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Comparative study of synthetic approaches to 1-arylmethylenepyrazino[2,1-*b*]quinazoline-3,6-diones

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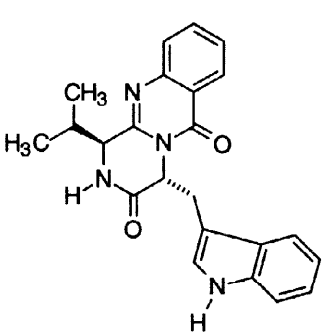
Abstract

The transformation of 3-arylmethylenepiperazine-2,5-diones (**1**) into 1-arylmethylene-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (**2**) was studied. Four synthetic methods were compared, namely direct condensation with the product of the reaction between anthranilic acid and thionyl chloride, transformation into monothioiminoethers or monoiminoethers followed by reaction with anthranilic acid derivatives, and monoacylation with *o*-azidobenzoyl chloride followed by intramolecular aza-Wittig reaction. The best results were obtained by the latter method.

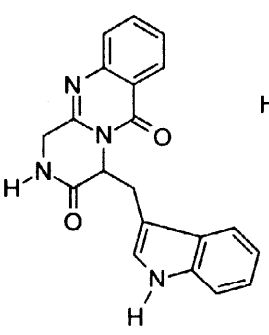
Keywords: Quinazolinones, piperazinones, imidic acids and derivatives, Wittig reactions.

1. Introduction

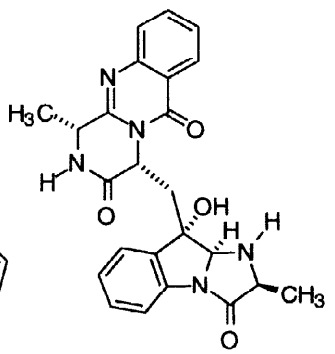
The pyrazino[2,1-*b*]quinazoline structure is present in several families of natural products, like the fiscalins [1], glyantrypine [2] the fumiquinazolines [3,4] and *N*-acetylardeemin [5,6]. Other natural products, like the asperlicins [7] and vasicinone [8,9], contain related heteroareno[2,1-*b*]quinazoline substructures. Some of these compounds exhibit interesting biological properties; for instance, *N*-acetylardeemin is one of the most potent known inhibitors of Multi-Drug Resistance (MDR) to antitumour agents [10,11].



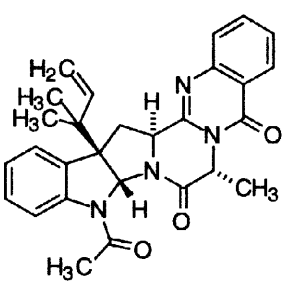
Fiscalin B



Glyantrypine



Fumiquinazoline A



N-Acetylardeemin

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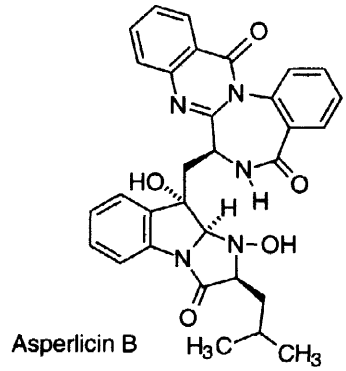
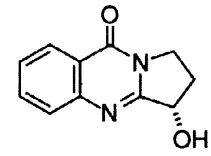
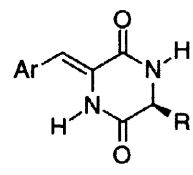
PII: S0040-4020(98)00744-3





Due to the excellent anti-MDR properties of *N*-acetylardeemin, and also to the existence in the patent literature of 3-arylmethylenepiperazine-2,5-diones (**1**) that also exhibit good anti-MDR activity [12,13], we became interested in the synthesis of 1-arylmethylene-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (**2**), which combine both substructures, and decided to investigate the transformation of compounds **1** into **2**.



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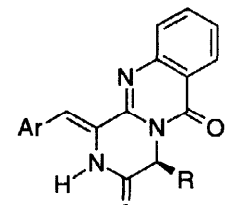

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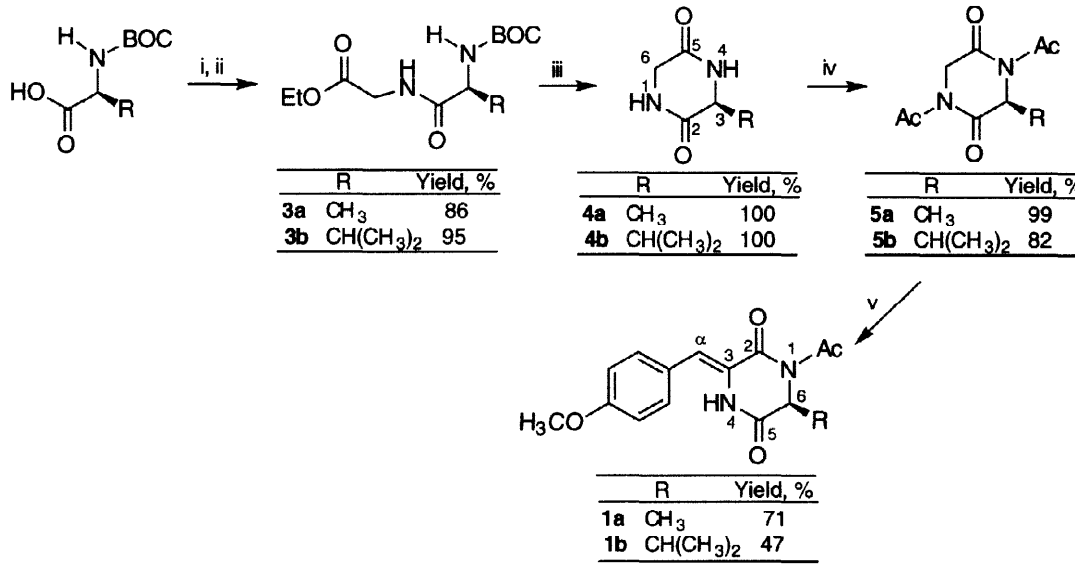
2. Results and discussion

We chose 3(*S*)-3-methyl-6-(*p*-methoxybenzylidene)-2,5-piperazinedione (**1a**) and its 3-isopropyl analogue (**1b**) as the starting materials. As shown in Scheme 1, they were prepared by condensation of the suitable



	R	Yield, %
3a	CH_3	86
3b	$CH(CH_3)_2$	95

	R	Yield, %
4a	CH_3	100
4b	$CH(CH_3)_2$	100

	R	Yield, %
5a	CH_3	99
5b	$CH(CH_3)_2$	82

	R	Yield, %
1a	CH_3	71
1b	$CH(CH_3)_2$	47

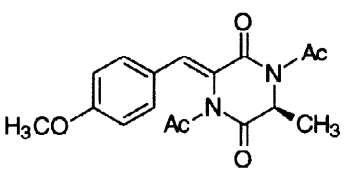
Reagents and conditions: i. $ClCO_2Et$, Et_3N, $CHCl_3$; r.t., 30 min. ii. H_2N-CH_2-CO_2Et.HCl, THF, $CHCl_3$; r.t., 1 h and then 50 °C, 30 min . iii. 200 °C, 30 min. iv. Ac_2O, 140 °C, 7 h. v. *p*-H_3CO-C_6H_4-CHO, KO^{t}Bu, DMF, r.t., 22 h

Scheme 1

N-BOC protected amino acids with glycine ethyl ester in the presence of ethyl chloroformate to give dipeptides **3**, which were cyclized under pyrolytic conditions to 2,5-piperazinediones **4**. Compounds **4** were diacetylated in order to facilitate base-catalyzed condensation with aldehydes [14,15,16] and compounds **5** thus obtained were finally treated with *p*-methoxybenzaldehyde in the presence of potassium *t*-butoxide at room temperature to yield the desired 2-arylmethylene-2,5-piperazinediones **1**. Alternatively, the condensation of **5a** with *p*-methoxybenzaldehyde in the presence of alumina-supported potassium fluoride [17,18] afforded **1a** in 48 % yield.

The stereochemical integrity of the alanine stereocenter under the strongly basic reaction conditions was established by the absence of splitting of any of the signals in the ^{1}H-NMR spectrum of compound **1a** after addition of 1 equivalent of Eu(hfc)$_3$. In a control experiment, racemic **1a**, prepared from (±)*N*-BOC-Ala using the method outlined in Scheme 1, gave a clear separation of the acetyl, methoxy and Ar-H$_2$ signals under the same NMR conditions. For independent confirmation, the enantiomer of **1a** was also prepared, starting from *N*-BOC-D-Ala and using again the conditions in Scheme 1, and was found to give the opposite optical rotation to **1a**.

The *Z* configuration of the double bond was assumed from literature precedent on similar reactions [14,15,16], and confirmed by the absence of a NOE enhancement of the vinyl proton upon irradiation of the N_1-H signal. Similarly, compound **6**, obtained by acetylation of **1a** (see below), failed to give a NOE enhancement of the vinyl proton upon irradiation of the N_1 acetyl signal.



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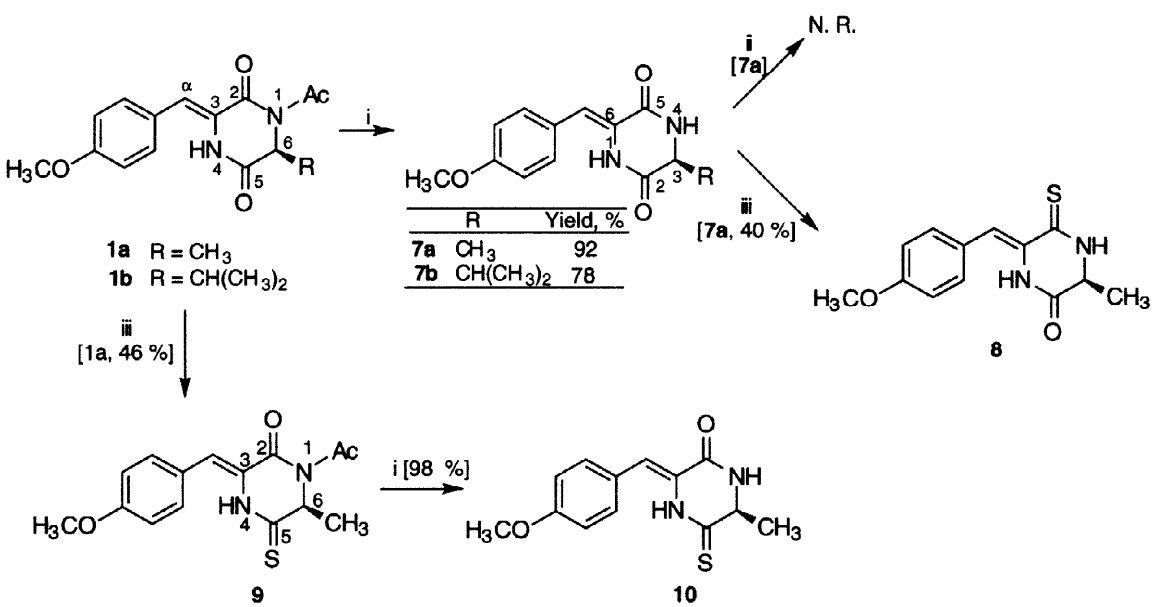
Compounds **1** were deacetylated by treatment with hydrazine hydrate, yielding derivatives **7**. Condensation of **7a** with anthranilic acid derivatives was attempted under several literature conditions (Scheme 2). The method described by Kametani for the synthesis of areno[2,1-*b*]quinazolines [19,20], consisting of the direct reaction

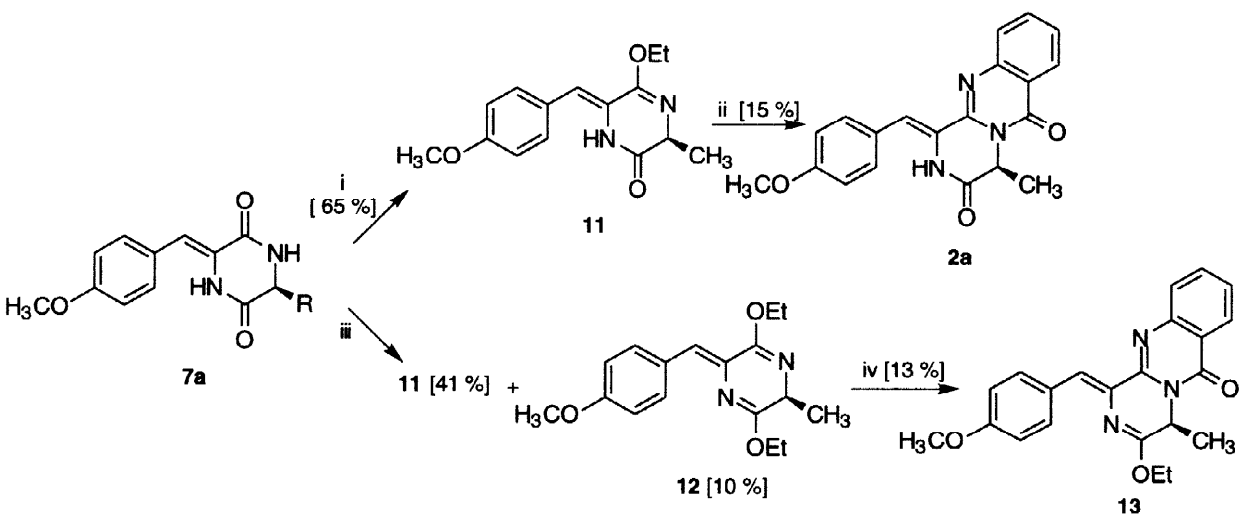


Reagents and conditions: i. NH_2-NH_2.H_2O, r.t., 3 h. ii. $SOCl_2$, anthranilic acid, benzene, r.t., 16 h or 80 °C, 2 h. iii. Lawesson's reagent, THF, r.t., 2 h.

Scheme 2

between **7a** and the product arising from the reaction between anthranilic acid and thionyl chloride [21], was unsuccessful. In an effort to take advantage of an alternative approach based on the reaction between thioiminoethers and methyl anthranilate [22], we obtained compound **8** by regioselective thionation of **7a** with Lawesson's reagent [23,24]. The regiochemistry of **8** was confirmed by preparation of the other possible regioisomer by treatment of the acetyl derivative **1a** with Lawesson's reagent to give compound **9**, followed by deacetylation with hydrazine hydrate to give **10**. Unfortunately, all attempts to transform **8** into the desired product via its *S*-methyl derivative failed.

In search for an alternative procedure, we selectively transformed **7a** into the monoiminoether **11** by treatment with triethyloxonium tetrafluoroborate in the presence of sodium carbonate [25]. Heating **11** with neat anthranilic acid [26,27] at 120 °C under a stream of argon afforded the desired compound **2a** in 15 % yield. Similarly, the rather unstable bis-iminoether **12**, prepared from **7a** with an excess of triethyloxonium tetrafluoroborate, afforded the tricyclic derivative **13** in 13 % yield (Scheme 3). Although, in our experience [28] and that of previous workers [26,27], the direct reaction between iminoethers and anthranilic acid rarely gives more than 30-40 % yield of quinazoline derivatives, the results obtained with compounds **11** and **12** suggest that the reactivity of the iminoether double bond is lowered by its conjugation with the arylmethylene moiety.

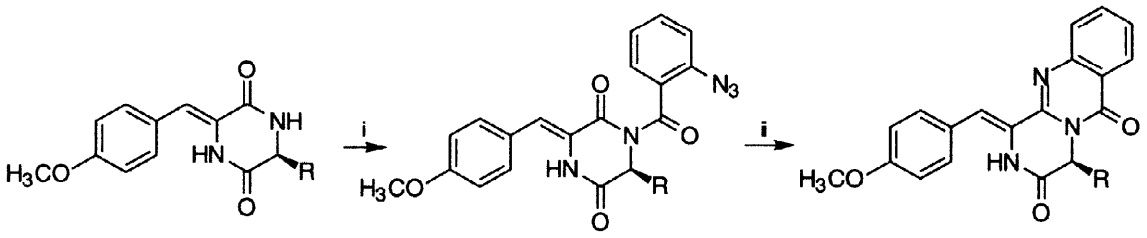


Reagents and conditions: i. $Et_3O^+BF_4^-$ (1.2 eq.), Na_2CO_3, CH_2Cl_2, r.t., 24 h. ii. Anthranilic acid (neat), 120 °C, 2 h. iii. $Et_3O^+BF_4^-$ (2.2 eq.), Na_2CO_3, CH_2Cl_2, r.t., 24 h. iv. Anthranilic acid (neat), 140 °C, 2 h.

Scheme 3

In view of these results, we decided to study a fourth approach, in which the $N^1{=}C^2$ bond of the quinazoline ring arises from an aza-Wittig reaction [29]. We envisaged that the required starting materials (compounds **14**) could be prepared by acylation of diketopiperazines **7** at their N-4 position with *o*-azidobenzoyl chloride, and that it should be possible to find conditions for regioselective acylation because of the steric hindrance of the arylmethylene side chain on the other nitrogen (N-1). This assumption was confirmed by the reluctance of compound **1a** to undergo acetylation at N-1 (thus, refluxing **1a** in acetic anhydride for 32 h afforded 43 % of the diacetylated derivative **6** and 52 % of recovered **1a**, while **4a**, not bearing the arylmethylene chain, was diacetylated in quantitative yield in 7 h). After some experimentation with several conditions, we found that the best results for regioselective acylation of **7a** were obtained by use of *o*-azidobenzoyl chloride in the presence of potassium hexamethylsilazide in THF, which afforded compound **14a** in 60 % yield with no trace of a diacylated derivative. In the case of **7b**, however, there was less difference between the reactivities of both nitrogen atoms, which can be attributed to an increased hindrance on N-4 due to the bulk of the isopropyl group and led to the isolation of the diacylated compound **15**. Nevertheless, selective monoacylation at N-4 could be achieved by interrupting the reaction before completion.

Finally, the aza-Wittig step was carried out in excellent yield by treatment of compounds **14** with tributylphosphine in toluene at room temperature (Scheme 4).

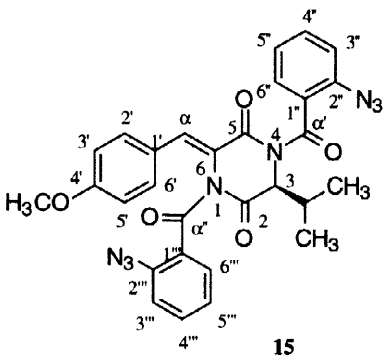


7a R = CH_3
7b R = $CH(CH_3)_2$

Cmpd.	R	Yield, %
14a	CH_3	60
14b	$CH(CH_3)_2$	23 (75*)

*Based on unrecovered starting material

Cmpd.	R	Yield, %
2a	CH_3	81
2b	$CH(CH_3)_2$	88



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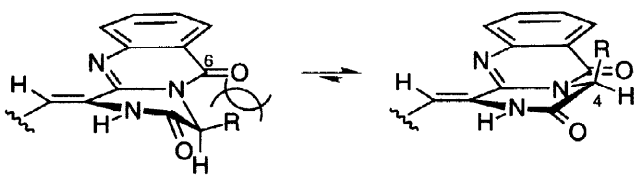
Reagents and conditions: i. KHMDS, THF, *o*-$N_3C_6H_4COCl$, - 78 °C to r.t., 16 h. ii. PBu_3, toluene, r.t., 3 h

Scheme 4

Formation of the tricyclic pyrazino[2,1-*b*]quinazoline system was easily characterized by ^{1}H-NMR spectroscopy thanks to the large shift (*ca.* + 0.5 ppm) of the H-4 proton. This shift can be attributed to the increased rigidity achieved upon cyclization, which anchors the C-4 substituent into a pseudoaxial position in order to avoid its repulsive interaction with the C-6 carbonyl, and causes the H-4 proton to be coplanar with the carbon-oxygen double bond:



3. Experimental

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS, Scharlau) were dried and purified using standard techniques. "Petroleum ether" refers to the fraction boiling at 40-60 °C. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Macherey-Nagel Alugram Sil G/UV_{254}). Catalytic hydrogenations were carried out using a Parr 3920 shaking reactor. Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh). Melting points were measured on a Reichert 723 hot stage microsope, and are

uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with solid compounds compressed into KBr pellets and liquid compounds placed between two NaCl disks. NMR spectra were obtained on a Bruker AC-250 spectrometer (250 MHz for ^{1}H, 63 MHz for ^{13}C), with $CDCl_3$ or DMSO-d_6 as solvents (Servicio de Espectroscopía, Universidad Complutense). When necessary, assignments were aided by DEPT, COSY and ^{13}C-^{1}H correlation experiments. Exchangeable assignments are marked with the symbols * and **. Optical rotations were determined at 25 °C on a 1 ml cell, using a Perkin Elmer 240 polarimeter operating at the emission wavelength of a sodium lamp; concentrations are given in g/100 ml. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer.

3.1. (3S)-3-Alkyl-2,5-piperazinediones (4).

To a cooled (0 °C), stirred solution of the suitable *N*-BOC aminoacid (23 mmol) and triethylamine (3.69 ml, 23 mmol) in dry chloroform (35 ml) was dropwise added ethyl chloformate (2.53 ml, 23 mmol) over 30 min. To the solution thus obtained was dropwise added a second solution, prepared from ethyl glycinate hydrochloride (3.197 g, 23.0 mmol), triethylamine (3.69 ml, 23.0 mmol) and chloroform (35 ml), at room temperature over 30 min. The reaction mixture was then refluxed for 10 min, cooled and washed with water (3 x 10 ml). The organic layer was dried (sodium sulphate) and evaporated. Yield, 5.431 g (86 %) of ethyl *N*-(*tert*-butyloxycarbonyl)-L-alanyl glycinate **3a** and 6,602 g (95 %) of ethyl *N*-(*tert*-butyloxycarbonyl)-L-valyl glycinate **3b**. Without further purification, the neat compounds **3** were heated at 200 °C for 30 min under a stream of argon and the dark residue was recrystallized from ethanol. Yield, 2.53 g (100 %) of (3*S*)-3-methyl-2,5-piperazinedione (**4a**) and 3.41 g (100 %) of (3*S*)-3-isopropyl-2,5-piperazinedione (**4b**).

Data for **4a**: Mp (EtOH), 237-239 °C. IR (KBr) ν 3196.1 (NH); 3049.3 (NH); 1667.2 (2 CO) cm^{-1}. ^{1}H-NMR (d_6-DMSO, 250 MHz) δ 8.17 (br s, 1H, H-4); 7.98 (br s, 1H, H-1); 3.84 (q, 1H, J = 6.9 Hz, CH); 3.73 (s, 2H, CH_2); 1.25 (d, 3H, J = 7.0 Hz, C_3-C$\underline{H}_3$) ppm. ^{13}C-NMR (d_6-DMSO, 63 MHz) δ 168.78 (C_2); 166.19 (C_5); 49.63 (C_3); 44.42 (C_6); 18.59 (C_3-$\underline{C}H_3$) ppm. Anal. Calcd. for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 46.60; H, 5.99; N, 20.94.

Data for **4b**: Mp (EtOH), 220-222 °C. IR (KBr) ν 3197.2 (NH); 3054.9 (NH); 1667.6 (2 CO) cm^{-1}. ^{1}H-NMR (d_6-DMSO, 250 MHz) δ 8.20 (br s, 1H, H-1); 8.02 (br s, 1H, H-4); 3.81 and 3.61 (AB, 2H, J = 17.7 Hz, CH_2); 3.52 (t, 1H, J = 3.5 Hz, H-3); 2.10 (m, 1H,C$\underline{H}$(CH_3)$_2$); 0.91 and 0.82 (d, 3H, J = 7.0 Hz, and d, 3H, J = 6.8 Hz, CH(C$\underline{H}_3$)$_2$) ppm. ^{13}C-NMR (d_6-DMSO, 63 MHz) δ 166.18 (C_2); 166.00 (C_5); 59.72 (C_3); 44.05 (C_6); 32.174 ($\underline{C}$H(CH_3)$_2$); 18.48; 16.98 (CH($\underline{C}H_3$)$_2$) ppm. Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.84; H, 7.74; N, 17.94. Found: C, 53.62; H, 7.51; N, 18.13.

3.2. (3S)-1,4-Diacetyl-3-alkyl-2,5-piperazinediones (5).

A solution of the suitable compound **4** (14.25 mmol) in acetic anhydride (40 ml) was refluxed for 7 h in an oil bath at 140 °C. Evaporation of the acetic anhydride, followed by addition and evaporation of dry toluene (10 ml), afforded compounds **5a** (3.00 g, 99 %) and **5b** (2.79 g, 82 %)

Data for **5a**. $[\alpha]^{25}_D$ (1.58, Cl_3CH) = +18.61. IR (KBr) ν 1712.2 (4 CO) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 5.25 (c, 1H, J = 7.3 Hz, H-3); 5.14 (H-6 pseudoequatorial) and 4.03 (H-6 pseudoaxial) (AB, 2H, J = 18.6 Hz, H-6); 2.59 and 2.57 (2s, 6H, 2 CO-CH_3); 1.53 (d, 3H, J = 7.3 Hz, C_3-C$\underline{H}_3$) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 171.34 (N_4-$\underline{C}$O-CH_3); 171.04 (N_1-$\underline{C}$O-CH_3); 168.82 (C_5); 54.03 (C_3); 46.52 (C_6); 27.17 and 27.04 (2 CO-$\underline{C}H_3$); 17.83 (C_3-$\underline{C}H_3$) ppm. Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.63; H, 6.09; N, 12.90.

Data for **5b**. $[\alpha]^{25}_D$ (1.12, Cl_3CH) = +36.78. IR (KBr) ν 1713.6 (4 CO) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 5.08 (H-6 pseudoequatorial) and 4.06 (H-6 pseudoaxial) (AB, 2H, J = 19.2 Hz, H-6); 4.98 (d, 1H, J = 9.8 Hz, H-3); 2.57 and 2.54 (2s, 6H, 2CO-CH_3); 1.23 (m, 1H, C$\underline{H}$(CH_3)$_2$); 1.07 and 0.95 (d, 3H J = 6.7 Hz and d, 3H, J = 6.7 Hz, CH(C$\underline{H}_3$)$_2$) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 171.53 (N_4-$\underline{C}$O-CH_3); 171.02 (N_1-$\underline{C}$O-

CH_3); 167.02 (C_2); 166.60 (C_5); 62.56 (C_3); 47.00 (C_6); 31.55 ($\underline{C}H(CH_3)_2$); 27.24 and 26.77 (2 CO-$\underline{C}H_3$); 19.50 and 19.45 ($CH(\underline{C}H_3)_2$) ppm. Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.68; H, 7.05; N, 11.93.

3.3. (6S,3Z)-1-Acetyl-6-alkyl-3-(p-methoxybenzylidene)-2,5-piperazinediones (1).

Method A. A solution of the suitable compound **5** (4.41 mmol) and *p*-methoxybenzaldehyde (6.61 mmol) in dry dimethylformamide (12 ml) was cooled to 0 °C and treated dropwise with a 1*M* solution of potassium *tert*-butoxide in *tert*-butyl alcohol (4.63 ml). The solution was stirred at room temperature for 22 h. After this time, the reacting mixture was neutralized with acetic acid and poured on ice. The precipitated solid was collected by filtration and identified as the corresponding compound **1**.

Method B. To a solution of compound **5a** (1 g, 4.739 mmol) and *p*-anisaldehyde (645 mg, 4.739 mmol) in dimethylformamide (7 ml) was added 40 % potassium fluoride on alumina (1.895 g). The suspension was stirred at room temperature for 16 h. After adding 5 ml of dimethylformamide, the suspension was filtered through celite. Evaporation of the solvent followed by silica gel column chromatography, eluting with 9:1 petroleum ether-ethyl acetate, afforded 657 mg (48 %) of compound **1a**.

Data for **1a**: Mp 123-125 °C. $[\alpha]^{25}_D$ (6.51, Cl_3CH) = -6.22. IR (KBr) ν 3365.7 (NH); 1694.0 (4 CO); 1230.0 (OCH_3) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 7.82 (br s, 1H, H-4); 7.38 (d, 2H, J = 8.4 Hz, H-2',6'); 7.11 (s, 1H, H_α); 6.95 (d, 2H, J = 8.4 Hz, H-3'-5'); 5.11 (q, 1H, J = 7.0 Hz, H-6); 3.83 (s, 3H, OCH_3); 2.57 (s, 3H, CO-C$\underline{H}_3$); 1.52 (d, 3H, J = 7.0 Hz, C_6-C$\underline{H}_3$) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 172.13 (N_1-$\underline{C}$O-CH_3); 167.16 (C_5); 161.18 (C_2); 160.58 ($C_{4'}$); 130.70 ($C_{2',6'}$); 124.97 and 124.02 (C_3 and $C_{1'}$); 120.66 (C_α); 115.06 ($C_{3',5'}$); 55.55 ($C_{4'}$-O$\underline{C}H_3$); 52.82 (C_6); 27.02 (N_1-CO-$\underline{C}H_3$); 19.73 (C_6-$\underline{C}H_3$) ppm. Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.43; H-5.64; N, 9.73.

Data for **1b**: Mp 103-105 °C. $[\alpha]^{25}_D$ (0.22, Cl_3CH) = -82.2. IR (KBr) ν 3241.6 (NH); 1701.1 (4 CO); 1235.1 (OCH_3) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 8.60 (br s, 1H, H-4); 7.36 (d, 2H, J = 8.7 Hz, H-2',6'); 7.03 (s, 1H, H_α); 6.86 (d, 2H, J = 8.7 Hz, H-3'-5'); 4.83 (d, 1H, J = 7.5 Hz, H-6); 3.74 (s, 3H, OCH_3); 2.47 (s, 3H, CO-C$\underline{H}_3$); 2.00 (m, 1H, C$\underline{H}(CH_3)_2$); 0.96 and 0.92 (d, 3H, J = 6.8 Hz and d, 3H, J = 6.8 Hz, $CH(C\underline{H}_3)_2$) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 171.88 (N_1-$\underline{C}$O-CH_3); 166.52 (C_5); 162.33 (C_2); 160.52 ($C_{4'}$); 131.12 ($C_{2',6'}$); 125.10 and 124.40 (C_3 and $C_{1'}$); 121.06 (C_α); 114.78 ($C_{3',5'}$); 61.16 (C_6); 55.44 ($C_{4'}$-O$\underline{C}H_3$); 33.46 ($\underline{C}H(CH_3)_2$); 26.52 (N_1-CO-$\underline{C}H_3$); 19.29 and 18.68 ($CH(\underline{C}H_3)_2$) ppm. Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 63.81; H, 6.15; N, 8.66.

3.4. (3S,6Z)-1,4-Diacetyl-6-(p-methoxybenzylidene)-3-methyl-2,5-piperazinedione (6).

A solution of compound **1a** (118 mg, 0.409 mmol) in acetic anhydride (1 ml) was was refluxed for 20 h in an oil bath at 140 °C. The acetic anhydride was evaporated and the residue was chromatographed on silica gel, eluting with 1:4 ethyl acetate-petroleum ether. Yield, 58 mg (43 %) of compound **6** and 61 mg (52 %) of recovered **1a**.

Data for **6**: Mp 125-127 °C. $[\alpha]^{25}_D$ (0.03, Cl_3CH) = -5.7. IR (KBr) ν 1745.2 and 1707.8 (4 CO) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 7.53 (s, 1H, H_α); 7.32 (d, 2H, J = 8.9 Hz, H-2',6'); 6.89 (d, 2H, J = 8.8 Hz, H-3',5'); 5.38 (q, 1H, J = 7.3 Hz, H-3); 3.82 (s, 3H, OCH_3); 2.61 (s, 3H, N_4-CO-C$\underline{H}_3$); 2.57 (s, 3H, N_1-CO-C$\underline{H}_3$); 1.53 (d, 3H, J = 7.3 Hz, C_3-C$\underline{H}_3$) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 171.45 (N_4-$\underline{C}$O-CH_3); 169.64 (N_1-$\underline{C}$O-CH_3); 167.72 (C_2); 164.08 (C_5); 161.38 ($C_{4'}$); 135.04 (C_α); 131.27 ($C_{2',6'}$); 125.43 ($C_{1'}$)*; 121.59 ($C_{6'}$)*; 114.57 ($C_{3',5'}$); 55.41 (O$\underline{C}H_3$); 53.78 (C_3); 27.15 and 26.46 (2 CO-$\underline{C}H_3$); 17.74 (C_3-$\underline{C}H_3$) ppm. Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.70; H, 5.46; N, 8.28.

3.5. (3S,6Z)-6-Arylmethylene-3-alkyl-2,5-piperazinediones (7).

A solution of the suitable compound **1** (0.71 mmol) in dimethylformamide (2 ml) was cooled to 0 °C and treated with 80 % hydrazine hydrate (81 µl, 1.33 mmol), under an argon atmosphere. The reaction mixture was stirred at room temperature for 3 h and was then poured on ice. The precipitated white solid was filtered and dried *in vacuo* in the presence of phosphorous pentoxide. Yield, 161 mg (92 %) of compound **7a**; 153 mg (78 %) of compound **7b**.

Data for **7a**. Mp 251-253 °C. $[\alpha]^{25}_D$ (0.22, DMSO) = +21.3. IR (KBr) ν 3197.2 (NH); 3055.6 (NH); 1672.9 (2 CO) cm^{-1}. ^{1}H-NMR (d_6-DMSO, 250 MHz) δ 9.81 (br s, 1H, H-1); 8.37 (br s,1H, H-4); 7.46 (d, 2H, J = 8.8 Hz, H-2', 6'); 6.96 (d, 2H, J = 7.5 Hz, H-3',5'); 6.64 (s, 1H, Ha); 4.11 (q, 1H, J = 7.5 Hz, H-3); 3.77 (s, 3H, OCH_3); 1.32 (d, 3H, J = 6.7 Hz, C_3-CH_3) ppm. ^{13}C-NMR (d_6-DMSO, 63 MHz) δ 167.59 (C_5); 160.66 (C_2); 158.92 ($C_{4'}$); 130.77 ($C_{2',6'}$); 125.73 ($C_{1'}$); 125.26 (C_6); 114.25 (C_α); 114.05 ($C_{3',5'}$); 55.14 (OCH_3); 50.18 (C_3); 19.12 (C_3-CH_3) ppm. Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.21; H, 5.68; N, 11.15.

Data for **7b**. Mp 218-220 °C. $[\alpha]^{25}_D$ (0.50, DMSO) = -60.2. IR (KBr) ν 3225.8 (NH); 2967.1 (NH); 1706.2 (2 CO); 1209.9 (OCH_3) cm^{-1}. ^{1}H-NMR (d_6-DMSO, 250 MHz) δ 9.93 (br s, 1H, H-1); 8.48 (br s, 1H, H-4); 7.46 (d, 2H, J = 8.6 Hz, H-2', 6'); 6.90 (d, 2H, J = 8.7 Hz, H-3',5'); 6.62 (s, 1H, H_α); 3.82 (s, 3H, OCH_3); 3.80 (m, overlapped with the methoxyl signal, 1H, H-3); 2.09 (m, 1H, $CH(CH_3)_2$); 0.97 and 0.93 (d, 3H, J = 6.9 Hz, and d, 3H, J = 6.7 Hz, $CH(CH_3)_2$) ppm. ^{13}C-NMR (d_6-DMSO, 63 MHz) δ 166.27 (C_2); 160.75 (C_5); 158.87 ($C_{4'}$); 130.63 ($C_{2',6'}$); 125.73 ($C_{1'}$); 125.05 (C_6); 114.05 ($C_{3',5'}$); 60.48 (C_3); 55.11 (OCH_3); 33.34 ($CH(CH_3)_2$); 18.18 and 16.95 ($CH(CH_3)_2$) ppm. Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 63.88; H, 6.53; N, 10.10.

3.6. (3S,6Z)-3-Methyl-6-(p-methoxybenzylidene)-5-thioxopiperazin-2-one (8).

To a stirred suspension of compound **7a** (150 mg, 0.609 mmol) in dry tetrahydrofuran (15 ml) was added a solution of Lawesson's reagent (122 mg, 0.304 mmol) in the same solvent (15 ml), under an argon atmosphere. The suspension was stirred at room temperature for 2 h and evaporated to dryness. The residue was purified by silica gel column chromatography, eluting with 1:3 ethyl acetate-petroleum ether. Yield, 62 mg (40 %) of compound **8**, as an oil. IR (KBr) ν 3422.9 (NH); 3154.9 (NH); 1678.0 (CO); 1256.5 (OCH_3) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 8.39 (s, 1H, H-4); 7.91 (s, 1H, H-1); 7.57 (s, 1H, H_α); 7.38 (d, 2H, J = 9 Hz, H-2',6'); 6.95 (d, 2H, J = 9.0 Hz, H-3'-5'); 4.25 (q, 1H, J = 9 Hz, H-3); 3.83 (s, 3H, OCH_3); 1.61 (d, 3H, J = 7.6 Hz, C_3-CH_3) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 187.02 (C_5); 165.73 (C_2); 160.36 ($C_{4'}$); 130.52 ($C_{2',6'}$); 128.82 (C_6); 125.53 ($C_{1'}$); 124.03 (C_α); 115.05 ($C_{3',5'}$); 55.53 (OCH_3); 53.66 (C_3); 19.08 (C_3-CH_3) ppm. Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.54; H, 5.34; N, 10.68. Found: C, 59.46; H, 5.69; N, 10.43.

3.7. (6S,3Z)-1-Acetyl-6-methyl-3-(p-methoxybenzylidene)-5-thioxopiperazin-2-one (9).

To a stirred solution of compound **1a** (236 mg, 0.819 mmol) in dry tetrahydrofuran (20 ml) was added a solution of Lawesson's reagent (165 mg, 0.410 mmol) in the same solvent (20 ml), under an argon atmosphere. The solution was stirred at room temperature for 2 h and evaporated to dryness. The residue was purified by silica gel column chromatography, eluting with 5:1 petroleum ether-ethyl acetate. Yield, 61 mg (26 %) of recovered **1a** and 115 mg (46 %) of compound **9**, as yellow crystals. Mp 106-108 °C. $[\alpha]^{25}_D$ (0.38, Cl_3CH) = -6.75. IR (KBr) ν 3261.8 (NH); 1703.4 (CO); 1242.6 (OCH_3) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 9.35 (s, 1H, H-4); 7.40 (d, 2H, J = 8.7 Hz, H-2',6'); 7.21 (s, 1H, H_α); 6.99 (d, 2H, J = 8.8 Hz, H-3',5'); 5.62 (q, 1H, J = 7.0 Hz, H-6); 3.85 (s, 3H, OCH_3); 2.56 (s, 3H, CO-CH_3); 1.59 (d, 3H, J = 7.0 Hz, C_6-CH_3) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 195.83 (CS); 171.638 (CO); 161.64 (C_2). 160.59 (C_4); 131.10 ($C_{2',6'}$); 124.62 and 124.48 ($C_{1',3}$); 121.73 (C_α); 115.37 ($C_{3',5'}$); 59.23 (C_6); 55.62 (OCH_3); 27.04 (CO-CH_3); 21.66 (C_6-CH_3) ppm. Anal. Calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.21. Found: C, 58.93; H, 5.51; N, 8.98.

*3.8. (6S,3Z)-6-Methyl-3-(p-methoxybenzylidene)-5-thioxopiperazin-2-one (**10**).*

A solution of compound **9** (60 mg, 0.197 mmol) in dimethylformamide (5 ml) was cooled to 0 °C and treated with 80 % hydrazine hydrate (22 µl, 0.36 mmol), under an argon atmosphere. The reaction mixture was stirred at room temperature for 3 h and was then poured on ice. The precipitated white solid was filtered and dried *in vacuo* in the presence of phosphorous pentoxide. Yield, 50 mg (98 %) of compound **10**. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 9.11 (s, 1H, H-4); 7.28 (s, 1H, H_α); 7.21 (d, 2H, J = 9.0 Hz, H-2',6'); 6.85 (d, 2H, J = 9.0 Hz, H-3',5'); 5.91 (s, 1H, H-1); 3.96 (q, 1H, J = 9.3 Hz, H-6); 3.79 (s, 3H, $OC\underline{H}_3$); 2.02 (d, 3H, J = 5.6 Hz, C_6-$C\underline{H}_3$) ppm. Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.54; H, 5.34; N, 10.68. Found: C, 59.52; H, 5.36; N, 10.89.

*3.9. (3S)-5-Ethoxy-3-methyl-6-(p-methoxybenzylidene)piperazin-2-one (**11**) and (3S)-2,5-Diethoxy-3-methyl-6-(p-methoxybenzylidene)piperazin-2-one (**12**).*

To a stirred suspension of compound **7a** (54 mg, 0.219 mmol) and anhydrous sodium carbonate (139 mg, 1.315 mmol) in dry dichloromethane (3 ml) was added triethyloxonium tetrafluoroborate (Meerwein's salt) (50 mg, 0.263 mmol), under an argon atmosphere. The suspension was stirred at room temperature for 24 h, poured on ice and extracted with dichloromethane (3 x 10 ml). The combined extracts were dried (sodium sulphate) and evaporated, yielding 39 mg (65 %) of compound **11**, as yellow crystals.

Starting from 142 mg (0.577 mmol) of compound **7a**, 366 mg (3.457 mmol) of anhydrous sodium carbonate and 219 mg (1.154 mmol) of triethyloxonium tetrafluoroborate in 8 ml of dichloromethane, the same procedure described above followed by silica gel column chromatography afforded 64 mg (41 %) of compound **11** and 17 mg (10 %) of compound **12**.

Data for **11**: Mp 82-84 °C. $[\alpha]^{25}_D$ (0.92, Cl_3CH) = -17.28. IR (KBr) ν 3250.0 (NH); 1682.4 (CO) and 1248.9 (OCH_3) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 7.70 (br s, 1H, H-1); 7.24 (d, 2H, J = 8.5 Hz, H-3',5'); 6.90 (d, 2H, J = 8.7 Hz, H-2',6'); 6.43 (s, 1H, H_α); 5.35 (q, 1H, J = 8.7 Hz, H-3); 4.20 (m, 2H, $OC\underline{H}_2CH_3$); 3.80 (s, 3H, $OC\underline{H}_3$); 1.50 (d, 3H, J = 8.3 Hz, C_3-$C\underline{H}_3$); 1.34 (t, 3H, J = 7.0 Hz, $OCH_2C\underline{H}_3$) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 170.50 (C_5); 159.32 (C_2); 152.85 (C_4); 129.64 ($C_{2',6'}$); 125.43 ($C_{1'}$); 122.70 (C_6); 144.71 ($C_{3',5'}$); 109.86 (C_α); 62.05 ($O\underline{C}H_2CH_3$); 55.87 (OCH_3); 55.32 (C_3); 21.53 (C_3-$\underline{C}H_3$); 14.22 ($OCH_2\underline{C}H_3$) ppm. Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.20. Found: C, 66.06; H, 7.00; N, 9.91.

Data for **12**: ^{1}H-NMR (Cl_3CH, 250 MHz) δ 7.96 (d, 2H, J = 8.9 Hz, H-2',6'); 6.88 (d, 2H, J = 8.9 Hz, H-3',5'); 6.66 (s, 1H, H_α); 4.40-4.15 (m, 5H, 2 $C\underline{H}_2CH_3$ and H-3); 3.83 (s, 3H, OCH_3); 1.45-1.25 (m, 9H, 3 CH_3) ppm.

*3.10. (4S,1Z)-4-Methyl-1-(p-methoxybenzylidene)-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione (**2a**).*

A mixture of compound **11** (91 mg, 0.332 mmol) and anthranilic acid (91 mg, 0.664 mmol) was heated for 2 h at 120 °C, under an argon stream. Silica gel column chromatography, eluting with 9:1 petroleum ether-ethyl acetate afforded 17 mg (15 %) of compound **2a** and 6 mg (14 %) of diketopiperazine **7a**.

Data for **2a**: Mp 149-151 °C. $[\alpha]^{25}_D$ (0.180, Cl_3CH) = -17.20. IR (KBr) ν 3211.4 (NH); 1672.2 (C=O); 1602.3 (CN); 1255.5 (OCH_3) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 8.29 (d, 1H, J = 8.2 Hz, H-7); 8.02 (s, 1H, H-2); 7.83 and 7.73 (m, 2H, H-9,10); 7.53 and 7.49 (m, 1H, H-8); 7.45 (d, 2H, J = 8.6 Hz, H-2',6'); 7.26 (s, 1H, H_α); 6.98 (d, 2H, J = 8.7 Hz, H-3',5'); 5.59 (q, 1H, J = 6.9 Hz, H-4); 3.85 (s, 3H, $OC\underline{H}_3$); 1.68 (d, 3H, J = 6.7 Hz, C_4-$C\underline{H}_3$) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 166.71 (C_6); 160.44 (C_3)*; 160.03 ($C_{4'}$)*; 147.39 (C_{11a}); 144.37 (C_{10a}); 134.94 (C_9); 130.36 ($C_{2',6'}$); 127.63, 127.22 and 126.99 ($C_{7,8,10}$); 125.59 ($C_{1'}$)**; 124.53 (C_6)**; 120.30 (C_{6a}); 116.75 (C_α); 114.92 ($C_{3',5'}$); 55.49 (OCH_3); 51.81 (C_4); 19.21 (C_4-$\underline{C}H_3$) ppm. Anal. Calcd. for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 68.71; H, 5.19; N, 11.89.

3.11.(4S,1Z)-3-Ethoxy-4-Methyl-1-(p-methoxybenzylidene)-1,4-dihydropyrazino[2,1-b]-quinazolin-6-one (13).

A mixture of compound **12** (100 mg, 0.331 mmol) and anthranilic acid (50 mg, 0.364 mmol) was heated for 2 h at 140 °C, under an argon stream. Silica gel column chromatography, eluting with 2:1 petroleum ether-ethyl acetate afforded 17 mg (13 %) of compound **13**. IR (KBr) ν 1672.7 (C=O), 1249.5 (C-O) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 8.26 (d, 1H, *J* = 7.9 Hz, H-7); 7.97 and 7.94 (m, 2H, H-9,10); 7.55 (s,1H, H_α); 7.48 and 7.35 (m, 3H, H-8, 2', 6'); 6.93 (d, 2H, *J* = 8.9 Hz, H-3',5'); 5.46 (q, 1H, *J* = 6.8 Hz, H-4); 4.46 (q, 2H, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$); 3.85 (s, 3H, OCH_3); 1.52 (d, 3H, *J* = 6.8 Hz, C_4-CH_3); 1.44 (t, 3H, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$) ppm.

3.12. Acylations with o-azidobenzoyl chloride.

To solution of anthranilic acid (10 g, 72.9 mmol) in 6*N* aqueous hydrochloric acid (290 ml) was dropwise added a solution of sodium nitrite (5.33 g, 77.2 mmol) in water (120 ml). The solution thus obtained was stirred at room temperature for 30 min, and added dropwise to a solution of sodium acetate (148.65 g) and sodium azide (5.022 g, 77.2 mmol) in water (291 ml). The reacting mixture was stirred at room temperature for 24 h and a white precipitate was filtered and dried *in vacuo* over phosphorous pentoxide. Yield, 11.807 g (99 %) of *o*-azidobenzoic acid, which was identified by spectral means and used without further purification. Spectral data for this compound were: IR (KBr) ν 3200-2275 (OH); 2105.6 (N_3); 1693.8 (C=O); 1268.0 (C-O) cm^{-1}. ^{1}H-RMN (Cl_3CD, 250 MHz) δ 8.18 (d, 1H, *J* = 8.1 Hz, H-6); 7.61 (t, 1H, *J* = 8.0 Hz, H-4); 7.20 (m, 2H, H-3,5); ^{13}C-NMR (Cl_3CD, 63 MHz) δ 168.32 (CO); 140.21 (C-2); 134.53 (C-6)*; 133.46 (C-4)*; 125.11 (C-5); 120.84 (C-1); 119.58 (C-3) ppm.

o-Azidobenzoyl chloride was prepared by heating for 3 h, under an argon atmosphere, a solution of *o*-azidobenzoic acid (1.3 eq.) in thionyl chloride (0.5 ml per 100 mg of *o*-azidobenzoic acid). The excess thionyl chloride was evaporated under reduced pressure. Dry benzene (2 x 1 ml) was added to the residue and evaporated. The crude *o*-azidobenzoyl chloride [IR (NaCl) ν 2128.8 (N_3); 1780.6 (CO) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 8.12 (d, 1H, *J* = 8.1 Hz, H-6); 7.68 (t, 1H, *J* = 8.2 Hz, H-4); 7.28 (m, 2H, H-3,5) ppm] was immediately used for the acylation step, which was performed as follows. To a cooled (-78 °C) solution of compound **7a** or **7b** (1 eq.) in dry tetrahydrofuran (5-7 ml) was added dropwise a 0.5 *M* solution of potassium bis(hexamethyldisilazide) in toluene (1.5 eq.), under an argon atmosphere. The solution was stirred at -78 °C for 15 min and was then treated with a solution of the crude *o*-azidobenzoyl chloride in THF (5-7 ml) and was left to warm to room temperature over 24 h (**7a**) or 12 h (**7b**), while protected from light. The solvent was evaporated and the residue was chromatographed on silica gel, eluting with 13:1 petroleum ether-ethyl acetate. Yields were: starting from **7a**, 60 % of compound **14a**; starting from **7b**, 68 % of recovered **7b** and 23 % of compound **14b** (75 %, based on unrecovered starting material). All attempts to carry to completion the reaction starting from **7a** led to variable amounts of the diacylated compound **15**.

Data for **14a**: Mp 135-137 °C. $[\alpha]^{25}_D$ (0.09, Cl_3CH) = -14.4. IR (KBr) ν 3237.6 (NH); 2118.9 (N_3); 1679.4 (3 CO) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 7.95 (s, 1H, H-4); 7.42 and 7.14 (m, 4H, H-3''-6''); 7.33 (d, 2H, *J* = 8.6 Hz, H-2',6'); 6.97 (s, 1H, H_α); 6.89 (d, 2H, *J* = 8.8 Hz, H-3',5'); 5.06 (q, 1H, *J* = 9.2 Hz, H-6); 3.77 (s, 3H, OCH_3); 1.6 (d, 3H, *J* = 7.1 Hz, C_6-$C\underline{H}_3$) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 168.39 (N^1-$\underline{C}O$); 167.26 (C_2); 161.00 ($C_{4'}$); 160.72 (C_5); 136.65 ($C_{2''}$); 131.94 ($C_{5''}$); 130.86 ($C_{2',6'}$); 129.33 ($C_{3''}$); 128.32 ($C_{1''}$); 125.17 ($C_{4''}$); 124.90 (C_6); 123.41 ($C_{1'}$); 121.03 (C_α); 118.41 ($C_{6''}$); 115.07 ($C_{3',5'}$); 55.56 (OCH_3); 54.018 (C_3); 19.81 (C_3-$\underline{C}H_3$) ppm. Anal. Calcd. for $C_{20}H_{17}N_5O_4$: C, 61.38; H, 4.38; N, 17.89. Found: C, 61.14; H, 4.67; N, 17.81.

Data for **14b**: $[\alpha]^{25}_D$ (0.060, Cl_3CH) = -63.3. IR (KBr) ν 3300 (NH); 2129.5 (N_3); 1690.4 (3 CO) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 7.94 (s, 1H, NH); 7.32 (m, 4H, H-3''-6''); 7.33 (d, 2H, *J* = 14 Hz, H-2',6'); 6.99 (s, 1H, H_α); 6.94 (d, 2H, *J* = 8.8 Hz, H-3',5'); 4.95 (d, 1H, *J* = 7.3 Hz, H-6); 3.82 (s, 3H, OCH_3); 2.26 (m,1H, $C\underline{H}(CH_3)_2$); 1.17 and 1.13 (d, 3H, *J* = 5.4 Hz, and d, 3H, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$) ppm. ^{13}C-NMR (Cl_3CD, 63 MHz) δ 168.26 ($C_{\alpha'}$); 165.84 (C_2); 161.80 ($C_{4'}$); 160.68 (C_5); 136.00 ($C_{2''}$); 131.66 ($C_{5''}$); 130.87

($C_{2',6'}$); 129.00 ($C_{1''}$); 128.36 ($C_{3''}$); 125.20 ($C_{4''}$); 124.98 (C_6); 124.07 ($C_{1'}$); 120.64 (C_α); 118.30 ($C_{6''}$); 115.06 ($C_{3',5'}$); 62.64 (C_3); 55.55 (OCH_3); 33.81 ($\underline{C}H(CH_3)_2$); 19.47 and 18.79 ($CH(\underline{C}H_3)_2$) ppm. Anal. Calcd. for $C_{22}H_{21}N_5O_4$: C, 63.00; H, 5.03; N, 16.70. Found: C, 62.80; H, 4.93; N, 16.57.

Data for **15**: IR (KBr) ν 2130.6 (2 N_3); 1692.6 (4 CO) cm^{-1}. ^{1}H-RMN (Cl_3CD, 250 MHz) δ 7.34 (m, 11H, H-α,2',6',3"-6",3'"-6'"); 6.83 (d, 2H, J = 11.2 Hz, H-3',5'); 5.13 (d, 1H, J = 10.0 Hz, H-3); 3.80 (s, 3H, OCH_3); 2.23 (m, 1H, $C\underline{H}(CH_3)_2$); 1.15 and 1.10 (d, 3H, J = 10.2 Hz and d, 3H, J = 6.7 Hz $CH(C\underline{H}_3)_2$) ppm. ^{13}C-RMN (Cl_3CD, 63 MHz) δ 167.72 and 167.40 ($C_{\alpha',\alpha''}$); 164.37 (C_2); 161.62 ($C_{5,4'}$); 137.11 ($C_{2'',2'''}$); 132.28 and 132.22 ($C_{2',6'}$); 131.77 ($C_{5'',5'''}$); 129.97 ($C_{1'',1'''}$); 129.32 ($C_{3'',3'''}$); 125.16 and 125.05 ($C_{4'',4''',6}$); 122.00 ($C_{1'}$); 119.00 (C_α); 118.28 and 118.28 ($C_{6'',6'''}$); 114.52 ($C_{3',5'}$); 63.83 (C_3); 55.54 (OCH_3); 32.26 ($\underline{C}H(CH_3)_2$); 19.64 ($CH(\underline{C}H_3)_2$) ppm. Anal. Calcd. for $C_{29}H_{24}N_8O_5$: C, 61.70; H, 4.25; N, 19.85. Found: C, 61.31; H, 4.33; N, 19.42.

*3.13. Aza-Wittig cyclizations of compounds **14**.*

A solution of the suitable compound **14** (0.125 mmol) and tributylphosphine (0.126 mmol) in dry toluene (5 ml) was stirred at room temperature for 3 h under an argon atmosphere. The solution was evaporated under reduced pressure and the residue was chromatographed on silica gel, eluting with 2:1 petroleum ether-dichloromethane, yielding 34 mg (81 %) of compound **2a** or 42 mg (88 %) of compound **2b**.

Data for **2b**: $[\alpha]^{25}_D$ (0.450, Cl_3CH) = -62.63. IR (KBr) ν 3353.4 (NH); 1682.2 (CO); 1607.4 (CN); 1253.6 (OCH_3) cm^{-1}. ^{1}H-NMR (Cl_3CD, 250 MHz) δ 8.27 (d, 1H, J = 7.1 Hz, H-7); 7.96 (s, 1H, H-2); 7.78 and 7.71 (m, 2H, H-9,10); 7.53 and 7.40 (m, 3H, H-8, 2', 6'); 7.24 (s, 1H, H_α); 6.97 (d, 2H, J = 8.7 Hz, H-3',5'); 5.45 (d, 1H, J = 5.5 Hz, H-4); 3.81 (s, 3H, $OC\underline{H}_3$); 2.33 (m, 1H, $C\underline{H}(CH_3)_2$); 1.15 and 1.04 (d, 3H, J = 6.9 Hz, and d, 3H, J = 6.9 Hz, $CH(C\underline{H}_3)_2$) ppm. Anal. Calcd. for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.02; H, 5.52; N, 11.32.

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5. References

[1] Wong, S.-M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum, A. M.; Cooper, R., *J. Antibiotics*, **1993**, *46*, 545.

[2] Penn, J.; Mantle, P. G.; Bilton, J. N.; Sheppard, R. N., *J. Chem. Soc. Perkin Trans. 1*, **1992**, 1495.

[3] Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Inone, M.; Ohishi, H.; Shingu, T., *Tetrahedron Lett.*, **1992**, *33*, 1621.

[4] Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A., *J. Chem. Soc. Perkin Trans. 1*, **1995**, 2345.

[5] Isolation: Karwowski, J. P.; Jackson, M.; Rasmussen, R. D.; Humphrey, P. E.; Poddig, J. B.; Kohl, W. L.; Scherr, M. H.; Kadam, S.; McAlpine, J. B., *J. Antibiotics*, **1993**, *46*, 374.

[6] Structure: Hochlowski, J. E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B., *J. Antibiotics*, **1993**, *46*, 380.

[7] Liesch, J. M.; Hensens, O. D.; Springer, J. P.; Chang, R. S. L.; Lotti, V. J., *J. Antibiotics*, **1985**, *58*, 1638.

[8] Isolation and structure: Mehta, D. R.; Naravane, J. S.; Desai, R. M., *J. Org. Chem.*, **1963**, *28*, 445.

[9] Absolute configuration: Joshi, B. S.; Newton, M. C.; Lee, D. W.; Barber, A. D.; Pelletier, S. W., *Tetrahedron: Asymmetry*, **1996**, *7*, 25.

[10] Roninson, I. B. (ed.), Molecular and Cellular Biology of Multidrug Resistance in Tumor Cells. Plenum Press, 1991.

[11] Kane, S. E., *Advances in Drug Research*, **1996**, *28*, 181.

[12] Bryans, J. S.; Latham, C. J.; Brocchini, S. J., *British Patent Application* 9402809.0 (14 February 1994).
[13] Brocchini, S. J.; Bryans, J. S.; Latham, C. J.; Folkes, A. J., *British Patent Application* 9402805.7 (14 February 1994)
[14] Gallina, C.; Liberatori, A., *Tetrahedron*, **1973**, 1135.
[15] Gallina, C.; Liberatori, A., *Tetrahedron*, **1974**, 667.
[16] Katritzky, A. R.; Fan, W. Q.; Szajda, M.; Li, Q. L.; Caster, K. C., *J. Heterocycl. Chem.*, **1988**, *25*, 591.
[17] Villemin, D.; Alloum, A. B., *Synth. Commun.*, **1990**, *20*, 3325.
[18] Review on the use of inorganic fluorides as bases: Radhakrishna, A. S.; Prasad, K. R. K.; Suri, S. K.; Sivaprakash, K.; Singh, B. B., *Synth. Commun.*, **1991**, *21*, 379.
[19] Kametani, T.; Higa, T.; Van Loc, C.; Ihara, M.; Koizum, M.; Fukumoto, K., *J. Am. Chem. Soc.*, **1976**, *98*, 6186.
[20] Kametani, T.; Higa, T.; Van Loc, C.; Ihara, M.; Fukumoto, K., *J. Am. Chem. Soc.*, **1977**, *99*, 2306.
[21] For the structure of this intermediate, see: Garin, J.; Merino, P.; Orduña, J.; Tejero, T.; Uriel, S., *Tetrahedron Lett.*, **1991**, *32*, 3263.
[22] Bock, M. G.; DiPardo, M.; Pitzenbetrger, S. M.; Homnick, C. F.; Sproger, J. P.; Freidinger, R. M., *J. Org. Chem.*, **1987**, *52*, 1646.
[23] Scheibye, S.; Pedersen, B. S.; Lawesson, S. O., *Bull. Soc. Chim. Belg.*, **1978**, *87*, 223.
[24] Cava, M. P.; Levinson, M. I., *Tetrahedron*, **1985**, *41*, 5061.
[25] Fukuyama, T.; Frank, R. K.; Laird, A. A:, *Tetrahedron Lett.*, **1985**, *26*, 2955.
[26] Rajappa, S.; Advani, B. G., *Tetrahedron*, **1973**, *29*, 1299.
[27] Rajappa, S.; Advani, B. G., *J. Chem. Soc. Perkin Trans. I*, **1974**, 2122.
[28] Sánchez, J. D.; Avendaño, C.; Ramos, M. T., *Tetrahedron*, **1998**, *54*, 969.
[29] Takeuchi, H.; Hagiwara, S.; Eguchi, S., *Tetrahedron*, **1989**, *45*, 6373.