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Stereochemical course of acylation and aldol condensation in (4*S*)-4-methyl-2-benzyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-diones

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Abstract

Acylation of **1** leads to the *syn* derivatives **2**. Traces of the *anti* isomers equilibrate to the *syn* isomers when stored in $CHCl_3$. Aldol condensation showed great diastereoselectivity, but racemization could not be avoided. The configuration of the new introduced stereogenic centres has been assigned on the basis of ^{1}H-NMR data and NOE measurements.

In a previous paper[1] we reported the *anti* 1,4-induction observed in alkylation of 2-substituted-(4*S*)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione **1**, a fragment of the fungal metabolite *N*-acetylardeemin, whose activity as a reversal agent of multiple drug resistance (MDR) in tumour cell lines has been described.[2] Other fungal metabolites, such as glyantrypine,[3a] fumiquinazolines F and G[3b,c] or fiscalin B[3d] also contain the 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione structure. Continuing our reactivity studies, we report here the stereochemical course of acylation and aldol condensation.

Conformational studies based on ^{1}H-NMR data showed that in the 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione structure, the introduction of a 4-methyl group (as in compounds **1a**,**b**) locks this ring in a boat conformation, in which that substituent adopts a pseudoaxial disposition.[4a] This conformation is a consequence of the steric interactions between the quinazolone carbonyl group (C^6=O) and the alternative pseudoequatorial C^4-methyl substituent.[4b] The same pseudoaxial disposition has been shown in the solid state, according to X-ray diffraction data of the 2,4-dimethyl analogue.[4c] This explains the observed diastereoselective alkylation with the preferential formation of the 1,4-*anti*-isomers under kinetic conditions according to the asymmetric induction of the stereogenic C^4-centre.

Acylation reactions in related compounds such as bis-lactim ethers derived from cyclic dipeptides[5] or 1,4-bis[(*S*)-1-phenylethyl]piperazine-2,5-diones,[6] take place in the same way as alkylations, showing an *anti* or *syn* diastereoselectivity, respectively.

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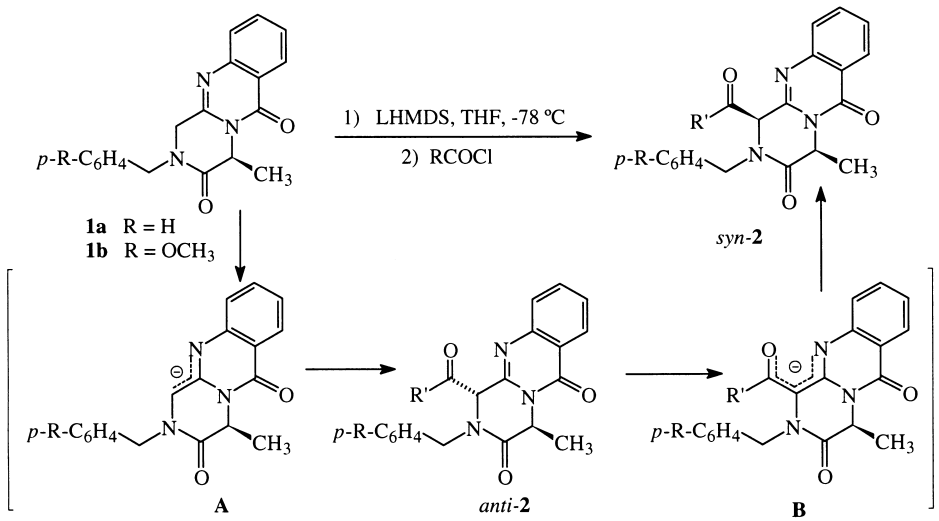
However, when **1a**,**b** were treated with LHMDS at −78°C followed by addition of an acyl chloride, the *syn*-1-acylderivatives **2** (1*R*,4*S*) were obtained in good yields, showing e.e. and d.e. >95% (Scheme 1). Their configurations were determined by NOE experiments. In fact, by irradiating the (C-4)-CH_3 in **2d**, a 1.5% NOE was registered on the pivaloyl methyl group. On the other hand, irradiation of (C-4)-CH_3 in the acetyl and benzoyl derivatives (Table 1) did not show the NOE on H-4 usually observed in *anti*-1,4-dialkyl compounds.[1]



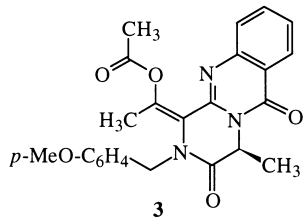
Scheme 1.

Taking into account the *anti*-1,4-induction above mentioned, the diastereoselectivity of the acylation reaction can be explained through initial kinetic formation of the *anti*-isomers, followed by thermodynamic equilibration *via* anion **B**, which give the more stable *syn*-isomers. The acidity of the C-1 proton facilitates this equilibration. Evidence for initial formation of *anti*-isomers was provided in the case of **2h**, where the *anti*-isomer could be isolated. Its conversion to the *syn*-diastereoisomer was observed when it was dissolved in chloroform and stored at 0°C for between 1 and 2 days. When acetyl chloride was contaminated with traces of acid, besides **2b**, the enolized acetylderivative **3** was isolated.

Table 1
Preparation of compounds **2**

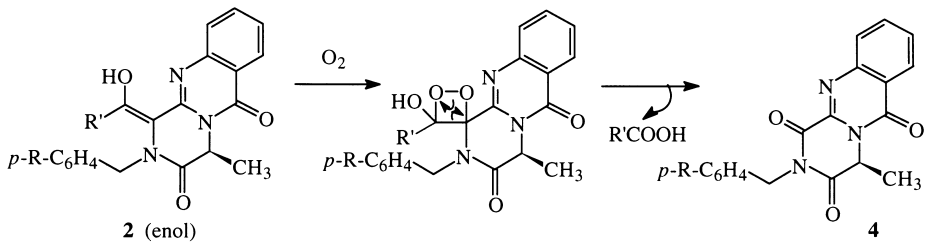
	R	Acyl chloride	$[\alpha]_D^{25}(c)$[a]	Yield (%)	d.e.
2a	H	acetyl	-32.7 (0.26)	68	>95
2b	OCH_3	acetyl	-34.4 (0.38)	81	>95
2c	H	pivaloyl	-124.8 (0.25)	80	>95
2d	OCH_3	pivaloyl	-152.5 (0.31)	75	>95
2e	H	benzoyl	-5.6 (0.25)	86	>95
2f	OCH_3	benzoyl	+0.7 (0.22)	81	>95
2g	H	*p*-MeO-benzoyl	+35.5 (0.10)	78	>95
2h	OCH_3	*p*-MeO-benzoyl	+24.2 (0.22)	87	60
2i	H	3,4,5-trimethoxybenzoyl	+34.4 (0.25)	72	>95
2k	OCH_3	3,4,5-trimethoxybenzoyl	+41.4 (0.15)	61	>95

[a] Chloroform



3

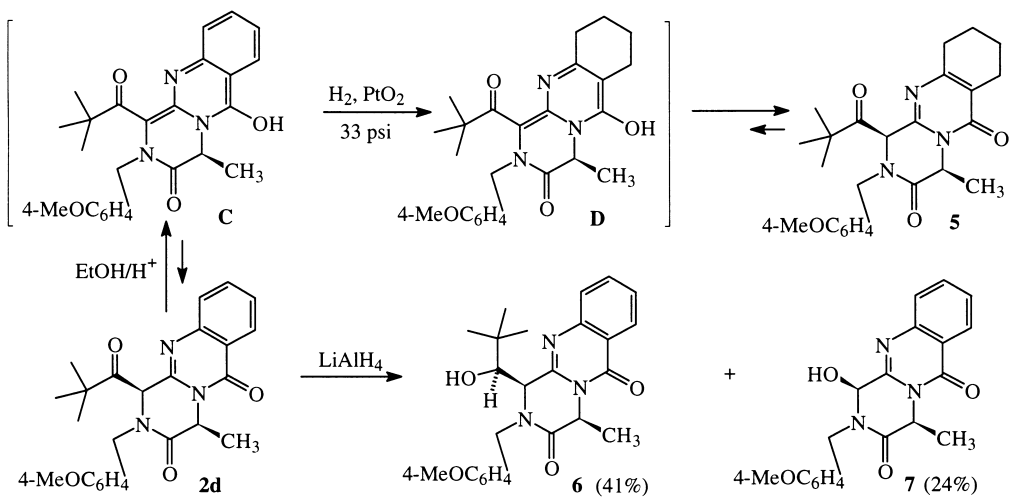
Pivaloyl derivatives **2c**,**d** are crystalline, stable products, but the remaining compounds decompose when stored at 0°C for 1–2 weeks, giving mainly **1a**,**b** (retro-reaction) and the 1-oxo derivative **4**.[7] Probably, auto-oxidation to ketones **4** occurs via the enol tautomer (Scheme 2).[8]



2 (enol) **4**

Scheme 2.

In order to obtain the more stable hydroxy compounds for pharmacological trials, reduction experiments on **2d** were performed. Catalytic hydrogenation with PtO_2 ($EtOH/H^+$) led to a partial reduction of the condensed benzene ring, leaving the carbonyl group unchanged (compound **5**, Scheme 3). This abnormal behaviour is probably due to acid induced enolization of **2d** to the **C** form, followed by hydrogenation to **D**. On the other hand, reduction with equimolecular amounts of $LiAlH_4$ in THF afforded stereoselectively one of the two possible diastereomeric alcohols **6**[9] together with the decomposition compound **7**.[7]

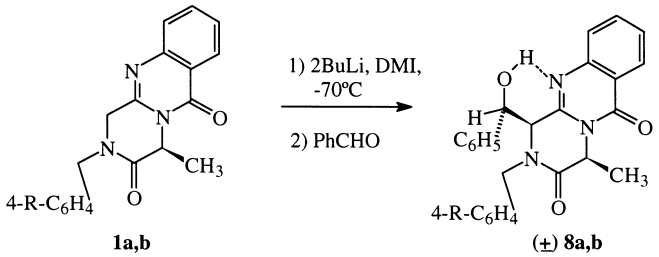


C **D** **5** **2d** **6** (41%) **7** (24%)

Scheme 3.

The alternative way to prepare hydroxy derivatives **8** by aldol condensation of **1a**,**b** with benzaldehyde showed great diastereoselectivity but, in spite of different trials, yields remained low probably due to retro-aldol reactions. The long reaction times required produced racemic **8**.

The configuration of (±)-**8** was established by NOE experiments on the basis of the presence of an intramolecular hydrogen bond[10] between the OH and N-11, which forces the molecule into a rigid conformation (a six-membered cyclic chelate; Scheme 4). In fact, by irradiating either (C-4)-CH3, (C-1)-Hα or (C-2)-Hα in **8,** an NOE was registered on the other protons mentioned.



Scheme 4.

This work reflects the different stereochemical behaviour of compounds **1** with respect to piparazinediones[6] or their bislactim ethers.[5] The *anti*-isomers of 1,4-dialkyl[1] and 1-acyl-4-alkyl derivatives of **1** are more inclined to equilibrate, due to the greater stabilisation of the C-1 anion through the conjugated N^{11}-benzene-C^{6}=O system, to the more stable *syn*-isomers in which the 1,2-steric interactions are minimised. This fact also explains the lower stability of acylation and aldol condensation products derived from compound **1**.

1. Experimental

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, U.C.M.). EI mass spectra were recorded at 70 eV with a quadrupole detector (Centro de Espectroscopía, U.C.M.). Elemental analyses were obtained from the Servicio de Microanálisis, U.C.M. 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). Tetrahydrofuran was freshly distilled from sodium-benzophenone. All commercial reagents were used as received. The expression 'petroleum ether' refers to the fraction boiling at 40–60°C.

*1.1. (4S)-2-(4-Methoxybenzyl)-4-methyl-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione **1b***

To a stirred solution of 3.17 g (14.2 mmol) of distilled ethyl *N*-(4-methoxybenzyl)glycinate[11] in 40 ml dry CH_2Cl_2, *N*-Cbz-(L)-alanine (3.17 g, 14.2 mmol) and DCC (3.22 g, 15.7 mmol) were added, and stirring was continued overnight. The reaction mixture was filtered, washed successively with HCl (1 N), $NaHCO_3$ (1 N) and water, dried over anhydrous Na_2SO_4 and evaporated. The syrupy residue (5.88 g, 13.8 mmol; yield 97%) was hydrogenated at 35 psi for 14 h with 0.55 g of C/Pd (10%) in 100 ml of methanol, filtered (Celite) and evaporated. The obtained syrup was refluxed in 30 ml of methanol for 12 h, concentrated and recrystallized to give 2.46 g (72%) of (3*S*)-3-methyl-1-(4-methoxybenzyl)piperazine-2,5-dione. Mp: 138–140°C (toluene). $[\alpha]_D$ −4.1 (c 0.23, chloroform). IR (KBr) ν: 3472, 1666, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.17 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.95 (1H, s, NH), 6.84 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 4.50 (2H, 't', *J*=14.9 Hz, Ar–CH_2–N), 4.10 (1H, q, *J*=7.0 Hz, H-3), 3.80 (2H, s, H-6), 3.77 (3H, s, OCH_3), 1.49 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 166.8, 166.3, 159.6, 129.9,

127.3, 114.4, 55.4, 51.2, 49.2, 48.9, 20.2. Analysis calc. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.78; H, 6.41; N, 11.27.

A mixture of 2 g (8.1 mmol) of the above described (3*S*)-3-methyl-1-(4-methoxybenzyl)piperazine-2,5-dione, triethyloxonium tetrafluoroborate (4.6 g, 24.2 mmol) and anhydrous Na_2CO_3 (4.27 g, 40.3 mmol) in 75 ml dry CH_2Cl_2 was stirred overnight at room temperature, poured on ice water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated. Anthranilic acid (1.48 g, 10.8 mmol) was added to the syrupy residue, 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. Column chromatography (EtOAc:MeOH=95:5) afforded 2.03 g (72%) of **1b** as a white solid. Mp: 164°C (methanol). $[\alpha]_D$ +24.2 (c 0.25, chloroform). IR (KBr) ν: 1669, 1611 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.27 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=8.0, 7.0, 1.5 Hz, H-9), 7.57 (1H, dd, *J*=8.0, 1.1 Hz, H-10), 7.48 (1H, ddd, *J*=8.0, 7.0, 1.1 Hz, H-8), 7.22 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.87 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.53 (1H, q, *J*=7.2 Hz, H-4), 4.84 (1H, d, *J*=14.3 Hz, Ar–CH_2–N), 4.47 (1H, d, *J*=16.9 Hz, H-1), 4.46 (1H, d, *J*=14.3 Hz, Ar–CH_2–N), 4.30 (1H, d, *J*=16.9 Hz, H-1), 3.79 (3H, s, OCH_3), 1.59 (3H, d, *J*=7.2 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 167.4, 160.0, 159.7, 148.1, 147.3, 134.9, 129.9, 127.3, 127.2, 127.0, 120.6, 114.6, 55.4, 52.2, 49.2, 49.1, 17.2. Analysis calc. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.54; H, 5.41; N, 11.88.

*1.2. General procedure for the acylation of compounds **1a** and **1b***

To a cold (−78°C), magnetically stirred solution of compounds **1a**[1] or **1b** (1 mmol) in dry THF (15 ml) was added, under argon, dropwise via syringe a 1 M solution of lithium hexamethyldisilazide in THF (1.3 ml), followed by the acyl chloride (1.1 mmol dissolved in 5 ml of THF) 6 min later. The reaction mixture was maintained at −78°C for 10 min, and at 0°C for 15 min, quenched with drops of glacial acetic acid and ice, and diluted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Column chromatography of the residue on silica gel afforded the acyl derivatives **2**. Yields and physical data are included in Table 1; mps, analytical and spectroscopic data follow.

*1.3. (1*R,*4*S*)-1-Acetyl-2-benzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione **2a***

IR (NaCl) ν: 1734, 1684, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.26 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=8.1, 7.1, 1.5 Hz, H-9), 7.61 (1H, dd, *J*=8.1, 1.2 Hz, H-10), 7.49 (1H, ddd, *J*=8.0, 7.1, 1.2, H-8), 7.31 (3H, m, ArH), 7.21 (2H, m, ArH), 5.63 (1H, q, *J*=7.1 Hz, H-4), 5.60 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 5.13 (1H, s, H-1), 3.95 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 2.38 (3H, s, CH_3), 1.58 (3H, d, *J*=7.1 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 200.5, 168.0, 160.0, 147.0, 146.3, 135.0, 134.6, 129.3, 129.0, 128.6, 129.9, 126.3, 126.2, 120.7, 68.9, 52.9, 49.1, 27.7, 18.5. Analysis calc. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.50; H, 5.38; N, 11.76.

*1.4. (1*R,*4*S*)-1-Acetyl-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione **2b***

IR (NaCl) ν: 1690, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.24 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=8.1, 7.3, 1.5 Hz, H-9), 7.60 (1H, dd, *J*=8.1, 1.2 Hz, H-10), 7.48 (1H, ddd, *J*=8.0, 7.3, 1.2 Hz, H-8), 7.12 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.84 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.35 (1H, q, *J*=7.1 Hz, H-4), 5.25 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 5.11 (1H, s, H-1), 3.96 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 3.77 (3H, s, OCH_3), 2.34 (3H, s, CH_3), 1.57 (3H, d, *J*=7.1 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 200.6, 167.9, 160.0,

159.8, 147.0, 145.4, 134.9, 130.5, 127.8, 127.1, 127.0, 126.3, 120.6, 114.6, 68.6, 55.4, 52.9, 48.5, 27.7, 18.5. Analysis calc. for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.81; H, 5.40; N, 10.69.

*1.5. (1*R,*4*S*)-2-Benzyl-4-methyl-1-pivaloyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***2c***

Mp: 128°C (ethyl ether). IR (KBr) ν: 1718, 1686, 1596 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.25 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=8.2, 7.1, 1.5 Hz, H-9), 7.60 (1H, dd, *J*=8.2, 1.2 Hz, H-10), 7.49 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 7.33 (3H, m, ArH), 7.25 (2H, m, ArH), 5.61 (1H, s, H-1), 5.37 (1H, q, *J*=7.1 Hz, H-4), 5.18 (1H, d, *J*=15.0 Hz, Ar–CH_2–N), 3.97 (1H, d, *J*=15.0 Hz, Ar–CH_2–N), 1.73 (3H, d, *J*=7.1 Hz, CH_3), 1.16 (9H, s, $3CH_3$). ^{13}C-NMR ($CDCl_3$) δ: 208.8, 169.4, 160.3, 146.7, 146.4, 134.9, 134.6, 129.2, 128.9, 128.5, 127.7, 127.1, 126.9, 120.5, 64.2, 53.3, 49.1, 44.8, 27.0, 18.4. Analysis calc. for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41. Found: C, 71.03; H, 6.36; N, 10.10.

*1.6. (1*R,*4*S*)-4-Methyl-2-*p*-methoxybenzyl-1-pivaloyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***2d***

Mp: 161–163°C (ethyl ether). IR (KBr) ν: 1694, 1651, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.25 (1H, dd, *J*=8, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=8.2, 7.1, 1.5 Hz, H-9), 7.56 (1H, dd, *J*=8.2, 1.2 Hz, H-10), 7.48 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 7.13 (2H, d, *J*=8.7, H-2′ and 6′), 6.86 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.57 (1H, s, H-1), 5.34 (1H, q, *J*=7.1 Hz, H-4), 5.10 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 3.91 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 3.78 (3H, s, OCH_3), 1.57 (3H, d, *J*=7.1 Hz, CH_3), 1.16 (9H, s, $3(CH_3)$). ^{13}C-NMR ($CDCl_3$) δ: 208.8, 169.4, 160.1, 159.7, 146.8, 146.5, 134.9, 130.4, 127.7, 127.1, 127.0, 126.5, 120.8, 114.5, 64.2, 55.4, 53.6, 48.7, 45.0, 27.3, 18.6. Analysis calc. for $C_{25}H_{27}N_3O_4$: C, 69.27; H, 6.28; N, 9.69. Found: C, 69.06; H, 6.19; N, 9.62.

*1.7. (1*R,*4*S*)-1-Benzoyl-2-benzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***2e***

IR (NaCl) ν: 1696, 1682, 1663 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.23 (2H, m, H-2″ and 6″), 8.21 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.67 (1H, ‘t’d, *J*=8.0, 1.5 Hz, H-9), 7.61 (1H, d, *J*=8.0 Hz, H-10), 7.45 (4H, m, H-3″, 4″, 5″ and H-8), 7.26 (3H, m, ArH), 7.15 (2H, m, ArH), 6.07 (1H, s, H-1), 5.42 (1H, q, *J*=7.0 Hz, H-4), 5.35 (1H, d, *J*=14.8 Hz, N–CH_2–Ar), 3.90 (1H, d, *J*=14.8 Hz, N–CH_2–Ar), 1.81 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 192.6, 169.1, 160.3, 146.9, 145.6, 134.6, 134.5, 134.4, 133.8, 130.3, 129, 128.9, 128.5, 128.3, 127.4, 126.9, 126.7, 120.4, 63.8, 53.2, 48.8, 18.7. MS (70 eV), m/z (%)=424 (1), 423 (M^+, 2), 335 (1), 334 (5), 333 (19), 320 (9), 319 (41), 318 (12), 305 (7), 304 (4), 262 (4), 229 (5), 228 (26), 215 (3), 214 (12), 200 (10), 186 (23), 185 (23), 160 (24), 146 (11), 132 (15), 117 (11), 106 (19), 105 (40), 102 (12), 92 (16), 91 (100), 92 (12), 77 (28), 76 (12), 65 (23). Analysis calc. for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.15; H, 5.12; N, 9.55.

*1.8. (1*R,*4*S*)-1-Benzoyl-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***2f***

IR (NaCl) ν: 1690, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.20 (2H, m, H-2″ and 6″), 8.20 (1H, dd, *J*=8, 1.4 Hz, H-7), 7.65 (1H, d‘t’, *J*=8.0, 1.5 Hz, H-9), 7.58 (1H, d, *J*=8.0 Hz, H-10), 7.45 (1H, d, *J*=8.0 Hz, H-8), 7.45 (3H, m, H-3″, 4″ and 5″), 7.07 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.74 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 6.07 (1H, s, H-1), 5.40 (1H, q, *J*=7.0 Hz, H-4), 5.18 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 3.98 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 3.72 (3H, s, OCH_3), 1.82 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ:

192.5, 168.9, 160.0, 159.5, 146.7, 145.5, 134.5, 134.4, 133.8, 130.6, 130.2, 128.4, 127.3, 126.8, 126.6, 126.1, 120.4, 114.2, 63.7, 55.3, 53.5, 48.4, 18.9. Analysis calc. for $C_{27}H_{23}N_3O_4$: C, 71.51; H, 5.11; N, 9.27. Found: C, 71.15; H, 5.32; N, 8.83.

*1.9. (1*R,*4*S*)-2-Benzyl-1-*p*-methoxybenzoyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***2g***

IR (NaCl) ν: 1683, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.24 (2H, d, *J*=9.0 Hz, H-2′′ and 6′′), 8.20 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.66 (1H, ddd, *J*=8.2, 7.2, 1.5 Hz, H-9), 7.48 (1H, dd, *J*=8.2, 1.2 Hz, H-10), 7.42 (1H, ddd, *J*=8, 7.2, 1.2 Hz, H-8), 7.25 (3H, m, ArH), 7.16 (2H, m, ArH), 6.93 (2H, d, *J*=9.0 Hz, H-3′ and 5′), 6.00 (1H, s, H-1), 5.41 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 5.40 (1H, q, *J*=7.1 Hz, H-4), 3.88 (3H, s, OCH_3), 3.80 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 1.83 (3H, d, *J*=7.1 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 190.3, 169.0, 164.7, 160.0, 146.7, 145.8, 134.6, 134.4, 132.9, 128.9, 128.8, 128.2, 127.3, 126.8, 126.7, 120.4, 113.7, 63.5, 55.5, 53.2, 48.6, 18.7. Analysis calc. for $C_{27}H_{23}N_3O_4$: C, 71.51; H, 5.11; N, 9.27. Found: C, 71.35; H, 5.44; N, 8.98.

*1.10. (1*R,*4*S*)-4-Methyl-1-*p*-methoxybenzoyl-2-*p*-methoxybenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione* syn-***2h***

IR (NaCl) ν: 1686, 1601 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.20 (2H, d, *J*=9.0 Hz, H-2′′ and 6′′), 8.18 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.62 (1H, ddd, *J*=8.2, 7.2, 1.5 Hz, H-9), 7.47 (1H, dd, *J*=8.2, 1.2 Hz, H-10), 7.37 (1H, ddd, *J*=8.0, 7.2, 1.2 Hz, H-8), 7.06 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.94 (2H, d, *J*=9.0 Hz, H-3′′ and 5′′), 6.72 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 6.00 (1H, s, H-1), 5.36 (1H, q, *J*=7.0 Hz, H-4), 5.22 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 3.86 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 3.86 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 1.80 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 190.4, 168.9, 164.7, 160.1, 159.4, 146.7, 145.8, 134.4, 132.8, 130.5, 126.8, 127.2, 126.8, 126.6, 126.3, 120.4, 114.2, 113.7, 63.4, 55.7, 55.3, 53.5, 48.3, 18.9. Analysis calc. for $C_{28}H_{25}N_3O_5$: C, 69.55; H, 5.21; N, 8.69. Found: C, 69.16; H, 5.54; N, 8.26.

*1.11. (1*S,*4*S*)-4-Methyl-1-*p*-methoxybenzoyl-2-*p*-methoxybenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione* anti-***2h***

^{1}H-NMR ($CDCl_3$) δ: 8.16 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.90 (2H, d, *J*=9.0 Hz, H-2′′ and 6′′), 7.59 (1H, ddd, *J*=8.2, 7.2, 1.5 Hz, H-9), 7.47 (1H, dd, *J*=8.2, 1.2 Hz, H-10), 7.32 (1H, ddd, *J*=8.0, 7.2, 1.2 Hz, H-8), 7.00 (2H, d, *J*=8.6 Hz, H-2′ and 6′), 6.85 (2H, d, *J*=9.0 Hz, H-3′′ and 5′′), 6.72 (2H, d, *J*=8.6 Hz, H-3′ and 5′), 5.88 (1H, s, H-1), 5.38 (1H, q, *J*=7.0 Hz, H-4), 5.22 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 3.86 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 3.84 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 1.73 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 191.2, 168.7, 164.3, 160.2, 159.4, 146.5, 146.1, 134.4, 132.0, 130.4, 127.4, 127.1, 126.9, 126.5, 126.3, 120.7, 114.1, 113.8, 61.9, 55.7, 55.3, 52.9, 47.2, 18.9.

*1.12. (1*R,*4*S*)-2-Benzyl-4-methyl-1-(3,4,5-trimethoxybenzoyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione* ***2i***

IR (NaCl) ν: 1688, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.22 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.68 (1H, ddd, *J*=8.3, 7.1, 1.5 Hz, H-9), 7.58 (2H, s, H-2′′ and 6′′), 7.46 (1H, dd, *J*=8.3, 1.1 Hz, H-10), 7.44 (1H, ddd, *J*= 8.0, 7.1, 1.1 Hz, H-8), 7.26 (3H, m, Ar–H), 7.18 (2H, m, Ar–H), 5.90 (1H, s, H-1), 5.40 (1H, q, *J*=7.0 Hz, H-4), 5.35 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 3.90 (9H, s, 3OCH_3), 3.87 (1H, d, *J*=14.8

Hz, Ar–CH_2–N), 1.79 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 190.7, 169.2, 160.0, 152.7, 146.6, 145.8, 143.9, 134.5 (2C), 129.3, 129.0, 128.9, 128.2, 127.4, 126.8, 126.7, 120.5, 107.8, 64.2, 61.0, 56.3, 53.4, 48.9, 18.6. Analysis calc. for $C_{29}H_{27}N_3O_6$: C, 67.83; H, 5.30; N, 8.18. Found: C, 67.72; H, 5.23; N, 7.97 N.

*1.13. (1*R,*4*S*)-2-*p-*Methoxybenzyl-4-methyl-1-(3,4,5-trimethoxybenzoyl)-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione* ***2k***

IR (NaCl) ν: 1688, 1599, 1584 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.20 (1H, dd, *J*=7.9, 1.6 Hz, H-7), 7.68 (1H, ddd, *J*=8.4, 7.1, 1.5 Hz, H-9), 7.55 (2H, s, H-2′′ and 6′′), 7.47 (1H, dd, *J*=8.4, 1.1 Hz, H-10), 7.42 (1H, ddd, *J*=7.9, 7.1, 1.1 Hz, H-8), 7.07 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 6.74 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 5.98 (1H, s, H-1), 5.37 (1H, q, *J*=7.0 Hz, H-4), 5.08 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 4.04 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 3.93 (9H, s, 3OCH_3), 3.72 (3H, s, OCH_3), 1.72 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 191.1, 169.2, 160.3, 159.7, 152.9, 146.8, 146.1, 143.9, 134.8, 131.0, 129.0, 127.6, 127.0, 126.9, 126.4, 120.6, 114.3, 107.9, 64.1, 61.2, 56.5, 55.3, 53.7, 48.6, 18.9. Analysis calc. for $C_{30}H_{29}N_3O_7 \cdot H_2O$: C, 64.16; H, 5.56; N, 7.48. Found: C, 64.47; H, 5.89; N, 7.10.

*1.14. (4*S*)-1-(1-Acetoxyethylidene)-2-*p-*methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione* ***3***

Mp: 67–68°C (ethyl ether). $[\alpha]_D$ +10.2 (c 0.23, CH_2Cl_2). IR (KBr) ν: 1766, 1682, 1592 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.26 (1H, dd, *J*=8.0, 1.2 Hz, H-7), 7.73 (1H, ddd, *J*=8.2, 7.1, 1.2 Hz, H-9), 7.64 (1H, dd, *J*=8.2, 1.3 Hz, H-10), 7.47 (1H, ddd, *J*=8.0, 7.1, 1.3 Hz, H-8), 7.07 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.76 (2H, d, *J*=8.7 Hz, 3′ and 5′), 5.58 (1H, q, *J*=7.2 Hz, H-4), 5.02 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 4.61 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 3.71 (3H, s, OCH_3), 2.38 (3H, s, CH_3), 1.97 (3H, s, CH_3), 1.59 (3H, d, *J*=7.2 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 167.9, 167.4, 159.8, 159.0, 147.2, 147.0, 146.2, 134.7, 128.8, 128.6, 127.7, 127.6, 127.0, 121.8, 120.4, 114.1, 55.3, 52.8, 49.7, 20.7, 18.5, 16.6. Analysis calc. for $C_{24}H_{23}N_3O_5 \cdot H_2O$: C, 63.85; H, 5.58; N, 9.31. Found: C, 63.84; H, 5.36; N, 8.98.

*1.15. (1*R,*4*S*)-2-*p-*Methoxybenzyl-4-methyl-1-pivaloyl-2,4,7,8,9,10-hexahydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione* ***5***

Compound **2d** (70 mg, 0.16 mmol) was hydrogenated at 33 psi for 14 h with 50 mg of PtO_2 in ethanol (50 ml) and 0.1 ml of acetic acid. The reaction mixture was filtered and concentrated. Column chromatography (ethyl acetate:petroleum ether=8:2) afforded 36 mg (51%) of **5**. Mp: 133–134°C (ethyl acetate:petroleum ether). $[\alpha]_D$ −75.1 (c 0.21, CH_2Cl_2). IR (KBr) ν: 1716, 1670, 1608 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.12 (2H, d, *J*=8.6 Hz, H-2′ and 6′), 6.87 (2H, d, *J*=8.6 Hz, H-3′ and 5′), 5.44 (1H, s, H-1), 5.22 (1H, q, *J*=7.1 Hz, H-4), 5.12 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 3.83 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 3.80 (3H, s, OCH_3), 2.5–1.73 (8H, m, H-7, 8, 9 and 10), 1.68 (3H, d, *J*=7.1 Hz, CH_3), 1.12 (9H, s, 3CH_3). ^{13}C-NMR ($CDCl_3$) δ: 208.8, 169.2, 160.5, 159.7, 159.1, 147.2, 130.3, 126.6, 121.2, 114.5, 63.7, 55.4, 53.3, 48.5, 45.0, 31.3, 27.3, 22.4, 22.1, 21.6, 18.5. Analysis calc. for $C_{25}H_{31}N_3O_4 \cdot H_2O$: C, 65.91; H, 7.30; N, 9.22. Found: C, 66.23; H, 7.15; N, 9.11.

*1.16. (1*R,*4*S*)-1-(1-Hydroxy-2,2-dimethylpropyl)-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***6***

50 mg (0.116 mmol) of **2d** in 15 ml dry THF and 4.4 mg (0.116 mmol) of lithium aluminium hydride were stirred for 1.5 h, quenched with ice, treated with dichloromethane, dried (Na_2SO_4) and evaporated. Column chromatography (ethyl acetate:petroleum ether=6:4) of the residue afforded 18 mg (41%) of **6** and 10 mg (24%) of **7**.[7] Mp: 214–216°C (ethyl acetate:petroleum ether). $[\alpha]_D$ −11.8 (c 0.20, CH_2Cl_2). IR (KBr) ν: 1682, 1650, 1604 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.25 (1H, dd, *J*=8.0, 1.2 Hz, H-7), 7.69 (1H, ddd, *J*=7.8, 7.2, 1.2 Hz, H-9), 7.52 (1H, dd, *J*=7.8, 1.1 Hz, H-10), 7.44 (1H, ddd, *J*=8.0, 7.2, 1.1 Hz, H-8), 7.12 (2H, d, *J*=8.6 Hz, H-2′ and 6′), 6.82 (2H, d, *J*=8.6 Hz, H-3′ and 5′), 5.51 (1H, d, *J*=15.0 Hz, Ar–CH_2–N), 5.34 (1H, q, *J*=7.0 Hz, H-4), 4.63 (1H, d, *J*=1.8 Hz, H-1), 3.89 (1H, d, *J*=15.0 Hz, Ar–CH_2–N), 3.75 (3H, s, OCH_3), 3.67 (1H, d, *J*=5.2 Hz, H-α), 2.25 (1H, d, *J*=5.2 Hz, OH), 1.89 (3H, d, *J*=7.0 Hz, CH_3), 1.05 (9H, s, $3CH_3$). ^{13}C-NMR ($CDCl_3$) δ: 169.2, 160.8, 159.5, 148.7, 146.8, 134.5, 129.4, 127.3, 127.1, 127.0, 126.8, 120.7, 114.5, 81.9, 61.5, 55.4, 53.5, 46.8, 35.7, 26.5, 18.1. Analysis calc. for $C_{25}H_{29}N_3O_4$: C, 68.95; H, 6.71; N, 9.65. Found: C, 68.73; H, 6.65; N, 9.71.

1.17. General procedure for the aldol condensation of compounds ***1a*** *and* ***1b***

To a cold (−78°C), magnetically stirred solution of compounds **1a** or **1b** (1 mmol) and 228 mg (2 mmol) of 1,3-dimethylimidazolidin-2-one in dry THF (15 ml) was added, under argon, drop wise via syringe a 2.5 M solution of butyl lithium in THF (1.3 ml), followed by benzaldehyde (1 mmol dissolved in 5 ml of THF) 6 min later. The reaction mixture was maintained at −78°C during 30 h, quenched with drops of glacial acetic acid and ice, and diluted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Column chromatography (ethyl acetate:petroleum ether=1:1) of the residue on silica gel afforded compounds **8a** and **b**.

*1.18. (±)-(1*R,*4*S*)-2-Benzyl-1-(α-hydroxybenzyl)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione (±)-****8a***

Yield: 127 mg (30%). Mp: 111–112°C (ethyl ether). IR (NaCl) ν: 3450, 1671, 1648 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.18 (1H, dd, *J*=8.0, 1.4 Hz, H-7), 7.7 (1H, ddd, *J*=8.0, 8.0, 1.4 Hz, H-9), 7.55 (1H, dd, *J*=8.0, 1.0 Hz, H-10), 7.42 (1H, ddd, *J*=8.0, 8.0, 1.0 Hz, H-8), 7.25 (8H, m, ArH), 7.05 (2H, m, ArH), 5.43 (1H, d, *J*=15.0 Hz, CH_2–N), 5.36 (1H, d, *J*=3.6 Hz, H-α), 5.1 (1H, q, *J*=7.0 Hz, H-4), 4.9 (1H, s, OH), 4.78 (1H, d, *J*=3.6 Hz, H-1), 3.46 (1H, d, *J*=15.0 Hz, CH_2–N), 1.16 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 167.4, 160, 149.2, 146.3, 139.6, 135, 134.7, 128.9, 128.8, 128.6, 128.4, 128.1, 127.1, 126.6, 126.5, 126.2, 120.2, 74.4, 64.2, 52.4, 47.8, 17.8. Analysis calc. for $C_{26}H_{23}O_3N_3 \cdot 2H_2O$: C, 67.66; H, 5.89; N, 9.10. Found: C, 67.27; H, 5.66; N, 9.34.

*1.19. (±)-(1*R,*4*S*)-1-(α-Hydroxybenzyl)-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione (±)-****8b***

Yield: 151 mg (33%). IR (NaCl) ν: 3011, 1682, 1609 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.21 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=7.7, 7.0, 1.5 Hz, H-9), 7.60 (1H, dd, *J*=7.7, 1.2 Hz, H-10), 7.46 (1H, ddd, *J*=8.0, 7.0, 1.2 Hz, H-8), 7.28 (3H, m, Ph), 7.24 (2H, m, Ph), 7.12 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.79 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.46 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 5.36 (1H, s, H-α), 5.08 (1H, q, *J*=6.9 Hz, H-4), 4.95 (1H, s, OH), 4.81 (1H, d, *J*=3.7 Hz, H-1), 3.73 (3H, s, OCH_3), 3.59 (1H, d, *J*=14.7

Hz, Ar–CH_2–N), 1.01 (3H, d, J=6.9 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 167.3, 160.0, 159.6, 149.3, 146.3, 139.7, 135.0, 130.1, 129.1, 128.9, 127.2, 127.3, 126.9, 126.7, 126.5, 120.4, 114.4, 70.2, 63.7, 55.4, 52.5, 47.3, 17.8. Analysis calc. for $C_{27}H_{25}N_3O_4 \cdot H_2O$: C, 68.49; H, 5.75; N, 8.87. Found: C, 68.10; H, 5.78; N, 8.85.

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