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Regio- and Diastereoselective Dialkylation of (4*S*)-2,4-dimethyl-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione

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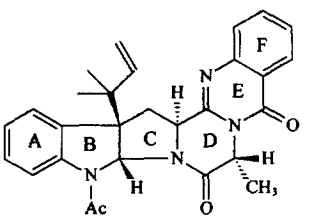
Abstract: Dialkylation of the title compound occurs regioselectively at C-1. Addition of *N,N'*-dimethyl-*N,N'*-propylene urea (DMPU) permits the one-pot synthesis of 1,1-dialkylation products in good yields. The asymmetric induction of the stereogenic C-4 center directs the first and the second alkylation steps.

In contrast to the diastereoselective alkylation of bis-lactim ethers derived from cyclodipeptides,[1] alkylation of the parent compounds (2,5-piperazinediones) has been scarcely used in organic synthesis.[2] In our current project directed to the synthesis of analogues of the fungal metabolite *N*-acetylardeemin (**1**), we decided to study the alkylation of the title compound (**2**),[3] with a fused piperazinedione structure, which contains three of the six rings of the natural product. Compound **1** is a cyclic tripeptide described as multiple drug resistance (MDR) reversal agent in tumour cell lines,[4] by inhibiting the membrane glycoprotein Pgp-170. This protein acts as a broad-substrate ATP-dependent pump that exports drugs out of the cell. MDR reversal agents could be valuable in combined cancer chemotherapy, because the intracellular drug concentration could be increased to the cytotoxic threshold, thus overcoming this resistance mechanism.[5]



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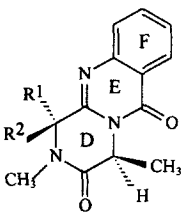
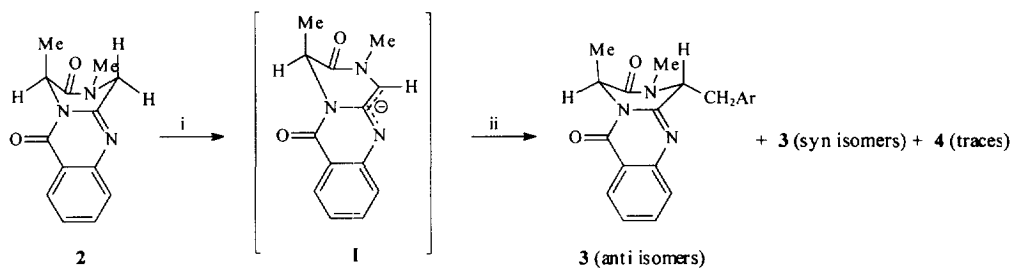


2, R1= R2= H
3, R1= alkyl, R2= H (anti isomers)
R1= H, R2= alkyl (syn isomers)
4, R1= alkyl, R2= alkyl, R1= or ≠ R2

By alkylation of the anion **I** derived from **2**, we obtained the enantiomerically pure compounds **3**. This reaction was studied with some detail, especially for R1(R2) = arylmethyl.[6] We showed that the anti isomers of

3 are the kinetically controlled products, as it was expected from the asymmetric induction of the C-4 methyl group. This substituent is pseudoaxial and locks ring D in a boat conformation. The alternative pseudoequatorial arrangement is very unstable because of the steric interaction with the quasi coplanar C-6 carbonyl group.[7] This geometry probably favours the regioselective deprotonation by a base at C-1, instead of at C-4, to give anion **I**. The electrophilic attack on this anion takes place at the face opposite to the C-4 substituent, giving diastereoselectively the anti isomers **3**, which can equilibrate to the thermodynamically controlled syn isomers. Due to 1,2 interactions between pseudoequatorial C-1 and N-2 substituents, the (1*R*, 4*S*) anti isomers are less stable than the (1*S*, 4*S*) syn isomers, in which the C-1 substituent is pseudoaxial. The calculated energies for the more favorable conformers were lower in the syn isomers.[6] In most cases, traces of the 1,1-dialkylated compounds **4** ($R^1 = R^2$), which showed a remarkable activity as MDR reversal agents, were also obtained (Scheme 1)



i : LiHMDS (1 eq.); ii : RX (1.2 eq.)

Scheme 1

Here we report the synthesis of compounds **4** ($R^1 = R^2$) by alkylation of **2** in one-pot procedures, as well as the stereochemical course of the alkylation of compounds **3** (anti and syn isomers) to yield compounds **4** ($R^1 \neq R^2$) (Eq. 1).

$$\mathbf{2} \xrightarrow{-H^+} [\mathbf{I}] \xrightarrow{RX} [\mathbf{3}\ \text{syn} + \mathbf{3}\ \text{anti}] \xrightarrow{-H^+} [\mathbf{II}] \xrightarrow{RX} \mathbf{4} \quad [\text{Eq. 1}]$$

Attempts to dialkylate anion **I** with two equivalents of base and alkyl halide (method A), gave low yields of compounds **4**, which were obtained in mixtures with the monoalkyl derivatives **3** (anti and syn isomers) and unreacted **2** (Table 1).

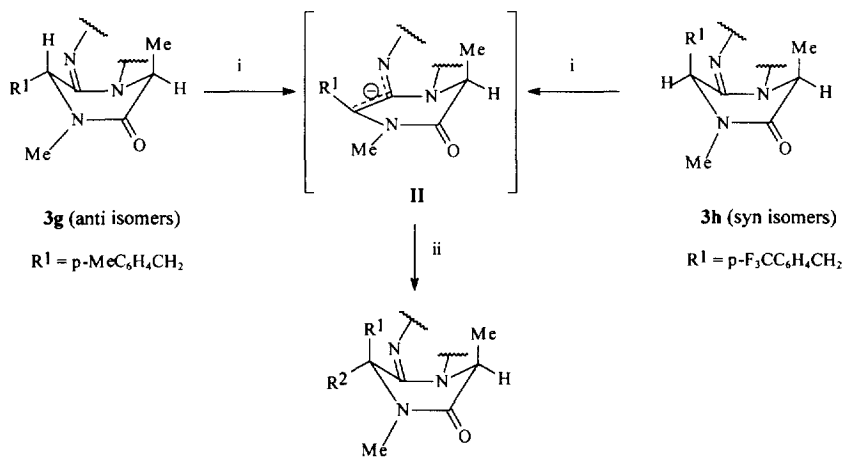
TABLE 1. Synthesis of compounds **4** ($R^1 = R^2$) by one-pot dialkylation of compounds **2**

Entry	Compound	R^1X	Method A **2** : anti **3** : syn **3** : **4**	Method B **2** : anti **3** : syn **3** : **4**
1	**4a**	*p*-$MeC_6H_4CH_2Br$	39 : 51 : 10 : 0	5 : 0 : 0 : 79
2	**4b**	*p*-$FC_6H_4CH_2Br$	20 : 30 : 35 : 15	0 : 11 : 9 : 80
3	**4c**	*p*-$O_2NC_6H_4CH_2Br$	22 : 8 : 50 : 20	25 : 0 : 0 : 75
4	**4d**	*p*-$FC_3C_6H_4CH_2Br$	25 : 45 : 10 : 20	24 : 4 : 28 : 44
5	**4e**	2-Naphthylmethyl bromide	70 : 30 : 0 : 0	0 : 15 : 15 : 70
6	**4f**	Allyl bromide	39 : 6 : 13 : 42	35 : 10 : 13 : 42

The best result was found for $R^1 = R^2$ = allyl (**4f**). In the search of different reaction conditions to enhace the reactivity of anions **II**, we found that addition of DMPU as an aprotic polar cosolvent together with the alkyl halide (method B) considerably improved the yields of compounds **4**. In some cases, (compounds **4a** and **4c**) the dialkylated compounds were the only reaction products. The most remarkable result was obtained with the bulkiest alkylating reagent, for which method A failed. Thus, 1,1-bisnaphthylmethyl derivative **4a** could be obtained in 70% yield (entry 5).

In order to explore the asymmetric induction of the C-4 chiral center in the second alkylation step, we studied the reaction of benzyl bromide with the anion derived from monoalkyl derivatives **3g** and **3h** (Scheme 2). As expected, in anions derived from either the anti isomers or the syn isomers of compounds **3**, the C-4 methyl group directed the second alkylation to the α-face, giving enantiopure compounds **4g** and **4h**.

Their stereochemistry was ascertained by ^{1}H NMR NOE experiments. The methylene benzylic protons appear as perfectly differentiated AB systems, reflecting the restricted rotation around the C-CH_2Ar bonds. While in the C-1 monobenzyl derivatives, these protons appear more equivalent.[6] In these compounds, the chemical shifts are larger for the methylene protons anti respect to the C-4 methyl group, while the Me protons are shielded by the aryl group of the syn benzyl substituent, which adopts a "folded" conformation where the aryl ring faces the pirazine ring.[1a] The Me protons resonate between 0.8 and 0.5 ppm, while they have δ values of about 1.5 ppm in the syn benzyl derivatives. The enantiomeric purity was checked by ^{1}H NMR spectroscopy in the presence of europium (III) tris-[3-(heptafluoropropylhydroxy methylene)-(+)-camphorate].



Scheme 2

It can be concluded that 1,1-dialkylation of **2** ($R^1 = R^2$) can be performed in good yields with DMPU as cosolvent and that the stereocenter at C-4 of compound **2** induces the diastereoselection of the dialkylation as well as the previously studied monoalkylation.

The preliminary biological activity studies have shown that several of the compounds here described are moderately active as resistance modifier agents.

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EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded with all solid compounds compressed into KBr pellets. NMR spectra were recorded at 250 MHz for ^1H and 62.5 MHz for ^{13}C in $CDCl_3$, with TMS or $CDCl_3$ as the internal reference (Servicio RMN, U. C. M.). Elemental analyses were obtained from the Servicio de Microanálisis, U. C. M. Optical rotations were determined at 25°C in EtOH at 589 nm. Separations by chromatography were performed on silica gel (35 - 70 μm). Tetrahydrofuran was freshly distilled from sodium - benzophenone. All reagents were of commercial quality and were used as received.

One-pot dialkylation:

Method A:

To a cold (-78°C), magnetically stirred solution of **2** (0.4 mmol) in dry THF (10 ml) was added, under argon, dropwise *via* syringe a 1M THF solution of lithium hexamethyldisilazide (0.4 ml), followed 5-10 min later by the appropriate halide (0.8 mmol dissolved in 5 ml of THF if solid, or neat if liquid).

Method B:

To a cold (-78°C), magnetically stirred solution of **2** (0.4 mmol) in dry THF (10 ml) was added, under argon, dropwise via syringe a 1M THF solution of lithium hexamethyldisilazide (0.4 ml), followed 5-10 min later by a mixture of the appropriate halide (0.8 mmol) and DMPU (1.6 mmol).

In both procedures, the reaction mixture was maintained at -78°C during 10-20 min, allowed to warm to 25°C until decoloration (or up to 1h), quenched with a cold saturated ammonium chloride solution and diluted with ethyl acetate. The separated aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were washed with water, dried and evaporated. The residue was chromatographed on silica gel (EtAcO/hexane). In method B the DMPU was distilled off before the chromatographic separation.

(4*S*)-2,4-Dimethyl-1,1-bis-(*p*-methylbenzyl)-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione (4a). Obtained (EtOAc/hexane 1:1) as a white solid: mp 199-200 °C; yield: 79%; $[\alpha]_D$ = +36.6° (c = 1, EtOH); IR (KBr, cm^{-1}) 1686, 1660; ^1H NMR ($CDCl_3$) δ 0.52 (d, 3H, *J* = 6.8 Hz, CH_3 at C-4), 2.14 (s, 3H, CH_3'*), 2.18 (s, 3H, CH_3"*), 3.34 (d, 1H, overlapped, H" benzylic), 3.35 (d, 1H, overlapped, H' benzylic), 3.37 (s, 3H, CH_3 at N-2), 3.81 (d, 1H, *J* = 13.9 Hz, H' benzylic), 3.98 (d, 1H, *J* = 13.8 Hz, H" benzylic), 4.53 (q, 1H, *J* = 6.8 Hz, H-4), 6.57 (d, 2H, *J* = 7.9 Hz, H-3" and H-5"), 6.79 (d, 2H, *J* = 7.9 Hz, H-2" and H-6"), 6.84 (d, 2H, *J* = 8.0 Hz, H-3' and H-5'), 6.93 (d, 2H, *J* = 8.0 Hz, H-2' and H-6'), 7.51 (m, 1H, H-8), 7.86 (d, 2H, *J* =

3.5 Hz, H-9 and H-10), 8.18 (d, 1H, J = 8.0 Hz, H-7) ppm; ^{13}C NMR ($CDCl_3$) δ 19.3, 21.0, 30.3, 43.9, 45.8, 50.7, 72.2, 120.2, 126.8, 127.0, 127.2, 129.0, 129.3, 129.5, 130.0, 131.6, 132.5, 134.8, 137.0, 137.3, 146.9, 152.0, 160.1, 167.4 ppm. Anal. Calcd. for $C_{29}H_{29}N_3O_2$: C, 77.16; H, 6.43; N, 9.31. Found: C, 76.95; H, 6.69; N, 9.27.

(4*S*)-2,4-Dimethyl-1,1-bis-(*p*-fluorobenzyl)-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione (4b). Obtained (EtOAc/hexane 5:5) as a white solid: mp 90-91 °C; yield: 80%; $[\alpha]_D$ = +9.5 °C (c = 0.5, EtOH); IR (KBr, cm^{-1}) 1684, 1663; ^{1}H NMR ($CDCl_3$) δ 0.56 (d, 3H, J = 6.8 Hz, CH_3 at C-4), 3.35 (overlapped m, 2H, H' and H" benzylic), 3.40 (overlapped s, 3H, CH_3 at N-2), 3.75 (d, 1H, J = 13.9 Hz, H' benzylic), 3.99 (d, 1H, J = 13.9 Hz, H" benzylic), 4.53 (q, 1H, J = 6.8 Hz, H-4), 6.68 (m, 4H, H-2", H-3", H-5" and H-6"), 6.84 (m, 2H, H-3' and H-5'), 6.94 (m, 2H, H-2' and H-6'), 7.53 (m, 1H, H-8), 7.86 (m, 2H, H-9 and H-10), 8.18 (dd, J = 7.6 and 1.5 Hz, H-7) ppm; ^{13}C NMR ($CDCl_3$) δ 19.7, 30.4, 43.2, 45.2, 50.6, 72.0, 115.6 (d, J = 21.3 Hz), 115.9 (d, J = 21.2 Hz), 120.1, 126.9, 127.1, 127.3, 130.3 (d, J = 3.4 Hz), 130.8 (d, J = 8.0 Hz), 131.3 (d, J = 3.4 Hz), 131.8 (d, J = 8.0 Hz), 135.0, 146.6, 151.4, 159.8, 162.0 (d, J = 256.3 Hz), 162.5 (d, J = 252.0 Hz), 168.9 ppm. Anal. Calcd. for $C_{27}H_{23}F_2N_3O_2$: C, 70.58; H, 5.01; N, 9.15. Found: C, 70.78; H, 5.38; N, 9.39.

(4*S*)-2,4-Dimethyl-1,1-bis-(*p*-nitrobenzyl)-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione (4c). Obtained (EtOAc/hexane 8:2) as a white solid: mp 235-236 °C; yield: 75%; $[\alpha]_D$ = +53.4° (c = 0.18, EtOH); IR (KBr, cm^{-1}) 1685, 1662; ^{1}H NMR ($CDCl_3$) δ 0.55 (dd, 3H, J = 6.8 Hz, CH_3 at C-4), 3.46 (s, 3H, CH_3 at N-2), 3.57 (d, 1H, J =13.7 Hz, H" benzylic), 3.58 (d, 1H, J = 13.8Hz, H' benzylic), 3.94 (d, 1H, J = 13.8Hz, H' benzylic), 4.18 (d, 1H, J =13.7 Hz, H" benzylic), 4.56 (q, 1H, J = 6.8 Hz, H-4), 7.18 (d, 2H, J = 8.6 Hz, H-2' and H-6'), 7.57 (m, 1H, H-8), 7.88 (m, 4H, H-9, H-10, H-3" and H-5"), 7.91 (d, 2H, J = 8.7 Hz, H-2" and H-6"), 8.09 (d, 2H, J = 8.6 Hz, H-3' and H-5'), 8.20 (dd, 1H, J = 7.9 and 1.3 Hz, H-7) ppm; ^{13}C NMR ($CDCl_3$) δ 20.1, 30.5, 44.1, 45.9, 50.6, 71.3, 120.2, 123.8, 124.1, 127.0, 127.3, 127.9, 130.2, 131.2, 135.4, 141.8, 142.5, 146.2, 147.3, 147.4, 149.1, 159.8, 167.1 ppm. Anal. Calcd. for $C_{27}H_{23}N_5O_6$: C, 63.15; H, 4.48; N, 13.64. Found: C, 63.54; H, 4.80; N, 13.73.

(4*S*)-2,4-Dimethyl-1,1-bis-(*p*-trifluoromethylbenzyl)-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione (4d). Obtained (EtOAc/hexane 4:6) as a white solid: mp 78-79 °C; yield: 44%; $[\alpha]_D$ = +22.3° (c = 0.5, EtOH); IR (KBr, cm^{-1}) 1690, 1663; ^{1}H NMR ($CDCl_3$) δ 0.50 (d, 3H, J = 6.8 Hz, CH_3 at C-4), 3.43 (s, 3H, CH_3 at N-2), 3.48 (d, 1H, J = 13.7 Hz, H" benzylic), 3.49 (d, 1H, J = 13.9 Hz, H' benzylic), 3.95 (d, 1H, J = 13.9Hz, H' benzylic), 4.09 (d, 1H, J = 13.7 Hz, H" benzylic), 4.55 (q, 1H, J = 6.8 Hz, H-4), 6.85 (d, 2H, J = 8.2 Hz, H-4" and H-6"), 7.10 (d, 2H, J = 8.1 Hz, H-4' and H-6'), 7.29 (d, 2H, J = 8.2 Hz, H-3" and H-5"), 7.42 (d, 2H, J = 8.1 Hz, H-3' and H-5'), 7.55 (m, 1H, H-8), 7.88 (m, 2H, H-9 and H-10), 8.20(dd, 1H, J = 7.6 and 1.4 Hz, H-7) ppm; ^{13}C NMR ($CDCl_3$) δ 19.4, 30.4, 44.2, 45.9, 50.6, 71.6, 121.6, 125.6 (d, J = 3.8 Hz), 125.9 (d, J = 3.8 Hz), 127.0, 127.1, 127.6, 129.6, 130.6, 135.2, 138.6, 139.3, 146.4, 150.8, 159.7, 167.2 (CF_3 and C-4' signals are not observed) ppm. Anal. Calcd. for $C_{29}H_{23}F_6N_3O_2$: C, 62.25; H, 4.11; N, 7.51. Found: C, 61.95; H, 4.28; N, 7.27.

(4*S*)-2,4-Dimethyl-1,1-bis-(2-naphthylmethyl)-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione (4e). Obtained (EtOAc/hexane 7:3) as a white solid: mp 223-224 °C; yield: 70%; $[\alpha]_D$ = -2.2° (c = 0.5, EtOH); IR (KBr, cm^{-1}) 1689, 1661; ^{1}H NMR ($CDCl_3$) δ 0.27 (d, 3H, J = 6.7 Hz, CH_3 at C-4), 3.51 (s, 3H, CH_3 at N-2), 3.61 (d, 1H, J = 13.8 Hz, H" benzylic), 3.62 (d, 1H, J = 13.9 Hz, H' benzylic), 4.07 (d, 1H, J = 13.9 Hz, H' benzylic), 4.27 (d, 1H, J = 13.8 Hz, H" benzylic), 4.36 (q, 1H, J = 6.7 Hz, H-4), 6.75 (d, 1H, J = 8.5

Hz, H-3"), 7.08 (d, 1H, J = 8.4 Hz, H-3'), 7.23 (m, 1H, H-1"), 7.28 to 7.39 (m, 5H, H-5", H-6', H-6", H-7' and H-7"), 7.48 (m, 3H, H-1', H-4" and H-8), 7.56 to 7.69 (m, 4H, H-4', H-5', H-8' and H-10), 7.93 (m, 2H, H-8" and H-9), 8.13 (d, 1H, J = 7.8 Hz, H-7) ppm; ^{13}C NMR ($CDCl_3$) δ 19.5, 31.0, 44.6, 46.6, 50.6, 72.1, 120.2, 126.1, 126.2, 126.3, 126.4, 126.7, 126.9, 127.1, 127.2, 127.5, 127.57, 127.6, 127.7, 127.9, 128.3, 128.5, 128.6, 129.3, 132.2, 132.4, 132.5, 133.0, 133.2, 133.4, 134.9, 146.8, 151.9, 159.8, 167.3 ppm. Anal. Calcd. for $C_{35}H_{29}N_3O_2$: C, 80.31; H, 5.54; N, 8.03. Found: C, 80.80; H, 5.72; N, 8.01.

(4*S*)-2,4-Dimethyl-1,1-diallyl-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione (4f). Obtained (EtOAc/hexane 7:3) as a white solid: mp 105-106 °C; yield: 42%; $[\alpha]_D$ = +111.1° (c = 0.8, EtOH); IR (KBr, cm^{-1}) 1685, 1657; ^{1}H NMR ($CDCl_3$) δ 1.66 (d, 3H, J = 6.8 Hz, CH_3 at C-4), 2.76 (m, 2H, CH_2' allylic), 3.09 (s, 3H, CH_3 at N-2), 3.24 (m, 2H, CH_2" allylic), 4.92 (dd, 1H, J = 16.0 and 1.6 Hz, H-3" *trans*), 4.95 (dd, 1H, J = 10.5 and 1.6 Hz, H-3" *cis*), 5.11 (dd, 1H, J = 15.8 and 2.4 Hz, H-3' *trans*), 5.20 (dd, 1H, J = 11.6 and 2.4 H-3' *cis*), 5.25 (overlapped q, 1H, J = 6.8 Hz, H-4), 5.30 (overlapped m, 1H, H-2"), 5.61 (m, 1H, H-2'), 7.47 (m, 1H, H-8), 7.67 (dd, 1H, J = 7.4 and 1.3 Hz, H-10), 7.78 (m, 1H, H-9), 8.36 (dd, 1H, J = 8.1 and 1.2 Hz H-7) ppm; ^{13}C NMR ($CDCl_3$) δ 21.4, 28.2, 43.2, 44.5, 51.2, 69.2, 120.1, 120.5, 120.9, 126.8, 127.0, 127.3, 130.7, 131.7, 134.7, 147.3, 147.3, 152.0, 160.5, 167.4 ppm. Anal. Calcd. for $C_{19}H_{21}N_3O_2$: C, 70.58; H, 6.50; N, 13.00. Found: C, 70.14; H, 6.66; N, 12.79.

Alkylation of compounds 3:

To a cold (-78°C), magnetically stirred solution of **3g** or **3h** (0.45 mmol) in dry THF (10 ml) was added, under argon, drop wise via syringe a 1M solution of lithium hexamethyldisilazide in THF (0.45 ml), followed by benzyl bromide (0.54 mmol) under argon, 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 1h), quenched with a cold saturated ammonium chloride solution and diluted with ethyl acetate. The separated aqueous layer was extracted with ethyl acetate (3 x 15 ml) and the combined organic layers were washed with water, dried and evaporated. The residue was chromatographied on silica gel (EtAcO/hexane)

(1*S*,4*S*)-2,4-Dimethyl-1-benzyl-1-(*p*-methylbenzyl)-2,4-dihydro-1*H*-pirazine[2,1-*b*]quinazoline-3,6-dione (4g). Obtained (EtOAc/hexane 6:4) as a white solid: mp 215-216 °C; yield: 52%; $[\alpha]_D$ = +14° (c = 0.5, EtOH); IR (KBr, cm^{-1}) 1684, 1654; ^{1}H NMR ($CDCl_3$) δ 0.53 (d, 3H, J = 6.8 Hz, CH_3 at C-4), 2.18 (s, 3H, CH_3'), 3.35 (d, 1H, overlapped with s at 3.37 ppm, H" benzylic), 3.37 (s, 3H, CH_3 at N-2), 3.39 (d, 1H, overlapped with s at 3.37 ppm, H' benzylic), 3.81 (d, 1H, J = 13.9 Hz, H' benzylic), 3.99 (d, 1H, J = 13.8 Hz, H" benzylic), 4.49 (q, 1H, J = 6.8 Hz, H-4), 6.65 (d, 2H, J = 7.0 Hz, H-3' and H-5'), 6.81 (d, 2H, J = 8.0 Hz, H-2" and H-6"), from 6.88 to 7.04 (m, 5H, H-2', H-3", H-4", H-5" and H-6'), 7.46 (m, 1H, H-8), 7.81 (m, 2H, H-9 and H-10), 8.13 (d, 1H, J = 8.0 Hz, H-7) ppm; ^{13}C NMR ($CDCl_3$) δ 19.2, 20.9, 30.2, 43.8, 46.1, 50.6, 71.9, 120.1, 126.7, 126.9, 127.1, 127.4, 128.4, 128.5, 129.4, 129.9, 132.3, 134.6, 134.7, 137.2, 146.7, 151.7, 159.9, 167.3 ppm. Anal. Calcd. for $C_{28}H_{27}N_3O_2$: C, 76.88; H, 6.17; N, 9.61. Found: C, 75.95; H, 6.39; N, 9.37.

(1*S*,4*S*)-2,4-Dimethyl-1-benzyl-1-(*p*-trifluoromethylbenzyl)-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione (4h). Obtained (EtOAc/hexane 7:3) as a white solid: mp 116-117 °C; yield: 85%; $[\alpha]_D$ = +7.3° (c = 0.15, EtOH); IR (KBr, cm^{-1}) 1685, 1660; ^{1}H NMR ($CDCl_3$) δ 0.52 (d, 3H, J = 6.8 Hz, CH_3 at C-4), 3.42

(s, 3H, CH_3 at N-2), 3.44 (d, 1H, overlapped with s at 3.42 ppm, H" benzylic), 3.47 (d, 1H, overlapped with s at 3.42 ppm, H' benzylic), 3.79 (d, 1H, J = 13.9 Hz, H' benzylic), 4.17 (d, 1H, J = 13.7 Hz, H" benzylic), 4.47(q, 1H, J = 6.8 Hz, H-4), 6.67 (d, 2H, J = 6.9 Hz, H-2" and H-6"), 6.97 to 7.08 (m, 3H, H-3", H-4" and H-5"), 7.13 (d, 2H, J = 8.2 Hz, H-2' and H-6'), 7.42 (d, 2H, J = 8.2 Hz, H-3' and H-5'), 7.54 (m, 1H, H-8), 7.88(m, 2H, H-9 and H-10), 8.20 (d, 1H, J = 8.1 Hz, H-7) ppm; ^{13}C NMR ($CDCl_3$) δ 19.5, 30.3, 43.6, 46.3, 50.4, 71.7, 120.1, 125.6, 126.8, 127.0, 127.5, 127.6, 128.6, 128.9, 130.5, 134.1, 134.9, 139.7, 146.5, 151.1, 159.7, 167.2 ppm. Anal. Calcd. for $C_{28}H_{24}F_3N_3O_2$: C, 68.43; H, 4.89; N, 8.55. Found: C, 68.68; H, 4.99; N, 8.43.

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