Regio- and Diastereoselective Alkylation of 2-Substituted 2,4-Dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones

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Alkylation of N^2-protected (4*S*)-4-alkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones was planned to afford compounds that contain a fragment of the fungal metabolite 5-*N*-acetylardeemin, which has been described as a potent reversal agent of multiple drug resistance (MDR) in tumor cell lines.[1] The MDR phenotype involves the overexpression of a 170 kDa membrane glycoprotein (Pgp-170), which is thought to function as a broad-substrate ATP-dependent pump that exports drugs out of the cell, thus lowering the intracellular drug concentration below the cytotoxic threshold.[2] In spite of the intrinsic problems derived from the expression of Pgp-170 in several normal tissues,[3] many failures in cancer chemotherapy could be overcome if this protein could be effectively inhibited by compounds with less toxicity at the active concentrations than those which have been studied so far for this purpose.[4]

A variety of fungal metabolites, such as auranthine[5a] and asperlicin,[5b] which are biosynthesized from α-amino acids and anthranilic acid, have fused benzodiazepine and quinazolinone moieties while other compounds, such as glyantrypine,[5c] fumiquinazolines F and G,[5d,e] or fiscalin B,[5f] contain the 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione structure. *N*-Acetylardeemin can be considered as a tripeptide derived from tryptophan, alanine, and anthranilic acid. According to that, its total synthesis has been accomplished starting from L-tryptophan methyl ester.[1c]

Here we report the synthesis of 2-methyl and 2-benzyl derivatives (compounds **a** and **b**, respectively) of the 1,4-dialkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione structure through alkylation of the parent 1-unsubstituted compounds **1a** and **1b**. Besides the possible biological activity as resistance modifier agents (RMAs) of these compounds, the change of substituents at the N^2-position was expected to permit, after deprotection of the analogues derived from 3-indolylmethylation at C^1-carbon atom, an alternative total synthesis of *N*-acetylardeemin.

Conformational studies based on ^{1}H NMR data showed that in compound **1a** unsubstituted at the C^4-position (incorporating sarcosine, glycine, and anthranilic acid), the piperazine ring has conformational flexibility, while the introduction of a 4-methyl group (as in compound **1a**, incorporating sarcosine, L-alanine, and anthranilic acid) locks this ring in a boat conformation, in which that substituent adopts a pseudoaxial disposition.[6a] This conformation is a consequence of the extremely severe steric interaction between the quinazolone carbonyl group (C^6═O) and the alternative pseudoequatorial C^4-methyl substituent.[6b] The same pseudoaxial disposition has been shown in the solid state, according to X-ray diffraction data of **1a**.[6c]

Stereoselective alkylation reactions on anions of bis-lactim ethers derived from cyclic dipeptides have been widely used in organic synthesis.[7] Examples dealing with anions of piperazine-2,5-diones have occurred to a lesser extent and have been mostly exploited in intramolecular enolate C−C bond-forming cyclizations.[8] We considered that alkylation of compounds **1** could take place regio- and diastereoselectively, with the preferential formation of the 1,4-*anti* isomers according to the asymmetric induction of the chiral C^4-center, thus providing access to interesting products.

Results and Discussion

Our first experiments of alkylation reactions on **1a** and **1b** (*n*-BuLi, THF, −78 °C, 1 h, followed by R^1X, where R^1 = methyl, allyl, and benzyl, method A) gave no traces of C^4-alkylation products, thus confirming the expected regioselectivity, but the observation of an NOE between the C^4-methyl group and the C^1-substituent of the obtained compounds, showed a 1,4-*syn* relationship, which was paired with racemization of the C^4-stereogenic center. These disappointing results were attributed to a thermodynamic control of the reaction, and we became motivated to study in more detail the influence of the lithiating agent and the electrophile, as well as time and temperature variation upon their addition.

The reaction of **1a** with LHMDS as base at −78 °C, followed by fast addition of benzyl bromide as electro-

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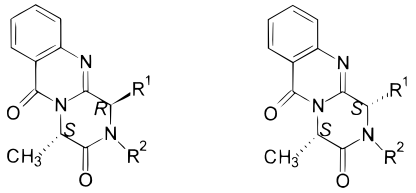
Table 1. 1-Alkylated Derivatives of 1a and 1b under Standard Reaction Conditions (Method B)



Anti-Isomers: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20

Syn-Isomers: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21

Compounds **a**; R =Me

Compounds **b**; R =Bn

entry	compound	R^1	R^2	% yield[a]	*anti*/*syn* ratio[b]
1	**2a, 3a**	Bn	Me	75	87:13
2	**2b, 3b**	Bn	Bn	72	74:26
3	**4a, 5a**	p-MeC6H4CH2	Me	58	86:14
4	**4b, 5b**	p-MeC6H4CH2	Bn	90	66:33
5	**6a, 7a**	p-F3CC6H4CH2	Me	68	74:26
6	**6b, 7b**	p-F3CC6H4CH2	Bn	35	60:40
7	**8a, 9a**	p-FC6H4CH2	Me	70	71:29[c]
8	**8b, 9b**	p-FC6H4CH2	Bn	68	74:26
9	**10a, 11a**	o-FC6H4CH2	Me	70	86:14
10	**10b, 11b**	o-FC6H4CH2	Bn	52	58:42
11	**12a, 13a**	m-ClC6H4CH2	Me	90	100:0
12	**12b, 13b**	m-ClC6H4CH2	Bn	54[d]	54:46
13	**14a, 15a**	2-naphthylmethyl	Me	20	100:0
14	**14b, 15b**	2-naphthylmethyl	Bn	60[d]	60:40
15	**16a, 17a**	allyl	Me	20[e]	*e*
16	**16b, 17b**	allyl	Bn	56	63:37
17	**18a, 19a**	p-O2NC6H4CH2	Me	50	10:90 [f]
18	**18b, 19b**	p-O2NC6H4CH2	Bn	57	30:70
19	**20a, 21a**	Me	Me	98	0:100
20	**20b, 21b**	Me	Bn	64	0:100

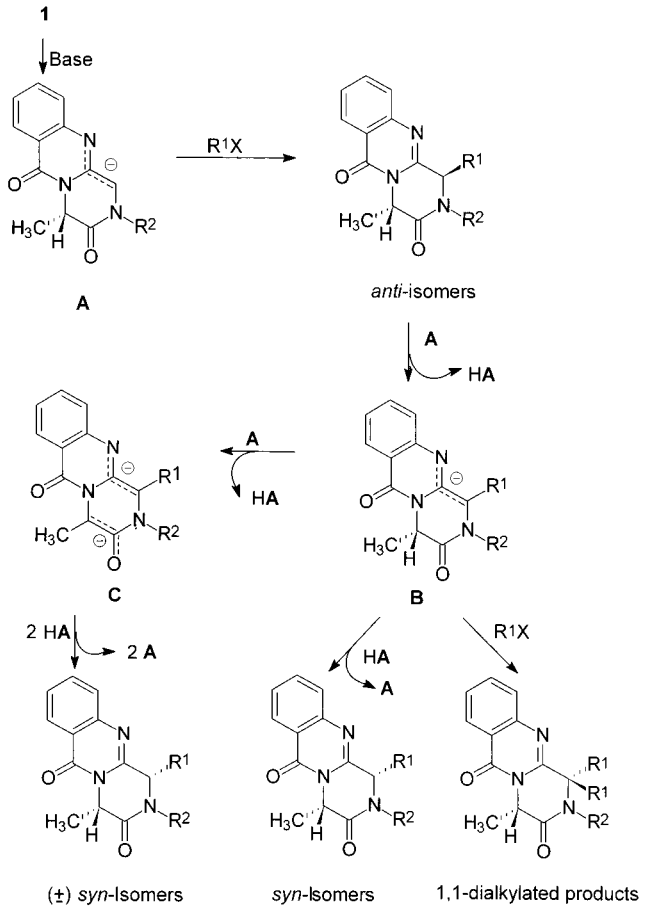
[a] Yields are given for isolated, purified compounds. [b] ee >95% for all compounds was showed. [c] *Syn* and *anti* isomers could not be separated. [d] The reaction time was longer. [e] Only the *syn* isomer **17a** was isolated. [f] Both isomers could not be obtained analytically pure.

phile, gave (method B) a diastereomeric excess of 74% in favor of the enantiopure *anti* diastereoisomer **2a** over the *syn* diastereoisomer **3a** after 20 min (Table 1). The same reaction on compound **1b** gave compounds **2b** (*anti* isomer) and **3b** (*syn* isomer) in lower diastereomeric excess (48%). Other benzyl halides gave similar results (see Table 1, entries 3−10), the most favorable diastereoselection (de >95%) being the one observed in the reactions of **1a** with *m*-chlorobenzyl bromide and 2-naphthylmethyl bromide (see Table 1, entries 11 and 13, respectively). The reaction of **1b** with allyl bromide gave lower diastereomeric excess (24%), while in analogous reactions with **1a**, only the *syn* isomer **17a** could be isolated. With *p*-nitrobenzyl bromide the observed diastereoselectivity was in favor of the *syn* isomers for both **1a** and **1b**, under the same reaction conditions (see Table 1, entries 17 and 18) while, in the case of methyl iodide as electrophile (see Table 1, entries 19 and 20), a diastereoisomeric excess >95% of the *syn* isomers was obtained.

Small amounts of 1,1-dialkylated compounds were also produced as secondary products, and in some reactions on compound **1b**, the dialkylation took also place in the 1,4-positions.

Whether or not racemization or epimerization had taken place in the alanine moiety was studied through ^{1}H-NMR spectroscopy in the presence of europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [(+)-Eu(HFC)$_3$] as chiral shift reagent. It was gratifying to observe that all compounds so far mentioned showed enantiomeric excess >95%. Racemized *syn* isomers were only obtained at much longer reaction times.

Scheme 1



The diastereoselection found in the synthesis of compounds **2**−**17** in favor of the *anti* isomers supported that the electrophilic substitution in compounds **1** is governed by the asymmetric induction imposed by the pseudoaxial methyl group at the C^4-position.

The apparent diastereoselection puzzle reflected in Table 1 can be interpreted through the scrambling of anions that can be present in the reaction. According to the mechanism outlined in Scheme 1, the kinetically favored *anti* isomers derived from anion **A** epimerize to the *syn* isomers through their transformation to anion **B**. This assumption was corroborated by treatment of compound **8a** and **8b** with LHMDS under standard reaction conditions, affording a mixture of compounds **8a**:**9a** and **8b**:**9b**, respectively, in a 1:3 and 1:9 ratios. The same experiment on compounds **9a** and **9b** left them unchanged.

Racemization of *syn* isomers at prolonged reaction times must involve the dianion **C** derived from anion **B** instead of anion **A**, since the same treatment of compounds **1** in base did not produce traces of racemized **1**. The alternative equilibration of *syn*-(1*S*,4*S*) or *anti*-(1*R*,4*S*) isomers to *syn*-(1*R*,4*R*) isomers through the C^4-anion was ruled out by alkylation experiments on (1*S*)-1,2-dialkylated compounds **4a**, **4b**, **7a**, and **8b**.

The diastereoselectivity is apparently controlled by the relative availability of anions **B**, that is, by the equilibrium between *anti* isomers and their **B** anions. The 1,4-

Table 2. Calculated Energies (MM2, kcal/mol) for Some Representative Compounds

anti isomers	calcd energies	calcd energies	*syn* isomers
2a	3.15	1.35	**3a**
2b	3.12	0.92	**3b**
16a	6.27	2.18	**17a**
16b	5.14	2.98	**17b**
20a	3.78	1.12	**21a**
20b	2.27	0.80	**21b**

syn diastereoselectivity observed for *p*-nitrobenzylation and methylation indicates that S_N2-like conditions tend to favor the formation of the thermodynamic product by a slower reaction, resulting in equilibration. Moreover, equilibration may occur faster when R^1 is methyl or allyl than when R^1 is benzyl (see later).

The steric interaction between R^1 and R^2 substituents will be rather high in anion **B** because of its planarity. Thus, the higher de of *anti* isomers corresponds to the bulkier substituents (2-naphthylmethyl and *m*-chlorobenzyl) in **a** series. The lower *anti* diastereoselectivity observed for the *N*-benzyl derivatives **b** as compared to the *N*-methyl compounds **a** suggests that in **1b** the asymmetric induction of the chiral C^4-center is in part counterbalanced with that of the phenyl moiety of the N^2-substituent at the opposite face.

A high-temperature molecular dynamics study of representative compounds was carried out by using HyperChem 3 program in order to explore their putative minimum energy conformations. To avoid the risks inherent to this methodology, additional molecular dynamics was used and, finally, the minimum energy conformers were minimized using MM calculations and Fletcher−Reeves algorithm (RMS gradient 0.01 kcal/Å mol) (Table 2). As expected, the calculated energies for the more favorable conformers were lower in the *syn* isomers.

The minimum energy calculated conformations for the *syn* isomers were in agreement with NMR data (see later). They showed a boat conformation for piperazine ring, in which the R^2-substituent adopts a pseudoequatorial disposition and both C^1- and C^4-substituents are in a pseudoaxial disposition (Figure 1). For the *anti* isomers, the conformations of minimum energy showed this ring in a more planar conformation, and the same disposition for the R^2-substituent. In allyl and methyl derivatives (**16** and **20**), molecular dynamics calculations of *anti* isomers show a pseudoaxial disposition for the C^4-methyl group and a pseudoequatorial one for the C^1-substituent, the chemical shift for C^4-H of **16b** being very similar to the value of the *syn* isomer (δ = 5.34 and 5.4 ppm, respectively). On the other hand, in *anti*-C^1-benzyl derivatives, the C^1-substituent is pseudoaxial and the C^4-substituent is pseudoequatorial. These conformations imply that the steric interactions between the substituents at C^1- and N^2-positions in the *anti*-benzylated compounds are greater than that of the C^4-methyl and the C^6═O groups. Furthermore, while in compounds **2** and **3**, and their analogues, the aryl group adopts an *exo* configuration, in 1,1-dibenzylated compounds, the *syn*-aryl group is in an *endo* configuration (see Figure 1), which also agrees with ^{1}H NMR data.

The difference in conformations for the *anti* isomers when R^1 is methyl or allyl versus *anti*-benzyl derivatives is consistent with a higher rate for the equilibration in methyl and allyl compounds, where the *anti* conformation is favorably aligned for deprotonation. In contrast, the epimerization of the *anti*-benzyl conformation might take place only through a higher energy conformation, resulting in a slower rate of equilibration.

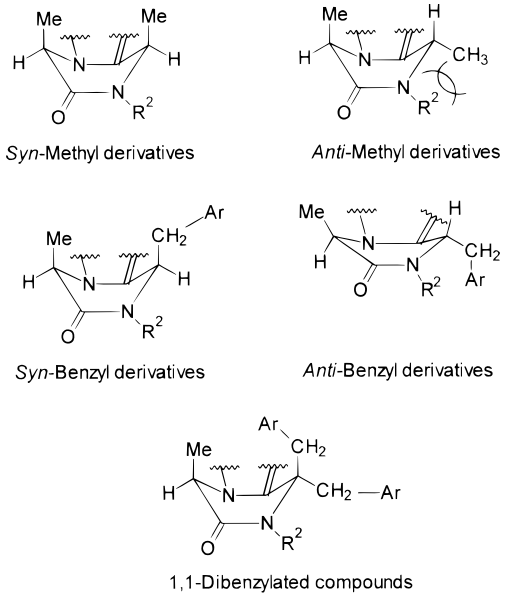


Figure 1. Proposed conformations of the piperazine ring according to NMR data and molecular mechanics calculations.

It has been previously mentioned that ^{1}H NMR spectroscopy was of great value in the assignment of *syn* and *anti* configurations through NOE experiments, and in determining the enantiomeric purity by using chiral reagents. In addition, ^{1}H NMR data of 1-benzylated compounds with an *anti*-1,4-relationship showed significant changes in the C^4-H resonances respect to the corresponding *syn* isomers, which corroborates the conformation proposed by MD studies. The changes were less significant in the C^4-Me resonances. For instance, δ values for these protons in **2a**/**2b** are 4/4.04 (C^4-H) and 1.5/1.54 (C^4-Me) ppm, while in **3a**/**3b** they are 5.2/5.27 and 1.1/1.2 ppm, respectively. These data clearly show that the C^4-H proton is coplanar with the C^6═O group in the *syn* isomers (pseudoequatorial) but not in the *anti* isomers. A twist boat conformation with the H^4-proton in a pseudoequatorial arrangement is also inferred from the chemical shift values of C^4-H protons in the *syn* isomers of allyl and methyl derivatives. All of them showed analogous low-field resonances, which are due to the fact that this proton is strongly deshielded by the anisotropic effect of the quasi-coplanar C^6═O carbonyl group. The same conformation has been observed in the oxopiperazine ring of fumiquinazolines.[5d] The general ^{13}C NMR spectral features of *syn* compounds closely resemble those of *anti* isomers, except for the signals of C^1- and C^4-carbon atoms, which appear at higher δ values in the *syn* isomers, especially the C^1 carbon atom.

We can conclude that alkylation of the title compounds may be useful from a synthetic point of view. Further studies with derivatives of **1** carrying bulkier substituents at C^4 are in progress. The preliminary biological activity studies have shown that several of the compounds here described are moderately active as resistance modifier agents.

Experimental Section

General. Melting points are uncorrected. IR spectra were recorded with all solid compounds compressed into KBr pellets and liquid compounds placed between NaCl plates. NMR

spectra were recorded at 250 MHz for ^{1}H and 62.5 MHz for ^{13}C in $CDCl_3$, with TMS as the internal reference (Servicio RMN, UCM). Mass spectra were recorded at 70 eV, quadrupole detector, EI (Servicio de Espectroscopía UCM). Elemental analyses were obtained from the Servicio de Microanálisis, UCM Optical rotations were determined at 25 °C in $CHCl_3$ or EtOH at 589 nm. Separations by chromatography were performed on silica gel (35−70 μm) for compounds **b** or alumina (63−200 μm) for compounds **a**. Tetrahydrofuran was freshly distilled from sodium benzophenone. All reagents were of commercial quality and were used as received. The expression "petroleum ether" refers to the fraction boiling at 40−60 °C. Starting material **1a** was obtained according to the literature.[6b]

(4*S*)-2-Benzyl-4-methyl-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione (1b). A mixture of 4.36 g (20 mmol) of (3*S*)-1-benzyl-3-methylpiperazine-2,5-dione,[9] triethyloxonium tetrafluoroborate (11.4 g, 60 mmol), and anhydrous Na_2CO_3 (10.6 g, 100 mmol) in 200 mL of dry CH_2Cl_2 was stirred overnight at room temperature, poured on ice water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated. Anthranilic acid was added to the syrupous residue, and the mixture was stirred vigorously at 130−140 °C for 2.5 h under argon, dissolved in CH_2Cl_2, extracted with diluted ammonium hydroxide, dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc/MeOH, 95:5) afforded 3.76 g (59%) of **1b** as a white solid: mp 133−135 °C (EtOAc−hexane); $[\alpha]^{25}_D$ +36.2 (*c* 0.25, $CHCl_3$); IR (KBr) 1670, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (d, 3H, *J* = 7.2 Hz), 4.30 (d, 1H, *J* = 16.9 Hz), 4.50 (d, 1H, *J* = 16.9 Hz), 4.53 (d, 1H, *J* = 14.6 Hz), 4.9 (d, 1H, *J* = 14.6 Hz), 5.55 (q, 1H, *J* = 7.2 Hz), 7.32 (m, 5H), 7.47 (ddd, 1H, *J* = 8, 7, and 1.2 Hz), 7.56 (dd, 1H, *J* = 8.2 and 1.6 Hz), 7.74 (ddd, 1H, *J* = 8.2, 7, and 1.6 Hz), 8.27 (dd, 1H, *J* = 8 and 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.6, 160.0, 148.0, 147.3, 135.2, 134.9, 129.2, 128.4, 127.4, 127.0, 120.6, 52.2, 49.8, 49.3, 17.2. Anal. Calcd for $C_{19}H_{17}O_2N_3$: C, 71.45; H, 5.36; N, 13.15. Found: C, 71.28; H, 5.56; N, 13.06.

General Procedures for the Alkylation of Compounds 1a and 1b. Method A. To a cold (−78 °C), magnetically stirred solution of **1a** or **1b** (1 mmol) in dry THF (15 mL) was added, under argon, dropwise via syringe 1.3 mmol of *n*-butyllithium (2.5 M in hexane), followed by the adequate halide (1 mmol in 5 mL of THF) 1 h later. The reaction mixture was maintained at −78 °C overnight, allowed to warm up to rt, quenched with a cold saturated solution of ammonium chloride, diluted with CH_2Cl_2 or ethyl acetate, and worked up as described in method B.

General Procedures for the Alkylation of Compounds 1a and 1b. Method B. To a cold (−78 °C), magnetically stirred solution of compounds **1a** or **1b** (1 mmol) in dry THF (15 mL) was added, under argon, dropwise via syringe a 1 M solution of lithium hexamethyl disilazide in THF (1 mL), followed by the adequate halide (1.1 mmol dissolved in 5 mL of THF if solid, or without solvent if liquid) 5−10 min later. The reaction mixture was maintained at −78 °C during 10−20 min, allowed to warm to rt until decoloration (or up to 1 h), quenched with a cold saturated ammonium chloride solution, and diluted with ethyl acetate (for **1a** derivatives) or CH_2Cl_2 (for **1b** derivatives). The separated aqueous layer was extracted with ethyl acetate or CH_2Cl_2 (3 × 20 mL), respectively, and the combined organic layers were washed with water, dried, and evaporated. Chromatography of the residue on silica gel (CH_2Cl_2/EtAcO, 9:1, for most **1b** derivatives) or alumina, provided first the 1,4-dialkylated, 1,1-dialkylated, if any, followed by the *anti*-1-alkylated and *syn*-1-alkylated compounds.

(1*R*,4*S*)-1-Benzyl-2,4-dimethyl-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione (2a) was obtained (EtOAc/hexane 7:3) as a white solid: mp 140−141 °C; yield 65%; $[\alpha]^{25}_D$ +180 (*c* = 1, EtOH); IR (KBr) 1684, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3H, *J* = 6.6 Hz), 3.25 (s, 3H), 3.33 (dd, 1H, *J* = 13.8 and 3.6 Hz), 3.43 (dd, 1H, *J* = 13.8 and 3.7 Hz), 4.0 (q, 1H, *J* = 6.6 Hz), 4.95 (m, 1H), 6.65 (m, 2H), 7.08−7.23 (m, 3H), 7.50 (m, 1H), 7.69 (dd, 1H, *J* = 7.3 and 1.3 Hz), 7.83 (m, 1H), 8.20 (dd, 1H, *J* = 8.0 and 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 167.5, 160.1, 152.0, 146.7, 134.7, 133.4, 129.3, 128.7, 127.9, 126.9, 126.8, 126.7, 120.5, 62.8, 51.9, 40.1, 33.1, 20.2. Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.07; H, 5.70; N, 12.61. Found: C, 71.96; H, 5.75; N, 12.53.

(9) Kiely, J. S.; Priebe, S. R. *Org. Prep. Proced. Int.* **1990**, *22*, 761.

(1*R*,4*S*)-1,2-Dibenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (2b) was obtained as a white solid: mp 161−163 °C; yield 53%; $[\alpha]^{25}_D$ +99.6 (*c* 0.25, $CHCl_3$); IR (KBr) 1704, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.54 (d, 3H, *J* = 6.7 Hz), 3.26 (dd, 1H, *J* = 13.9 and 3.4 Hz), 3.46 (dd, 1H, *J* = 13.9 and 3.9 Hz), 4.04 (q, 1H, *J* = 6.7 Hz), 4.07 (d, 1H, *J* = 14.9 Hz), 4.82 ("t", 1H, *J* = 3.6 Hz), 5.79 (d, 1H, *J* = 14.9 Hz), 6.7 (m, 2H), 7.09−7.37 (m, 8H), 7.46 (td, 1H, *J* = 8 and 1.1 Hz), 7.6 (dd, 1H, *J* = 8 and 1.1 Hz), 7.73 (td, 1H, *J* = 8 and 1.5 Hz), 8.17 (dd, 1H, *J* = 8 and 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ 167.8, 160.2, 149.9, 146.8, 135.4, 134.9, 133.6, 129.6, 129.3, 128.8, 128.5, 128.3, 128.1, 127.1, 127.0, 126.7, 120.6, 59.2, 52.1, 46.6, 39.9, 20.8. Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 76.28; H, 5.62; N, 10.26. Found: C, 75.90; H, 5.62; N, 10.33.

(1*S*,4*S*)-1-Benzyl-2,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (3a) was obtained (EtOAc/hexane, 7:3) as a white solid: mp 151−152 °C; yield 10%; $[\alpha]^{25}_D$ −6.5 (*c* 2, EtOH); IR (KBr) 1684, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 3H, *J* = 7.1 Hz), 2.92 (s, 3H), 3.41 (m, 2H), 4.79 (m, 1H), 5.15 (q, 1H, *J* = 7.1 Hz), 7.09 (dd, 2H, *J* = 6.5 and 1.9 Hz), 7.25 (m, 3H), 7.50 (t, 1H, *J* = 7.5 Hz), 7.69 (dd, 1H, *J* = 7.4 and 1.4 Hz), 7.81 (m, 1H), 8.26 (dd, 1H, *J* = 7.9 and 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 167.2, 160.4, 150.3, 147.3, 135.5, 134.9, 129.9, 127.9, 127.2, 127.0, 126.9, 120.3, 65.2, 52.4, 41.6, 34.1, 18.4. Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.07; H, 5.70; N, 12.61. Found: C, 71.87; H, 5.68; N, 12.52.

(1*S*,4*S*)-1,2-Dibenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (3b) was obtained as a white solid: mp 188−189 °C (ethyl ether); yield 19%; $[\alpha]^{25}_D$ −11 (*c* 0.25, $CHCl_3$); IR (KBr) 1680, 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 3H, *J* = 7.1 Hz), 3.33 (dd, 1H, *J* = 13.8 and 7.1 Hz), 3.45 (dd, 1H, *J* = 13.8 and 4.8 Hz), 3.5 (d, 1H, *J* = 14.9 Hz), 4.75 (dd, 1H, *J* = 7.1 and 4.9 Hz), 5.27 (q, 1H, *J* = 7.1 Hz), 5.48 (d, 1H, *J* = 14.9 Hz), 7.11 (m, 2H), 7.28 (m, 3H), 7.47 (ddd, 1H, *J* = 8, 8 and 1.2 Hz), 7.55 (dd, 1H, *J* = 8 and 1.2 Hz), 7.74 (ddd, 1H, *J* = 8, 8 and 1.5 Hz), 8.25 (dd, 1H, *J* = 8 and 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 167.4, 160.4, 150.4, 147.2, 135.7, 135.3, 134.8, 129.9, 129.3, 129.1, 128.5, 127.9, 127.6, 127.1, 127.0, 126.9, 120.4, 61.1, 52.4, 47.8, 41.6, 18.5. Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 76.28; H, 5.62; N, 10.26. Found: C, 75.95; H, 5.30; N, 10.04.

(1*R*,4*S*)-1-Allyl-2-benzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (16b) was obtained as a white solid: mp 107−109 °C; yield 35%; $[\alpha]^{25}_D$ +77 (*c* 0.25, $CHCl_3$); IR (KBr) 1684, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68 (d, 3H, *J* = 6.9 Hz), 2.9 (ddd, 1H, *J* = 14.9, 7.6, and 4.6 Hz), 3.08 (dddd, 1H, *J* = 14.9, 6.4, 3.1, and 1.6 Hz), 4.04 (d, 1H, *J* = 14.9 Hz), 4.6 (dd, 1H, *J* = 4.6 and 3.1 Hz), 5.05 (dd, 1H, *J* = 17.4 and 1.5 Hz), 5.07 (dd, 1H, *J* = 10.5 and 1.5 Hz), 5.34 (q, 1H, *J* = 6.9 Hz), 5.57 (dddd, 1H, *J* = 17.4, 10.5, 7.6, and 6.4 Hz), 5.71 (d, 1H, *J* = 14.9 Hz), 7.3 (m, 5H), 7.45 (ddd, 1H, *J* = 8, 8 and 1.2 Hz), 7.56 (dd, 1H, *J* = 8 and 1.2 Hz), 7.72 (ddd, 1H, *J* = 8, 8, and 1.5 Hz), 8.23 (dd, 1H, *J* = 8 and 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 167.9, 160.2, 149.5, 146.9, 135.4, 134.6, 130.7, 129.0, 128.0, 127.9, 127.0, 126.9, 126.7, 120.7, 120.2, 56.9, 51.9, 45.6, 35.9, 20.0. Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.14; H, 5.67; N, 11.60.

(1*S*,4*S*)-1-Allyl-2,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (17a) was obtained (EtOAc/hexane, 7:3) as a white solid: mp 191−192 °C; yield 20%; $[\alpha]^{25}_D$ +1.6 (*c* 0.81, EtOH); IR (film) 1666, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.77 (d, 3H, *J* = 7.0 Hz), 2.82 ("t", 2H, *J* = 6.7 Hz), 3.12 (s, 3H), 4.58 (t, 1H, *J* = 6.7 Hz), 5.19 (dd, 1H, *J* = 11.1 and 1.3 Hz), 5.21 (dd, 1H, *J* = 15.8 and 1.3 Hz), 5.32 (q, 1H, *J* = 7.1 Hz), 5.91 (m, 1H), 7.49 (m, 1H), 7.65 (dd, 1H, *J* = 7.5 and 1.2 Hz), 7.79 (m, 1H), 8.38 (dd, 1H, *J* = 7.9 and 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ 167.3, 160.5, 150.2, 147.3, 134.8, 132.4, 127.2, 127.1, 126.8, 120.4, 120.1, 63.6, 52.4, 40.8, 34.3, 19.5. Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.84; H, 6.01; N, 14.84. Found: C, 67.61; H, 5.93; N, 14.66.

(1*S*,4*S*)-1-Allyl-2-benzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (17b) was obtained as a white solid: mp 138−140 °C (ethyl ether); yield 21%; $[\alpha]^{25}_D$ +19.9 (*c* 0.25, $CHCl_3$); IR (KBr) 1686, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.79 (d, 3H, *J* = 7.1 Hz), 2.80 (t, 2H, *J* = 7.0 Hz), 4.14 (d, 1H, *J* = 14.9 Hz), 4.54 (t, 1H, *J* = 6.6 Hz), 5.13 (ddd, 1H, *J* = 16.8, 2.7, 1.5 Hz), 5.17 (dd, 1H, *J* = 10, 1.5 Hz), 5.40 (q, 1H, *J* = 7.1 Hz), 5.45 (d, 1H, *J* = 14.9 Hz), 5.85 (ddt, 1H, *J* = 16.8, 10.1, and 7.3 Hz), 7.24 (m, 5H), 7.45 (ddd, 1H, *J* = 7.9, 7.0, and 1.2 Hz), 7.55 (dd, 1H, *J* = 8.2 and 0.6 Hz), 7.71 (ddd, 1H, *J* = 8.2, 7.0, and 1.5

Hz), 8.25 (dd, 1H, $J = 7.9$ and 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.2, 160.3, 150.0, 147.0, 135.2, 134.6, 132.3, 128.9, 128.3, 128.1, 127.0, 126.9, 126.6, 120.2, 119.7, 59.9, 52.4, 48.3, 40.6, 19.6. Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.25; H, 5.80; N, 11.42.

(1*S*,4*S*)-1,2,4-Trimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (21a) was obtained (EtOAc/hexane, 7:3) as a white solid: mp 181−182 °C; yield 98%; $[\alpha]^{25}_D$ +101.8 (*c* 1, EtOH); IR (KBr) 1654, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70 (d, 3H, $J = 7.1$ Hz), 1.75 (d, 3H, $J = 7.1$ Hz), 3.10 (s, 3H), 4.60 (q, 1H, $J = 7.1$ Hz), 5.30 (q, 1H, $J = 7.1$ Hz), 7.45 (m, 1H), 7.61 (dd, 1H, $J = 8.1$ and 1.2 Hz), 7.82 (m, 1H), 8.30 (dd, 1H, $J = 8.0$ and 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.1, 160.3, 151.5, 147.3, 134.8, 127.1, 126.9, 126.8, 120.2, 59.1, 52.1, 32.5, 21.1, 19.2. Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.37; H, 5.84; N, 16.34. Found: C, 65.03; H, 5.61; N, 16.08.

(1*S*,4*S*)-2-Benzyl-1,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (21b) was obtained (EtOAc/petroleum ether, 7:3) as a light yellow oil; yield 64%; $[\alpha]^{25}_D$ +11 (*c* 0.25, $CHCl_3$); IR (film) 1684, 1659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (d, 3H, $J = 7.0$ Hz), 1.73 (d, 3H, $J = 7.0$ Hz), 4.13 (d, 1H, $J = 15$ Hz), 4.53 (q, 1H, $J = 7.0$ Hz), 5.30 (d, 1H, $J = 15.0$ Hz), 5.39 (q, 1H, $J = 7.0$ Hz), 7.26 (m, 5H), 7.42 (ddd, 1H, $J = 8.2$, 7.3, 1.2 Hz), 7.52 (ddd, 1H, $J = 8.0$, 1.5, 0.6 Hz), 7.69 (ddd, 1H, $J = 8.2$, 7.0, 1.5 Hz), 8.22 (dd, 1H, $J = 8.0$ and 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.2, 160.4, 151.7, 147.4, 135.6, 134.8, 128.9, 128.3, 128.1, 126.9, 126.7, 126.6, 120.1, 55.8, 52.2, 47.6, 21.4, 19.2. Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.07; H, 5.70; N, 12.61. Found: C, 71.85; H, 5.86; N, 12.70.

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Supporting Information Available: Complete spectroscopic and analytical data of compounds **4**−**15**, **18**, and **19** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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