddd, $J = 1.3$, 7.0 and 8.0 Hz, H-11), 5.15 (1H, d, $J = 19.3$ Hz, H-7), 4.60 (1H, ddt, $J = 2.0$, 4.7 and 13.8 Hz, H-4), 4.27 (1H, dd, $J = 1.0$ and 19.3 Hz, H-7), 2.95 (1H, d, $J = 13.8$ Hz, H-4), 2.90 (1H, m, H-1), 2.60 (1H, ddt, $J = 1.9$, 3.2 and 13.0 Hz, H-1), 2.0–1.6 (4H, m, H-1, 2 and 3), 1.45 (1H, m, H-3), 1.00 (3H, s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 164.6 (C-6), 161.1 (C-9), 155.0 (C-14a), 147.7 (C-13a), 135.0 (C-12), 127.9* (C-13), 127.5* (C-11), 127.0 (C-10), 120.3 (C-9a), 59.9 (C-14b), 44.7 (C-7), 38.8 (C-4), 36.9 (C-1), 24.2* (C-3), 23.7 (CH_3), 20.0* (C-2). $C_{16}H_{17}O_2N_3$ requires: C, 67.83; H, 6.05; N, 14.83. Found: C, 66.91; H, 6.14; N, 14.13.

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