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Vilsmeier and Mannich Reactions on (4*S*)-N^2-Substituted 4-Methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones

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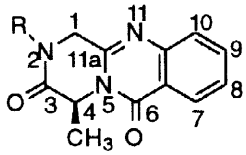
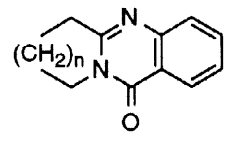
Abstract: The enamine character of the CH_2-C(11a)=N(11) fragment in the title compounds was studied. Compounds **1** gave 1-dimethylaminomethylene products **5** after Vilsmeier reaction. The 1-formyl derivatives, obtained by alkaline hydrolysis of **5**, were isolated as enol tautomers and were very unstable in acid media. On the other hand, acid-promoted elimination of dimethylamine from the Mannich reaction products **7** gave 1-methylene derivatives **8**, which showed an interesting reactivity. Thus, **8a** dimerized in acid to the ethylidene derivative **9a**. 1,4-Dialkyl-compounds **7** and **9a** showed a 1,4-*syn*-stereochemistry.

Following our current studies on the synthesis of *N*-acetylardeemin analogues,[1,2] which might reverse the multi drug resistance phenotype in tumour cells,[3] we have found that some simpler compounds, prepared by diastereoselective alkylation of anions derived from N^2,C^4-disubstituted-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (**1**),[2] retain most of the biological activity. Here we study the enamine character of the -CH_2-C(11a)=N(11) fragment in compounds **1** by exploring their reactivity against strong electrophiles such as the Vilsmeier and Mannich reagents.

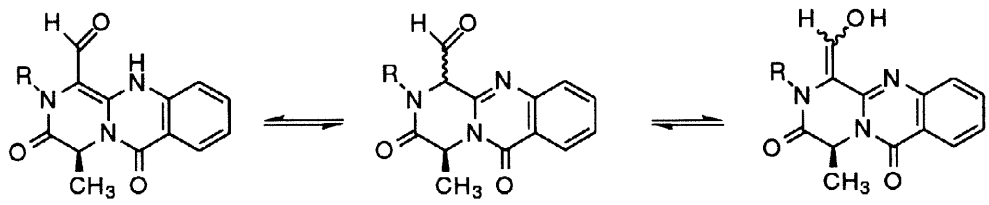
According to previous results obtained in related compounds (**2**),[4,5] which have been studied in connection with the synthesis of rutecarpine[6] and deoxyvasicinone alkaloids,[5,7] reaction of **1** with the Vilsmeier reagent was expected to give the formyl derivatives **3**, either as enol or carbonyl tautomers.



1a; R = Me
1b; R = PMB
1c; R = Bn



2, n = 1, 2



3

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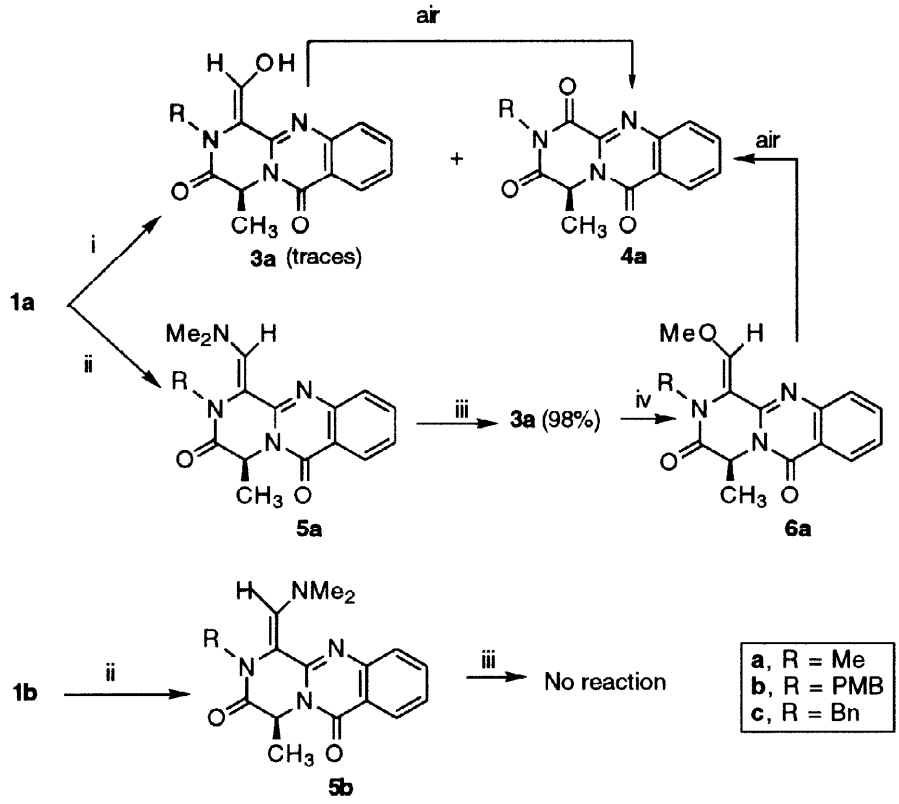
PII: S0040-4020(98)00026-X

When **1a** was treated with $POCl_3$/DMF[8] we recovered most of the starting material together with a very low yield of the formylation product **3a** (*E*-enol isomer) and the oxidation compound **4a**, which is probably derived from the enol **3a**.[9-11] Alternatively, enamines **5a** (*Z*-isomer) and **5b** (*E*-isomer) were obtained almost quantitatively when the corresponding Vilsmeier reaction mixtures were poured onto ice. Since acid hydrolysis of compounds **5** seemed to give unstable compounds, alkaline hydrolysis was studied. Thus, **5a** (R = Me) gave **3a** in quantitative yield (98%), but **5b** did not react at all. Finally, **3a** gave the unstable *O*-methyl derivative **6a**,[12] which was oxidized *in situ* to ketone **4a** (Scheme 1). The stereochemistry of compounds **3** and **5** was confirmed by NOE experiments. The different configuration of the exocyclic double bond in that enamines **5a** and **5b** show that steric interactions between the dimethylamino group and the N^2-substituent are greater when R = *p*-methoxybenzyl than when R = methyl.



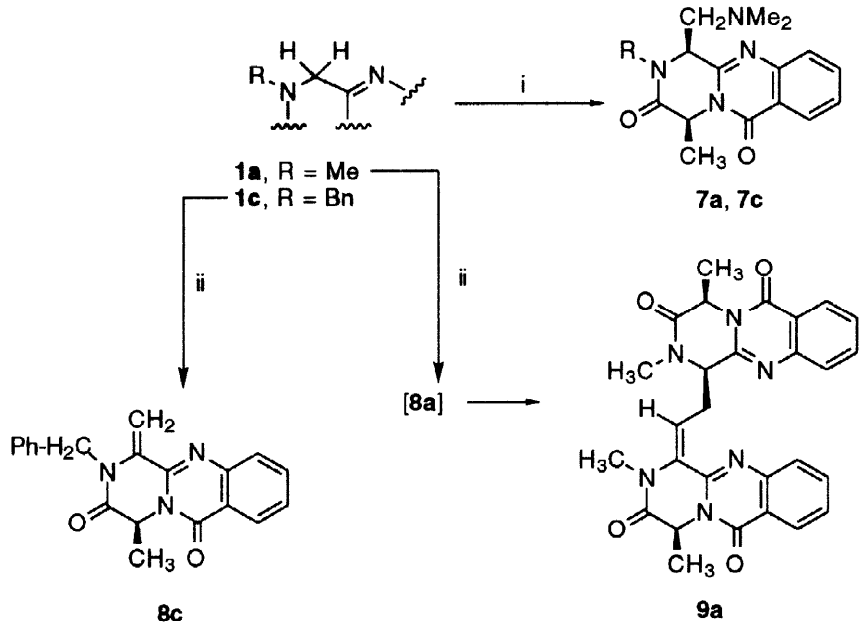
Scheme 1

The failure of the alkaline hydrolysis of **5b** points to a diastereoselective process, in which the acetate anion approaches to the α face, opposite to the 4-methyl substituent. This attack would be prevented in the **b** series because of the *p*-methoxybenzyl substituent at *N*-2.

The Mannich reaction[13] was next studied on compounds **1a** and **1c** (Scheme 2), which reacted with dimethylmethyleneammonium trifluoroacetate to give compounds **7**, **8** or **9**. Compounds **7** were quantitatively

obtained by reaction with a large excess of bis(dimethylamino)methane, while equimolecular amounts of this reagent and starting materials **1** gave either **9a** (R= Me) or **8c** (R= Bn).

The 1,4-*syn*-stereochemistry of compounds **7** and **9a** was deduced from our previous experience on 1,2,4-trialkylderivatives, for which we found significative differences in the ^{1}H-NMR chemical shifts of the C_4-H protons (deshielded in the *syn*-isomers with respect to the *anti*-isomers)[2] and from NOE experiments (irradiation of C_1-H and C_4-H protons).[14] Determination of the *syn*, *E* stereochemistry of **9a** required some additional NMR experiments (see ^{1}H-NMR assignments in Figure 1).



i: $(Me_2N)_2CH_2$ (2 equiv.), F_3CCO_2H (6 equiv.), 65 °C, 3.5 h. ii $(Me_2N)_2CH_2$ (1 equiv.), F_3CCO_2H (5 equiv.), 65 °C, 3.5 h.

Scheme 2

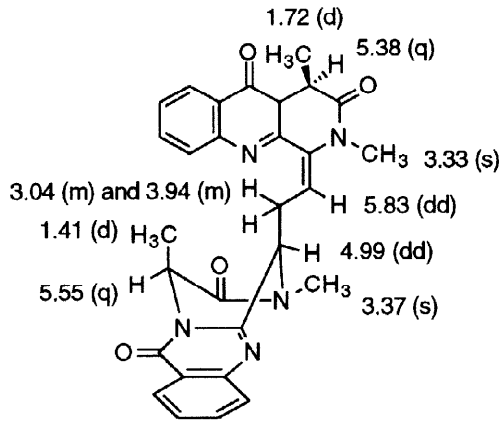
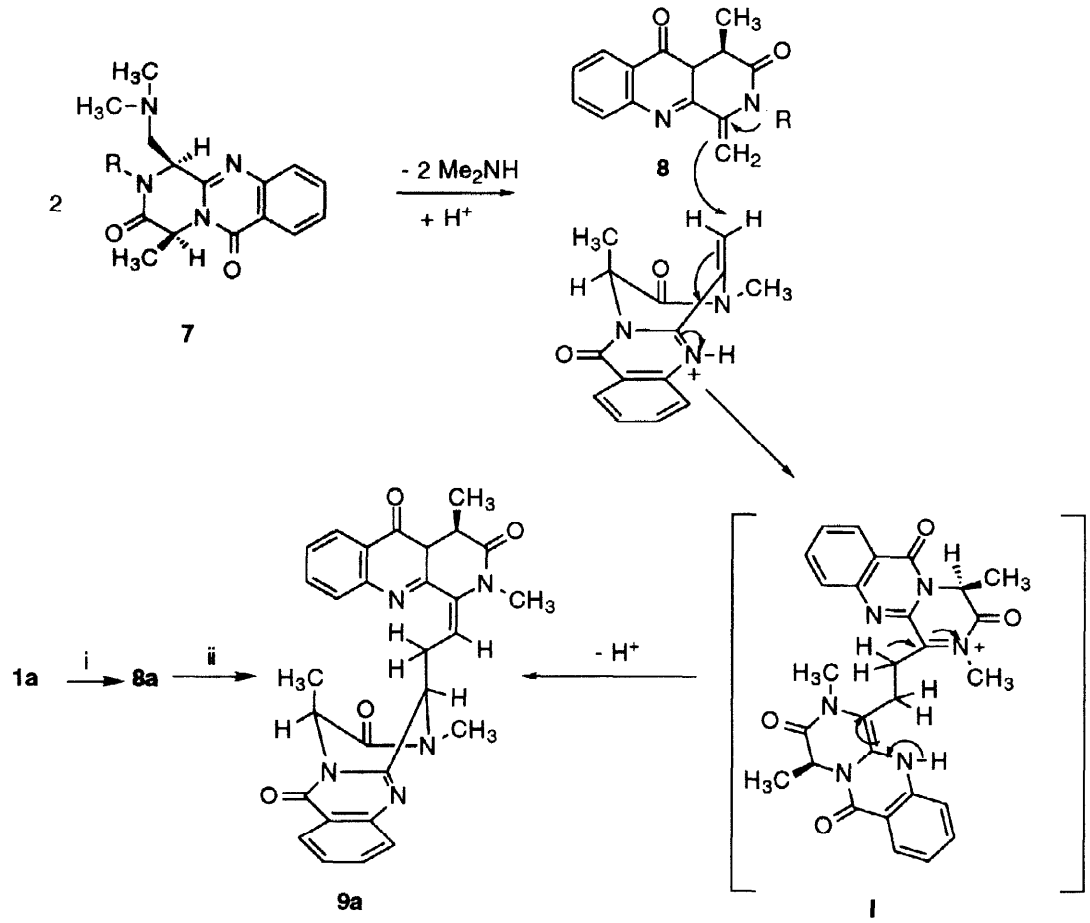


Fig. 1: ^{1}H NMR data of compound **9a** ($CDCl_3$)

We rationalize the formation of compound **8a** by dimerization of the 1-methylene derivative **8a** through intermediate **I** (Scheme 3). To corroborate this assumption, we isolated **8a** by performing the Mannich reaction with **1a** at higher dilution (CH_2Cl_2 as solvent). As expected, compound **9a** was formed after heating of isolated **8a** in trifluoroacetic acid. Steric interactions with the N^2-substituent must prevent a similar dimerization in **8c**.



i: $(MeN)_2CH_2$ (1 equiv.) , F_3CCO_2H (5 equiv.), CH_2Cl_2 , 65 °C , 3.5 h
ii: F_3CCO_2H, reflux

Scheme 3

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EXPERIMENTAL

NMR spectra were obtained on a Bruker AC-250 (250 MHz for ^1H, 62.5 MHz for ^{13}C) spectrometer; and $CDCl_3$ as the internal reference (Servicio de Espectroscopía, U.C.M.). Elemental analyses of new compounds were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyser. Mass spectra were recorded on a Hewlett-Packard 5993C (EI, 70 eV) (Servicio de

Espectroscopía U.C.M.). Melting points were measured in open capillary tubes using a Büchi immersion apparatus, and are uncorrected. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Scharlau Cf 530). Separations by chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh, and Scharlau Ge 048). All reagents were of commercial quality (Aldrich, Fluka, Merck, SDS, Probus) and were purified following standard procedures. Starting materials **1a**[15a], **1b**[15b] and **1c**[2] were obtained according to known procedures.

(4*S*)-2,4-Dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-1,3,6-trione (4a).

To a cooled solution of **1** (200 mg, 0.822 mmol) in DMF (1.23 ml, 0.164 mmol), $POCl_3$ (0.15 ml, 0.164 mmol) was added dropwise at 15-20 °C. The reaction mixture was stirred at 25 °C during 6 h, poured onto crushed ice and the pH adjusted to 7 with 20% aqueous Na_2CO_3. The solution was extracted with CH_2Cl_2 and the extracts were combined, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography, by using EtOAc as eluent to yield **4a** (50 mg, 24%). Mp 220-1 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.27 (dd, 1H, *J*= 8.1 and 1.4 Hz), 7.97 (dd, 1H, *J*= 8.1 and 1.4 Hz), 7.84 (m, 1H), 7.60 (m, 1H), 5.57 (q, 1H, *J*= 6.9 Hz), 3.38 (s, 3H), 1.72 (d, 3H, *J*= 6.9 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 168.5, 159.2, 157.1, 146.3, 138.4, 135.3, 129.7, 129.5, 126.7, 121.6, 52.5, 27.9, 21.0. Anal. calcd. for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31; N, 16.33. Found: C, 60.37; H, 4.37; N, 16.03.

Vilsmeier reaction: Synthesis of compounds 5.

To a magnetically stirred solution of **1** (200 mg, 0.822 mmol) in 5 ml of dry CH_2Cl_2 at room temperature under argon, was added chloromethylene-dimethylammonium chloride (250 mg, 1.95 mmol). The reaction mixture was stirred overnight and treated with 5 ml of H_2O. The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel by eluting with EtOAc.

(4*S*, *Z*)-2,4-Dimethyl-1-dimethylaminomethylen-2,4-dihydro-1*H*-pyrazino[2,1-*b*] quinazoline-3,6-dione (5a) Yield: 235 mg (96%); Mp 145 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.33 (dd, 1H, *J*= 7.9 and 1.4 Hz), 7.80 (m, 1H), 7.64 (d, 1H, *J*= 7.9 Hz), 7.46 (m, 1H), 7.25 (s, 1H), 5.78 (q, 1H, *J*= 7.1 Hz), 3.28 (s, 3H), 3.10 (s, 6H), 1.65 (d, 3H, *J*= 7.1 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 167.9, 160.5, 149.5, 148.3, 137.2, 134.4, 126.8, 126.2, 125.2, 119.4, 106.3, 52.0, 42.1, 34.1, 15.4. Anal. calcd. for: $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.77. Found: C, 64.35; H, 6.01; N, 18.49.

(4*S*, *E*)-4-Methyl-2-(*p*-methoxybenzyl)-1-dimethylaminomethylen-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (5b) Yield: 220 mg (95%). Mp 45-6 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.04 (d, 1H, *J*= 7.9 Hz), 7.51 (m, 1H), 7.40 (d, 1H, *J*= 8.1 Hz), 7.17 (m, 1H), 7.10 (s, 1H), 7.06 (d, 2H, *J*= 8.6 Hz), 6.69 (d, 2H, *J*= 8.6 Hz), 5.52 (q, 1H, *J*= 7.1 Hz), 5.12 (d, 1H, *J*= 13.9 Hz), 4.2 (d, 1H, *J*= 13.9 Hz), 3.65 (s, 3H), 2.92 (s, 6H), 1.44 (d, 3H, *J*= 7.1 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 167.5, 160.5, 158.9, 149.5, 148.3, 137.3, 134.2, 129.5, 128.4, 126.6, 126.3, 125.0, 119.3, 113.7, 105.2, 54.9, 51.9, 46.8, 42.2, 15.4. Anal. calcd. for: $C_{23}H_{24}N_4O_3.H_2O$: C, 65.38; H, 6.20; N, 13.26. Found: C, 65.40; H, 5.99; N, 13.08.

(4*S*, *E*)-2,4-Dimethyl-1-hidroxymethylen-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (3a) To a solution of **5a** (250 mg, 0.838 mmol) in CH_2Cl_2 (10 ml); NaOAc (100 mg, 1.21 mmol) in H_2O (10 ml) was added and stirred at room temperature overnight. The reaction mixture was extracted with CH_2Cl_2, washed with H_20, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel

columm chomatography by using EtOAc as eluent. Yield: 275 mg (98%). Mp 190-2 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.23 (m, 1H), 7.91 (s, 1H), 7.74 (m, 1H), 7.49-7.39 (m, 2H), 5.49 (q, 1H, *J*= 6.9 Hz), 3.30 (s, 3H), 1.53 (d, 3H, *J*= 6.9 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 163.1, 159.1, 155.9, 146.8, 143.0, 135.5, 127.6, 126.4, 122.7, 118.9, 108.7, 51.6, 30.0, 18.7. Anal. calcd. for: $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.89; H, 5.05; N, 15.26.

(4*S*, *Z*)-2,4-Dimethyl-1-methoxymethylen-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (6a) A mixture of **3a** (100 mg, 0.368 mmol), dimethyl sulfate (102 mg, 0.809 mmol) and $KHCO_3$ (49 mg, 0.496 mmol) in acetone (20 ml), was heated at reflux for 15.5 h. The reaction was cooled and filtered. The solution was concentrated and the residue was purified by silica gel columm chomatography by using EtOAc as eluent. Yield: 99 mg (95%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.23 (m, 1H), 7.73 (m, 1H), 7.6 (m, 1H), 7.42 (m, 1H), 7.15 (s, 1H), 5.6 (q, 1H, *J*= 7.1 Hz), 3.99 (s, 3H), 3.32 (s, 3H), 1.52 (d, 3H, *J*= 7.1 Hz).

Mannich reaction: Method A.

To stirred and cooled (ice-salt bath) anhydrous trifluoroacetic acid (0.418 ml, 5.43 mmol), bis(dimethylamino)methane (185 mg, 1.81 mmol) was added slowly. The temperature of the resulting solution was kept below -10 °C and **1** (0.905 mmol) was then added. The cooling bath was removed and the solution was heated at 65 °C for 3.5 h. To the cooled solution, H_2O (5 ml) was added, and the precipitate formed was removed by filtration and washed with MeOH.

(4*S*, *syn*)-2,4-Dimethyl-1-dimethylaminomethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*] quinazoline-3,6-dione (7a) Yield: 267 mg(98%). Mp 104-6 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.13 (dd, 1H, *J*= 7.9 and 1.1 Hz), 7.71 (m, 1H), 7.59 (d, 1H, *J*= 7.5Hz), 7.45 (m, 1H), 5.94 (m, 1H), 5.38 (q, 1H, *J*= 7.1 Hz), 4.62 (dd, 1H, *J*= 14.7 and 6.8 Hz), 4.29 (dd, 1H, *J*= 14.7 and 7.5 Hz), 3.23 (s, 3H), 2.89 (s, 6H), 1.43 (d, 3H, *J*= 7.1 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 165.9, 159.1, 146.1, 143.3, 134.8, 128.0, 127.3, 126.5, 120.0, 55.4, 51.1, 42.8, 34.4, 31.3, 18.3. Anal. calcd. for: $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.79; H, 6.62; N, 18.48.

(4*S*, *syn*)-2-Benzyl-4-methyl-1-dimethylaminomethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*] quinazoline-3,6-dione (7c) Yield: 167 mg (98%). Mp 75 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.30 (m, 1H), 7.77 (m, 1H), 7.58-7.51 (m, 2H), 7.34-7.20 (m, 5H), 5.97 (dd, 1H, *J*= 8.4 and 6.5 Hz), 5.65 (q, 1H, *J*= 7.1 Hz), 5.39 (d, 1H, *J*= 15.7 Hz), 4.89 (d, 1H, *J*= 15.7 Hz), 4.73 (dd, 1H, *J*= 13.9 and 8.4 Hz), 4.07 (dd, 1H, *J*= 13.9 and 6.5 Hz), 2.67 (s, 3H), 2.51 (s, 3H), 1.64 (d, 3H, *J*= 7.1 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 166.4, 159.2, 146.1, 143.5, 135.8, 134.8, 129.1, 127.9, 127.8, 127.6, 127.0, 126.9, 120.3, 54.8, 51.3, 46.8, 42.7, 41.7, 34.4, 18.5. Anal. calcd. for: $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.42; N, 14.88. Found: C, 70.02; H, 6.51; N, 14.69

Method B: The same as method A, but using anhydrous trifluoroacetic acid (0.348 ml, 4.525 mmol), bis(dimethylamino)methane (92.5 mg, 0.905 mmol), **1** (0.905 mmol) and 6 ml of CH_2Cl_2 yielded compound **8a**.

(4*S*)-2,4-Dimethyl-1-methylene-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (8a). Yield: 103 mg (75%,). Mp 170 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.28 (m, 1H), 7.79-7.70 (m, 2H), 7.50 (m, 1H), 6.24 (d, 1H, *J*= 1.6 Hz), 5.56 (q, 1H, *J*= 6.9 Hz), 5.13 (d, 1H, *J*= 1.6 Hz,), 3.34 (s, 3H), 1.57 (d, 3H, *J*= 6.9 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 165.9, 160.0, 147.5, 144.5, 138.1, 134.9, 127.9,

127.5, 126.9, 120.6, 103.1, 51.6, 31.0, 19.3. Anal. calcd. for: $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.75; H, 5.28; N, 16.34.

Method C: The same as method B, without solvent (CH_2Cl_2) yielded compounds **8c** and **9a**.

(4*S*)-2-Benzyl-4-methyl-1-methylene-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**8c**). Yield: 68 mg (65 %). Mp 175-76 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.30 (m, 1H), 7.78 (m, 1H), 7.69 (m, 1H), 7.51 (m, 1H), 7.39-7.23 (m, 5H), 6.19 (d, 1H, *J*= 1.7 Hz), 5.68 (q, 1H, *J*= 6.9 Hz), 5.33 (d, 1H, *J*= 15.7 Hz), 5.13 (d, 1H, *J*= 1.7 Hz), 4.84 (d, 1H, *J*= 15.7 Hz), 1.69 (d, 3H, *J*= 6.9 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 166.1, 160.0, 147.4, 144.2, 136.9, 135.5, 134.8, 128.9, 127.7, 127.6, 127.4, 126.8, 126.6, 120.5, 104.4, 51.5, 47.7, 19.3. Anal. calcd. for: $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.69; H, 5.17; N, 12.39.

(4*S*)-2,4-Dimethyl-1-{2-[(4'*S*)-2',4'-dimethyl-3',6'-dioxo-2',4'-dihydro-1'*H*-pyrazino[2,1-*b*]quinazolinyliden]ethyl}-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (9a). Yield: 138 mg (95%). Mp 275 °C (methanol). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.29 (m, 2H), 7.80 (m, 2H), 7.67 (d, 1H, *J*= 7.4 Hz), 7.59 (d, 1H, *J*= 7.1 Hz), 7.52 (m, 2H), 5.83 (dd, 1H, *J*= 9.2 and 7.7 Hz,), 5.55 (q, 1H, *J*= 7.1 Hz), 5.38 (q, 1H, *J*= 7.2 Hz), 4.98 (dd, 1H, *J*= 10.4 and 4.8 Hz,), 3.94 (m, 1H), 3.37 (s, 3H), 3.33 (s, 3H), 3.04 (m, 1H), 1.72 (d, 3H, *J*= 7.2 Hz), 1.41 (d, 3H, *J*= 7.1 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 167.2, 166.4, 160.7, 159.8, 149.4, 146.9, 146.9, 144.7, 135.0, 134.9, 132.7, 127.9, 127.4, 127.2, 127.1, 126.9, 126.8, 120.4, 120.3, 118.7, 63.1, 52.3, 51.5, 33.5, 33.1, 32.0, 19.2, 17.8. Anal. calcd. for: $C_{28}H_{26}N_6O_4$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.05; H, 5.39; N, 16.34. MS: *m/z* 510 (M^+, 12), 268 (100).

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