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Nucleophilic additions to (4*S*)-1-alkylidene-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones

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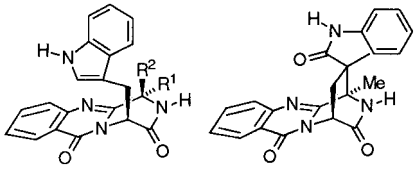
Abstract—Investigation of the title compounds as didehydro amino acid templates showed their lack of reactivity against amines or Grignard reagents under copper(I) catalysis, but efficient additions to the exocyclic double bond took place with mercaptides or stabilized carbanions. Regio- and diastereoselective addition of organometallic reagents occurred at the C(3)-position and, in 1-methylene derivatives, these reactions were followed by a rearrangement of the intermediate oxy-anion to give pyrido[2,1-*b*]quinazolines.

1. Introduction

The pyrazino[2,1-*b*]quinazoline-3,6-dione system, which can be considered as a constrained peptidomimetic, is present in several natural products that in many cases exhibit interesting biological activities. Among them glyantrypine,[1] the fumiquinazolines,[2] the fiscalins,[3] alantrypinone,[4] spiroquinazoline,[5] and *N*-acetylardeemin[6] may be mentioned. Other natural products like the asperlicins,[7] vasicinone,[8] and the luotonins,[9] among others, contain related heteroareno[2,1-*b*]quinazoline substructures.



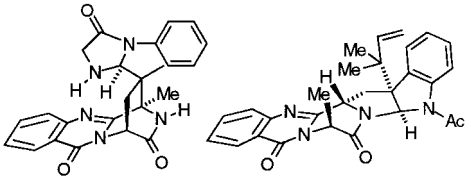
Glyantrypine; R^1=R^2=H (Conf. C-4 unknown)

(+)-Alantrypinone

Fumiquinazoline F; R^1= Me, R^2= H

Fumiquinazoline G; R^1= H, R^2= Me

Fiscalin B; R^1= ^{i}Pr, R^2= H



Spiroquinazoline

N-Acetylardeemin

In the context of the synthesis of analogues of the fungal metabolite *N*-acetylardeemin, a reversor of the the Pgp-mediated multi drug resistance in tumors,[10] we have shown that anions derived from 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (**1**), similarly to those derived from piperazinediones[11] and their bis-lactim ether derivatives,[12,13] can be alkylated[14] or acylated[15] regio- and diastereoselectively at C(1). Furthermore, the readily accessible 1-tosyloxyderivatives of **1** are good substrates for intra or intermolecular nucleophilic substitution reactions.[16] We have also shown that this system can be manipulated by reduction of the C(11a)=N(11) bond.[17]

This chemistry has established that the 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione system can be used as a nucleophilic or electrophilic glycine template and, additionally, that this system retains most of the activity of *N*-acetylardeemin.[18]

The title compounds **2** resemble to *N*-acylderivatives of didehydro amino acids (DDAA) which, by reacting with nucleophiles similarly to acrylates or acrylamides,[19] afford uncommon amino acids.[20] Here, we study the reactivity of the title compounds **2** against nucleophiles as possible DDAA templates.

2. Methods and results

Compounds **2a**–**d** were obtained from **1** through Mannich reactions followed by Hofmann eliminations of the 1-dimethylaminomethyl derivatives (1,4-*cis*-isomers).[21] Vilsmeier reactions on **1** gave enamines **2e**–**g** (*Z*-isomers), and compounds **2h** and **2i** were obtained as a 2:1 mixture of *Z*/*E* isomers by aldol condensations of the corresponding compound **1** with an aromatic aldehyde in base. This last

Keywords: piperazinones; addition reactions; amino acids and derivatives; carbanions; rearrangements.

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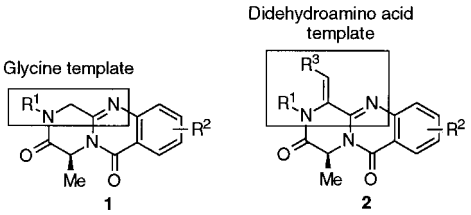
reaction is remarkable, because when it is performed with piperazine-2,5-diones generally requires their activation by *N*-acylation,[22] but it occurs with partial epimerization of the C-4 stereocenter.



Compd.	R^1	R^2	R^3
2a	Me	H	H
2b	Bn	H	H
2c	Me	8,9(OMe)$_2$	H
2d	Bn	8,9(OMe)$_2$	H
2e	Me	H	Me_2N
2f	Bn	8,9(OMe)$_2$	Me_2N
2g	4-MeOC$_6$H$_4$CH$_2$	H	Me_2N
2h	Me	H	Ph
2i	Me	H	4-ClC$_6$H$_4$

It is known that *C*-nucleophiles, such as copper(I)-catalyzed Grignard reagents give conjugate addition with DDAA derivatives,[23,24] while with lithium diorganocuprates this reaction is minoritary.[25] Treatment of 1-methylene compound **2a** with different combinations of phenyl magnesium bromide and CuI (with or without cosolvents or additives) following the literature procedures,[26] failed or gave complex reaction mixtures.

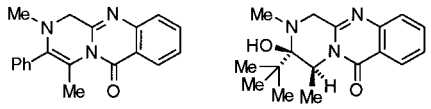
Table 1. Compounds obtained by reaction of **2** with organometallic reagents

Compd	R^1	R^2	R^3	R^4	Yield (%)
3	Me	H	Me_2N	H	95
4	Me	H	Me_2N	$(CH_2)_2CH_3$	68
5	Me	H	4ClC$_4$H$_6$	–	37
6	Me	H	–	H	20
7a	Me	H	–	–	82
7c	Me	8,9(OMe)$_2$	–	–	45
7d	Bn	8,9(OMe)$_2$	–	–	52
8a	Me	H	–	–	Traces
8c	Me	8,9(OMe)$_2$	–	–	Traces
9a	Me	H	–	–	Traces
9d	Bn	8,9(OMe)$_2$	–	–	11

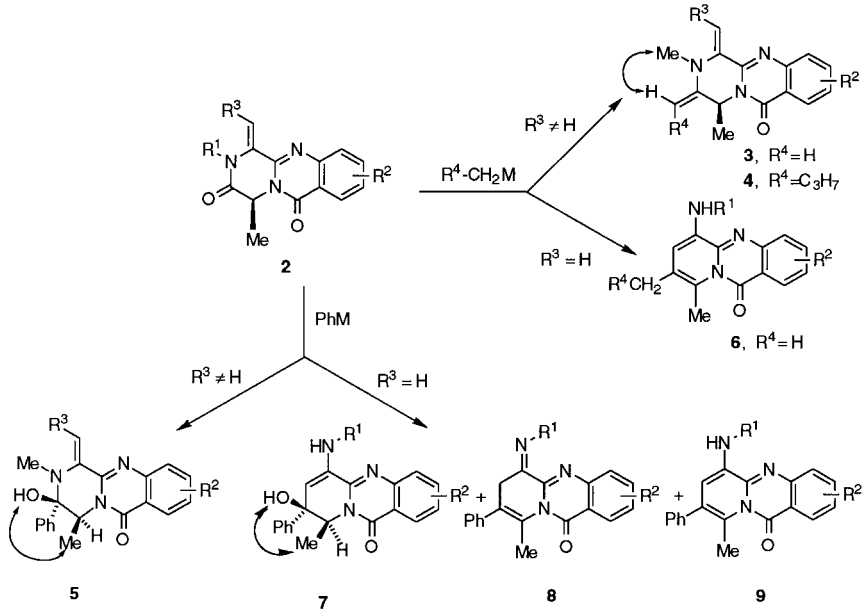
The reactivity of the dimethylaminomethylene compound **2e** against organometallics also differed from that reported for α-dimethylaminomethylene ketones. Thus, while these compounds react with organolithium reagents at the conjugate carbon atom to give alkyl substituted conjugated enones,[27] addition of MeLi or *n*-BuLi to **2e** occurred at the C(3)═O group. The in situ exocyclic dehydration of these aducts gave compounds **3** and **4**, whose unstability in solution precluded the measurement of their enantiomeric purity. These reactions failed with **2f** and **2g** probably for steric reasons.

Compound *Z*-**2i** gave with PhM the adduct at C(3)═O **5**, but 1-methylene derivatives (**2a**, **2c** and **2d**) gave complex reaction mixtures from which compounds **7**–**9** were isolated. Their structure revealed an unexpected heterocyclic rearrangement of the pirazine to a pyridine ring, which was also observed in the treatment of **2a** with MeMgBr to give compound **6** (Scheme 1 and Table 1).

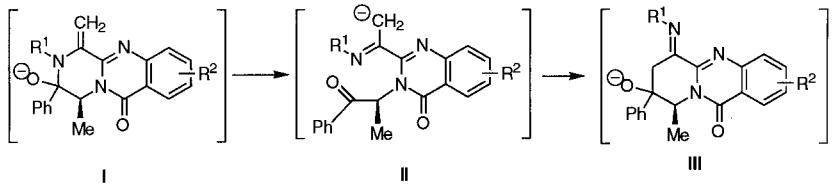
This rearrangement was exclusive of methylene derivatives, since reactions of **1** with PhMgBr or *t*-BuLi gave compounds **10** and **11**, respectively.



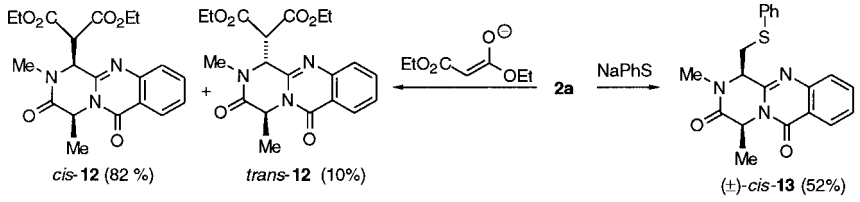
The above results show that the nucleophilic attack of organometallics to compounds **1** and **2** ($R^3 \neq H$) takes place diastereselectively at the *Si* face of the C(3) carbonyl group and that, in absence of rearrangement, the exocyclic



Scheme 1.



Scheme 2.



Scheme 3.

dehydration of the hydroxy derivatives is preferent over the endocyclic.

Structure elucidation of compound **7a** required several NMR experiments, specially long-range C–H correlations because, although its mass spectrometry and elemental analysis data were in agreement with the molecular formula $C_{20}H_{19}N_3O_2$ which could arise from addition of PhMgBr to the C(3)-carbonyl group of **2a**, the spectroscopic data were not. For instance, the ^{1}H NMR spectrum of **7a** showed two signals at 5.60 and 5.94 ppm exchangeable with D_2O. Long-range correlations between the H-2 proton (a doublet of J=1.2 Hz at δ=4.94 ppm), the C(4) signal at δ=55.5 ppm and the C(11a) signal at δ=145.6 ppm, were especially relevant to determine the connectivity of atoms in the pyridine ring.

The diastereoselective attack to the *Si* face of the carbonyl group was here also confirmed (as in the case of compounds **5** and **11**) by NOE experiments, which showed a *cis*-relationship between the C(4)–Me and the C(3)–OH substituent. Analogues **7c** and **7d** were similarly obtained starting from the corresponding **2**. All compounds **7** were optically active, although the enantiomeric purity could not be determined because of their high unstability in solution.

Formation of compounds **6**–**9**, which is rationalized in Scheme 2, must involve the ring-cleavage of the oxy-anions **I** to the C-anions **II** that, by acting as C-nucleophiles, rearrange to the cyclic oxy-anions **III** to give finally the pyrido[2,1-*b*]quinazoline derivatives. This process has no precedent in the chemical literature, although previous experiences related to addition of sodium borohydride to compounds **1** showed other transannular rearrangement in this system.[17]

Attempts to perform conjugate additions of primary and secondary amines to **2a** either in basic[28] or acid media[29,30] failed, but the sodium enolate of diethyl malonate gave nearly quantitatively compounds **12** (Scheme 3). The relative stereochemistry of the products was established from NOE experiments in the *trans*-isomer, and the enantiomeric purity was confirmed by HPLC through the synthesis of racemic analogs by using hexane/2-propanol (90:10) as a mobile phase in a system equipped with a Chiracel OD column and a UV–Vis detector. Conjugate addition of **2a** with one or two equivalents of sodium phenyl mercaptide gave **13** (yields were better in the first case), as a racemic mixture due to the competence between the nucleophilicity and the basicity of this reagent. The relative stereochemistry of the C(1) and C(4) centers was corroborated by the observed NOEs between Me-4 and CH_2–S-protons.

The reluctance of the title compounds to give conjugate additions at the hexocyclic double bond may be explained by assuming that the unshared N(2) electron pair is for geometric reasons more effectively delocalized into the C(1)=CH_2 bond that into the C(3)=O group. In fact, we have previously observed that the substructure N(2)–C(1)=CH_2 of compounds **2** reacts as a nucleophylic 'enamine', giving dimers in acid media through conjugate additions of this group to the CH_2=C(1)–C(11a)=N^+H(11) portion.[21]

Summarizing the above results, we conclude that 1-alkylidene derivatives **2** cannot be considered as DDAA templates, since they give conjugate additions with a very restricted range of nucleophiles. The rearrangement of the oxy-anions formed in the addition of organometallics at the C(3)=O of 1-methylene compounds to 1-aminopyrido[2,1-*b*]-quinazolines may be exploited in the future.

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. Reactions were monitored by thin layer chromatography, on aluminum plates coated with silica gel or aluminum oxide with fluorescent indicator (Merck 60 F_{254}). Separations by flash chromatography were performed on silica gel (Merck 60, 230–400 mesh) or aluminum oxide (Merck 90, 70–230 mesh). Melting points were measured in open capillary tubes using a Büchi immersion apparatus, or on a Reichert

723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer, with solid compounds compressed into KBr pellets. NMR spectra were obtained at 250 or 300 MHz for ^{1}H and at 63 or 75 MHz for ^{13}C (Servicio de Espectroscopía, Universidad Complutense). When necessary, assignments were aided by DEPT, COSY, CH COLOC and ^{13}C–^{1}H correlation experiments. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense on a Leco 932 microanalyzer. Optical rotations were measured at 25°C on a 1 mL cell in $CHCl_3$ or MeOH at 589 nm, using a Perkin–Elmer 240 polarimeter; concentrations are given in g/100 mL. Mass spectra were recorded on a Hewlett–Packard 5993C (EI, 70 eV) (Servicio de Espectroscopía U.C.M). HPLC analysis were performed using a Constametric 4100 system equipped with a chiral column (Chiracel OD) and UV–Vis detector. Mobile phase: hexane/2-propanol (90:10).

3.1. Mannich reaction: general procedure to obtain compounds 2a–d

To cold (−15°C) magnetically stirred anhydrous trifluoroacetic acid (13 mmol), bis(dimethylamino)methane (2.6 mmol) was added slowly and diluted with 10 mL of dry CH_2Cl_2. The temperature of the resulting solution was kept below −10°C and compounds **1**[21] (2.6 mmol) in 10 mL of dry CH_2Cl_2 were 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 (15 mL) was added and the separated aqueous layer was extracted with CH_2Cl_2, the combined organic layers were washed with water, dried and evaporated. Chromatography of the residue in silica gel provided the corresponding methylene compounds **2**.

3.1.1. (−)-(4*S*)-2,4-Dimethyl-1-methylene-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (2a). It was obtained (EtOAc/Hexane, 1: 1) as a white solid, yield: 75%. (Found: C, 65.75; H, 5.28; N, 16.34. $C_{14}H_{13}N_3O_2$ requires: C, 65.87; H, 5.13; N, 16.46); mp 170°C; $[\alpha]^{25}_D$= −146 (*c* 0.27, $CHCl_3$); ν_{max} (KBr): 1686, 1624 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.17 (dd, 1H, *J*=7.9 and 1.2 Hz), 7.70 (m, 1 H), 7.61 (d, 1H, *J*=7.3 Hz), 7.41 (m, 1H), 6.16 (d, IH, *J*=1.5 Hz), 5.44 (q, 1H, *J*=6.9 Hz), 5.06 (d, 1H, *J*=1.5 Hz,), 3.27 (s, 3H), 1.50 (d, 3H, *J*=6.9 Hz). δ_C ($CDCl_3$, 63 MHz) 165.8, 159.9, 147.4, 144.4, 138.0, 134.8, 127.8, 127.4, 126.8, 120.5, 103.1, 51.6, 31.0, 19.3.

3.1.2. (−)-(4*S*)-2-Benzyl-4-methyl-1-methylene-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (2b). It was obtained (EtOAc/Hexane, 1:2) as a white solid, yield: 69%. (Found: C, 72.69; H, 5.17; N, 12.39. $C_{20}H_{17}N_3O_2$ requires: C, 72.49; H, 5.17; N, 12.68); mp 175–176°C; $[\alpha]^{25}_D$=−54.7 (*c* 0.28, $CHCl_3$); ν_{max} (KBr): 1679, 1614 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.26 (dd, 1H, *J*= 8.0 and 1.1 Hz), 7.72 (m, 1H), 7.67 (d, 1H, *J*=7.6 Hz), 7.48 (m, 1H), 7.32–7.20 (m, 5H), 6.16 (d, 1H, *J*=1.7 Hz), 5.65 (q, 1H, *J*=6.9 Hz), 5.31 (d, 1H, *J*=15.7 Hz), 5.10 (d, 1H, *J*=1.7 Hz), 4.80 (d, 1H, *J*=15.7 Hz), 1.65 (d, 3H, *J*= 6.9 Hz); δ_C ($CDCl_3$, 63 MHz) 166.2, 160.0, 147.5, 144.6, 137.0, 135.7, 134.9, 129.1, 127.9, 127.8, 127.5, 126.9, 126.7, 120.6, 104.6, 51.6, 47.9, 19.4.

3.1.3. (−)-(4*S*)-8,9-Dimethoxy-2,4-dimethyl-1-methylene-2,4.dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (2c). It was obtained (EtOAc/Hexane, 9:1) as a white solid, yield: 40%. (Found: C, 60.76; H, 5.70; N, 13.46. $C_{16}H_{I7}N_3O_4$ requires: C, 60.94; H, 5.43; N, 13.32); mp 220°C; $[\alpha]^{25}_D$=−96 (*c* 0.3, $CHCl_3$); ν_{max} (KBr): 1689, 1662, 1609 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.57 (s, 1H), 7.09 (s, 1H), 6.15 (d, 1H, *J*=1.6 Hz), 5.55 (q, 1H, *J*= 6.9 Hz), 5.07 (d, 1H, *J*=1.6 Hz), 3.99 (s, 3H), 3.98 (s, 3H), 3.31 (s, 3H), 1.55 (d, 3H, *J*=6.9 Hz); δ_c ($CDCl_3$, 63 MHz) 166.0, 159.2, 155.4, 149.7, 143,.8, 143.3, 138.2, 114.1, 108.0, 105.6, 102.2, 56.5, 51.6, 30.9, 19.4.

3.1.4. (−)-(4*S*)-2-Benzyl-8,9-dimethoxy-4-methyl-1-methylene-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (2d). It was obtained (EtOAc/Hexane, 1:2) as a white solid, yield: 67%. (Found: C, 67.22; H, 5.85; N, 10.45. $C_{22}H_{21}N_3O_4$ requires: C, 67.5; H, 5.41; N, 10.74); mp 162°C; $[\alpha]^{25}_D$=−51.4 (*c* 0.25, $CHCl_3$); ν_{max} (KBr): 1690, 1667, 1622, 1616 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.58 (s, 1H), 7.37–7.21 (m, 5H), 7.07 (s, 1H), 6.10 (d, 1H, *J*=1.7 Hz), 5.66 (q, 1H, *J*=6.9 Hz), 5.31 (d, 1H, *J*=15.7 Hz), 5.08 (d, 1H, *J*=1.7 Hz), 4.83 (d, 1H, *J*=15.7 Hz), 3.99 (s, 3H), 3.98 (s, 3H), 1.67 (d, 3H, *J*=6.9 Hz); δ_C ($CDCl_3$, 63 MHz) 166.3, 159.3, 155.4, 149.7, 143.8, 143.4, 137.1, 135.7, 129.1, 127.7, 126.7, 114.1, 108.0, 105.6, 103.6, 56.5, 56.4, 51.6 47.8, 19.5.

3.2. Vilsmeier reaction: general procedure

To a magnetically stirred solution of **1** (0.822 mmol) in 5 mL of dry CH_2Cl_2 at room temperature under argon, was added (chloromethylene)dimethylammonium chloride (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.

3.2.1. (−)-(4*S*,*Z*)-2,4-Dimethyl-1-dimethylaminomethylen-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (2e). It was obtained (EtOAc/benzylamine, 9:1) as a yellow solid; yield: 96%. (Found: C, 64.35; H, 6.01; N, 18.49. $C_{16}H_{18}N_4O_2$ requires: C, 64.41; H, 6.08; N, 18.77); mp 145°C; $[\alpha]^{25}_D$=−348 (*c* 0.2, $CHCl_3$); ν_{max} (KBr): 1687, 1606 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 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), 7.27 (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); δ_C: ($CDCl_3$, 63 MHz) 168.1, 160.7, 149.7, 148.4, 137.4, 134.6, 126.9, 126.4, 125.4, 119.5, 106.5, 52.1, 42.2, 34.3, 15.6.

3.2.2. (−)-(4*S*,*Z*)-2-Benzyl-4-methyl-8,9.dimethoxy-1-dimethylaminomethylen-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]-quinazoline-3,6-dione (2f). It was obtained ($CHCl_3$/Et_2O 3:1) as a yellow solid; yield: 68%. (Found: C, 66.52; H, 6.01; N, 12.75. $C_{24}H_{26}N_4O_4$ requires: C, 66.34; H, 6.03; N, 12.89); mp 118–120°C; $[\alpha]^{25}_D$=−412 (*c* 0.11, $CHCl_3$); ν_{max} (KBr): 1669, 1613 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.49 (s, 1H), 7.17–7.13 (m, 5H), 7.03 (s, 1H), 6.90 (s, 1H), 5.62 (q, 1H, *J*=7.1 Hz), 5.28 (d, 1H, *J*=14.1 Hz), 4.32 (d, 1H, *J*=14.1 Hz), 3.92 (s, 6H), 2.97 (s, 6H), 1.57 (d, 3H, *J*=7.1 Hz); δ_C ($CDCl_3$, 63 MHz) 167.9, 160.0, 155.2,

148.7, 148.2, 144.7, 136.9, 136.4, 128.7, 128.2, 127.8, 112.8, 106.9, 106.1, 105.8, 56.4, 56.3, 52.1, 47.3, 42.5, 15.8.

3.2.3. (−)-(4*S*,*Z*)-2-*p*-Methoxybenzyl-4-methyl-1-dimethylaminomethylen-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (2g). It was obtained (EtOAc/Hexane 2:1) as a yellow solid; yield: 95%. (Found: C, 68.35; H, 5.72; N, 13.78. $C_{23}H_{24}N_4O_3$ requires: C, 68.29; H, 5.98; N, 13.85); mp 45–46°C; $[\alpha]^{25}_D$=−254 (*c* 0.24, $CHCl_3$); ν_{max} (KBr): 1677, 1610 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 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); δ_C ($CDCl_3$, 63 MHz) 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.

3.3. Condensations with aldehydes. General procedure

To a solution of **1** (0.62 mmol) and the corresponding aldehyde (0.92 mmol) in anhydrous DMF (3 mL) was added under argon atmosphere 0.92 mL of 1 M *t*BuOK/*t*BuOH at 0°C. The reaction was kept at room temperature overnight and quenched with a saturated NH_4Cl solution, extracted with ether, and dried over Na_2SO_4. The evaporation of solvents under reduced pressure and purification by column chromatography in silica gel gave the products. The *ee* varied from 0 to 30%.

3.3.1. (*Z*)-1-Benzyliden-2,4-dimethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (*Z*-2h). It was obtained (EtOAc/Hexane 2:3) as a white solid; yield: 43%. (Found: C, 72.65; H, 5.04; N, 12.75. $C_{20}H_{17}N_3O_2$ requires: C, 72.49, H, 5.17, N, 12.68); mp 165–166°C; ν_{max} (KBr): 1682, 1636 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.24 (d, 1H, *J*=7.6 Hz), 7.85–7.68 (m, 2H), 7.48–7.23 (m, 7H), 5.64 (q, 1H, *J*=7.1 Hz), 2.95 (s, 3H), 1.61 (d, 3H, *J*=7.1Hz); δ_C ($CDCl_3$, 63 MHz) 167.9, 159.9, 147.9, 147.7, 134.9, 133.4, 131.3, 129.4, 129.1, 128.8, 127.6, 127.3. 127.0, 122.7, 120.4, 52.1, 35.1, 17.6.

3.3.2. (*E*)-1-Benzyliden-2,4-dimethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (*E*-2h). It was obtained (EtOAc/Hexane 2:3) as a white solid: yield: 25%. (Found: C, 72.72; H, 5.01; N, 12.73. $C_{20}H_{I7}N_3O_2$ requires: C, 72.49, H, 5.17, N, 12.68); mp 156–158°C; ν_{max} (KBr): 1682, 1633 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.25 (dd,1H, *J*=7.9 and 1.3 Hz), 7.64 (m, 1H), 7.46 (m, 1H), 7.38–7.35 (m, 2H), 7.26–7.23 (m, 4H), 6.73 (s, 1H), 5.61 (q, 1H, *J*=7.1 Hz), 3.40 (s, 3H), 1.65 (d, 3H, *J*=7.1 Hz); δ_C ($CDCl_3$, 63 MHz) 166.9, 159.9, 147.0, 145.2, 134.7, 134.1, 131.1, 129.8, 128.3, 128.1, 127.9, 127.8, 126.8, 123.2, 120.8, 51.9, 31.8, 18.1.

3.3.3. (*Z*)-1-*p*-Chlorobenzyliden-2,4-dimethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (*Z*-2i). It was obtained (EtOAc/Hexane 1:2) as a white solid; yield: 53%. (Found: C, 65.31; H, 4.53; N, 11.55. $C_{20}H_{16}N_3O_2Cl$ requires: C, 65.67, H, 4.41, N, 11.49); mp 209–211°C; ν_{max} (KBr): 1687, 1637 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.25 (dd, 1H, *J*=8.0 and 1.1 Hz), 7.76–7.71 (m, 2H), 7.49–7.28 (m, 6H), 5.64 (q, 1H, *J*=7.1 Hz), 2.95 (s, 3H), 1.61 (d, 3H, *J*=7.1 Hz); δ_C ($CDCl_3$, 63 MHz) 167.9, 159.9, 147.6 (2C), 134.9, 131.9, 131.8, 130.6, 129.1, 127.6, 127.4, 127.0, 126.8. 121.2, 120.4, 52.0, 35.2, 17.8.

3.3.4. (*E*)-1-*p*-Chlorobenzyliden-2,4-dimethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (*E*-2i). It was obtained (EtOAc/Hexane 1:2) as a white solid; yield: 28%. (Found: C, 65.72; H, 4.13; N, 11.55. $C_{20}H_{16}N_3O_2Cl$ requires: C, 65.67, H, 4.41, N, 11.49); mp 155–158°C; ν_{max} (KBr): 1687, 1636 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.27 (dd, 1H, *J*=7.9, 1.3 Hz), 7.68 (m, 1H), 7.48 (m, 1H), 7.34–7.21 (m, 5H), 6.65 (s, 1H), 5.62 (q, 1H, *J*=7.1 Hz), 3.40 (s, 3H), 1.65 (d, 3H, *J*=7.1 Hz); δ_C ($CDCl_3$, 63 MHz) 166.6, 159.6, 146.6, 144.7, 134.7, 133.8, 132.4, 131.4, 130.9, 128.1, 127.8, 127.6, 126.6, 121.4, 120.6, 51.6, 31.6, 18.1.

3.4. Additions of alkyllithium reagents to 2e. General procedure

To a solution of **2e** (0.82 mmol) in dry THF was added under argon atmosphere 1.1 equiv. (0.9 mmol) of the organometallic solution in ether at −30°C. The reaction was kept at −30°C for 15 min and then at room temperature overnight. After this time, it was quenched with a saturated solution of NH_4Cl, extracted with ether and dried over Na_2SO_4. Evaporation of solvents under reduced pressure and chromatographic separation gave the products.

3.4.1. (−)-(4*S*,*Z*)-2,4-Dimethyl-1-dimethylaminomethylen-3-methylen-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazolin-6-one (3). It was obtained (EtOAc, alumina) as a yellow solid; yield: 95%. (Found: C, 68.75; H, 6.67; N, 19.10. $C_{17}H_{20}N_4O$ requires: C, 68.89; H, 6.80; N, 18.90); mp 62–64°C; $[\alpha]^{25}_D$=−327 (*c* 0.1, $CHCl_3$); ν_{max} (KBr): 1675, 1646 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.12 (dd, 1H, *J*=7.9 and 1.3 Hz), 7.56 (m, 1H), 7.42 (d, 1H, *J*=7.8 Hz), 7.22 (m, 1H), 6.76 (s, 1H), 5.59 (q, 1H, *J*=6.9 Hz), 3.86 (s, 1H), 3.85 (s, 1H), 2.84 (s, 6H), 2.82 (s, 3H), 1.43 (d, 3H, *J*=6.9 Hz); δ_C ($CDCl_3$, 63 MHz) 160.6, 151.6, 148.6, 147.6, 134.2, 133.3, 126.9, 126.4, 124.9, 119.7, 112.0, 80.1, 51.0, 41.5, 36.7, 18.9. EIMS *m*/*z*(rel. intensity) 296 (M^+, 100), 281 (34), 253 (52), 238 (59).

3.4.2. (−)-(4*S*,1*Z*, 3*E*)-3-Butyliden-2,4-dimethyl-1-dimethylaminomethylen-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazolin-6-one (4). It was obtained (EtOAc, benzylamine, silica gel) as a yellow oil; yield: 68%. (Found: C, 70.45; H, 7.98 N, 16.48. $C_{20}H_{26}N_4O$ requires: C, 70.97; H, 7.74; N, 16.55); $[\alpha]^{25}_D$=−261 (*c* 0.17, $CHCl_3$); ν_{max} (KBr): IR 1675, 1649 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.16 (dd, 1H, *J*=7.9, 1.3 Hz), 7.59 (m, 1H), 7.46 (d, 1H, *J*=7.9 Hz), 7.24 (m, 1H), 6.74 (s, 1H), 6.11 (q, 1H, *J*=6.9 Hz), 4.23 (t, 1H, *J*=7.4 Hz), 2.86 (s, 6H), 2.81 (s, 3H), 2.16 (m, 2H), 1.40 (d, 3H, *J*=6.9 Hz), 1.33 (m, 2H), 0.89 (t, 3H, *J*=7.2 Hz); δ_C ($CDCl_3$, 63 MHz) 160.5, 151.9, 148.5, 140.2, 133.9, 132.4, 126.7, 126.2, 124.6, 119.5, 113.2, 96.5, 44.4, 41.2, 36.1, 28.9, 24.5, 18.0, 13.7.

3.5. Additions of Grignard reagents or *tert*-butyllithium to compounds 1 and 2a–2c, 2d. General procedure

To a cold (−78°C) magnetically stirred solution of **1** or **2** (0.78 mmol) in dry THF (7 mL) the organometallic reagent

(0.97 mmol for **1** and 1.95 mmol for **2**) was added, followed by stirring at −78°C for 15 min. The red reaction mixture was maintained stirring for 3 h at −30°C and at room temperature overnight. Then the mixture was poured in saturated NH_4Cl solution, extracted with diethyl ether or ethyl acetate, and dried over Na_2SO_4. Concentration of the resulting extracts and chromatography separation in silica or alumina gave the products.

3.5.1. (±)-(3*R,4*S**,*Z*)-1-*p*-Chlorobenzyliden-3-hydroxy-2,4-dimethyl-3-phenyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]-quinazolin-6-one (5).** It was obtained (chloroform, alumina) as a yellow solid; yield: 37%. (Found: C, 70.01; H, 5.15; N, 9.39. $C_{26}H_{22}N_3O_2Cl$ requires: C, 70.35, H, 4.99, N, 9.47); mp 109–111°C; ν_{max} (KBr): 2924, 1655, 1610 cm^{-1}; δ_H (DMSO, 250 MHz) 7.90 (dd, 1H, *J*=7.9 and 1.2 Hz), 7.79 (m 1H), 7.69 (d, 1H, *J*=7.6 Hz), 7.46 (s, 2H), 7.44 (s, 2H), 7,40 (m, 1H), 7.23–7.15 (m, 5H), 6.90 (s, 1H), 6.80 (s, 1H), 5.09 (q, 1H, *J*=6.8 Hz), 2.55 (s, 3H), 1.47 (d, 3H, *J*=6.8 Hz); δ_C (DMSO, 63 MHz) 160.7, 151.6, 149.0, 143.5, 139.5, 137.1, 136.6, 132.2, 131.8, 130.1, 129.8. 129.6, 129.1, 128.4, 128.0, 127.8, 120.9, 106.9, 89.3, 56.7, 38.9, 15.8.

3.5.2. 3,4-Dimethyl-1-methylamino-pyrido[2,1-*b*]quinazolin-6-one (6). It was obtained (AcOEt/Hexane 1:7, silica gel) as a yellow oil, yield: 10%. δ_H ($CDCl_3$, 250 MHz) 8.27 (d, 1H, *J*=7.9 Hz), 7.72–7.62 (m, 2H), 7.34 (m, 1H), 6.05 (s, 1H), 5.54 (ws, 1H), 6.18 (s, 1H), 2.94 (d, 3H, *J*=54.7 Hz), 2.64 (s, 3H), 2.22 (s, 3H).

3.5.3. (−)-(3*S*,4*R*)-3-Hydroxy-4-methyl-1-methylamino-3-phenyl-3,4-dihydro-pyrido[2,1-*b*]quinazolin-6-one (7a). It was obtained (chloroform, alumina) as an orange solid; yield: 82%. (Found: C, 71.88; H, 5.62; N, 12.87. $C_{20}H_{19}N_3O_2$ requires: C, 72.05, H, 5.74, N, 12.60); mp 86°C; $[\alpha]^{25}_D$=−100 (*c* 0.25, MeOH); ν_{max} (KBr): 2928, 1644 cm^{-1}; δ_H (DMSO, 300 MHz) 8.02 (dd, 1H, *J*=7.9, 1.3 Hz), 7.81 (m, 1H), 7.65 (d, 1H, *J*=7.8 Hz), 7,49 (m, 1H), 7.39 (m, 2H), 7.22 (m, 2H), 7.14 (m, 1H), 5.94 (s, 1H), 5.60 (q, 1H, *J*=5.1 Hz), 5.18 (qd, 1H, *J*=6.5, 1.6 Hz), 4.94 (d, 1H, *J*=1.2 Hz), 2.77 (d, 3H, *J*=5.1 Hz), 1.36 (d, 3H, *J*=6.5 Hz); δ_C (75 MHz, DMSO) 159.8, 147.2, 146.3, 145.6, 136.5, 134.9, 128.2, 127.4, 126.6, 125.7, 120.3, 102.3, 72.7, 55.5, 30.3, 15.4. EIMS *m*/*z* (rel. intensity) 333 (M^+, 80), 256 (37), 228 (100).

3.5.4. (−)-(3*S*,4*R*)-3-Hydroxy-8,9-dimethoxy-4-methyl-1-methylamino-3-phenyl-3,4-dihydro-pyrido[2,1-*b*]-quinazolin-6-one (7c). It was obtained (EtOAc/Hexane 1:1, silica gel) as an orange solid; yield: 45 %. (Found: C, 67.42, H, 5.51; N, 10.71. $C_{22}H_{23}N_3O_4$ requires: C, 67.16, H, 5.89, N, 10.68); mp 105–107°C; $[\alpha]^{25}_D$=−89 (*c* 0.13, MeOH); ν_{max} (KBr): 2933, 1642 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.46 (s, 1H), 7.46–7.43 (m, 2H), 7.32–7.13 (m, 3H), 6.98 (s, 1H), 5.47 (q, 1H, *J*=6.5 Hz), 5.14 (ws, 1H), 4.91 (d, 1H, *J*= 1.6 Hz), 3.93 (s, 3H), 3.90 (s, 3H), 2.85 (s, 3H), 1.49 (d, 3H, *J*=6.5 Hz); δ_C (63 MHz, $CDCl_3$) 159.8, 154.8, 149.2, 145.3, 144.0, 142.5, 137.3, 128.4, 127.9, 125.5, 114.3, 107.5, 105.9, 100.8, 74.2, 56.2, 55.4, 30.3, 15.1. EIMS *m*/*z* (rel. intensity) 393 (M^+, 34), 375 (32), 288 (100).

3.5.5. (−)-(3*S*,4*R*)-1-Benzylamino-3-hydroxy-8,9-dimethoxy-4-methyl-3-phenyl-3,4-dihydro-pyrido[2,1-*b*]quinazolin-6-one (7d). It was obtained (EtOAc/Hexane 1:1, silica gel) as an orange solid; yield: 52%. (Found: C, 71.25, H, 5.92; N, 9.01. $C_{28}H_{27}N_3O_4$ requires: C, 71.62, H, 5.79, N, 8.95); mp 106–108°C; $[\alpha]^{25}_D$=−20 (*c* 0.15, $CHCl_3$); ν_{max} (KBr): 2925, 1652 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.48 (s, 1H), 7.43–7.14 (m, 10H), 7.0 (s, 1H), 5.64 (ws, 1H), 5.49 (q, 1H, *J*=6.5 Hz), 4.96 (s, 1H), 4.36 (m, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 1.50 (d, 3H, *J*=6.5 Hz); δ_C (63 MHz, $CDCl_3$) 159.9, 154.9, 149.4, 145.2, 144.0, 142.7, 138,6, 135.9, 128.8, 128.6, 128.1, 127.7, 127.5, 125.7, 114.5, 107.8, 106.1, 102.6, 74.3, 56.4, 56.3, 55.3, 48.1, 15.3.

3.5.6. 4-Methyl-1-methylimino-3-phenyl-1,2-dihydro-pyrido[2,1-*b*]quinazolin-6-one (8a). It was obtained (chloroform, alumina) as traces of a yellow oil. δ_H ($CDCl_3$, 250 MHz) 8.37 (m, 1H), 7.84 (m, 1H), 7.73 (m, 1H), 7.53 (m, 1H), 7.44–7.40 (m, 2H), 7.15–7.02 (m, 3H), 4.04 (d, 1H, *J*=14.5 Hz), 3.69 (d, 1H, *J*=14.5 Hz), 2.67 (s, 3H), 1.99 (s, 3H).

3.5.7. 8,9-Dimethoxy-4-methyl-1-methylimino-3-phenyl-1,2-dihydro-pyrido[2,1-*b*]quinazolin-6-one (8c). It was obtained (AcOEt/Hexane 1:1, silica gel) as traces of a yellow oil. δ_H ($CDCl_3$, 250 MHz) 7.68 (s, 1H), 7.44–7.33 (m, 2H), 7.13 (m, 1H), 7.02 (s, 1H), 7.00–6.82 (m, 2H), 4.07 (s, 3H), 4.00 (s, 3H), 3.96 (d, 1H, *J*=14.7 Hz), 3.70 (d, 1H, *J*=14.7 Hz), 2.63 (s, 3H), 1.97 (s, 3H).

3.5.8. 4-Methyl-1-methylamino-3-phenyl-pyrido[2,1-*b*]-quinazolin-6-one (9a). It was obtained (chloroform, alumina) as traces of a yellow oil; (Found: C, 76.54; H, 5.45; N, 13.01. $C_{20}H_{I7}N_3O$ requires: C, 76.17, H, 5.43, N, 13.32); ν_{max} (KBr): 1674, 1400 cm^{-1}; δ_H (DMSO, 250 MHz) 8.19 (dd, 1H, *J*=8.1 and 1.3 Hz), 7.85 (m, 1H), 7.7 (d, 1H, *J*=7.7 Hz), 7.49–7.38 (m, 6H), 6.49 (q, 1H, *J*= 5.2 Hz), 6.18 (s, 1H), 2.87 (d, 3H, *J*=5.2 Hz), 2.49 (s, 3H); δ_C (63 MHz, DMSO) 162.3, 146.3, 143.1, 140.2, 139.6, 134.8, 130.1, 129.4, 128.9, 128.1, 127.2, 126.4, 125.4, 123.2, 118.9, 104.9, 30.0, 21.2.

3.5.9. 1-Benzylamino-4-methyl-8,9-dimethoxy-3-phenyl-pyrido[2,1-*b*]quinazolin-6-one (9d). It was obtained (EtOAc/Hexane 1:1, silica gel) as a yellow oil; yield: 11%. (Found: C, 74.29, H, 5.79; N, 9.39. $C_{28}H_{25}N_3O_3$ requires: C, 74.48, H, 5.58, N, 9.31); ν_{max} (KBr): 2923, 1665 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.62 (s, 1H), 7.44–7.27 (m, 10H), 7.09 (s, 1H), 6.36 (ws, 1H), 6.20 (s, 1H), 4.45 (d, 2H, *J*=5.6 Hz), 4.01 (s, 3H), 4.0 (s, 3H), 2.62 (s, 3H); δ_C (63 MHz, $CDCl_3$) 161.9, 155.3, 150.0, 148.2, 142.3, 140.2, 138.1, 137.6, 129.7, 128.9, 128.6, 128.3, 127.4, 127.3, 124.9, 112.4, 106.0, 105.3, 56.2, 56.1, 47.5, 21.1.

3.5.10. 2,4-Dimethyl-3-phenyl-1,2-dihydro-pyrazino[2,1-*b*]quinazolin-6-one (10). It was obtained (EtOAc/Hexane 1:3, alumina) as a yellow oil; yield: 25%. (Found: C, 75.11; H, 5.87; N, 13.78. $C_{19}H_{17}N_3O$ requires: C, 75.23, H, 5.65, N, 13.85); ν_{max} (KBr): 1684, 1399 cm^{-1}; δ_H (DMSO, 250 MHz) 8.17 (dd, 1H, *J*=7.9 and 1.3 Hz), 7.81 (m, 1H), 7.64 (d, 1H, *J*=8.3 Hz), 7.54–7.42 (m, 6H), 4.21 (s, 2H), 2.44 (s, 3H), 2.24 (s, 3H); δ_C (DMSO, 63 MHz) 159.3,

152.1, 146.9, 140.9, 134.4, 133.9, 130.5, 129.3, 128.7, 128.5, 126.7, 126.6, 121.9, 118.4, 55.3, 38.2, 18.5.

3.5.11. (+)-(3*R*,4*S*)-3-*tert*-Butyl-3-hydroxy-2,4-dimethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazolin-6-one (11). It was obtained as a white solid; yield: 30%. (Found: C, 67.37, H, 7.92; N, 14.01. $C_{17}H_{23}N_3O_2$ requires: C, 67.75, H, 7.69, N, 13.94); mp 157–159°C; $[\alpha]^{25}_D$=+274 (*c* 0.13, $CHCl_3$); ν_{max} (KBr): 2974, 1684 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.34 (dd, 1H, *J*=8.1 and 1.7 Hz), 7.23 (m, 1H), 7.08–7.03 (m, 2H), 4.68 (q, 1H, *J*=7.0 Hz), 4.61 (s, 1H), 3.96 (d, 2H, *J*=1.6 Hz), 2.96 (s, 3H), 1.25 (d, 3H, *J*=7.0 Hz), 0.82 (s, 9H); δ_C ($CDCl_3$, 63 MHz) 170.0, 151.8, 142.7, 129.2, 125.9, 125.1, 123.7, 122.4, 89.5, 53.6, 51.1, 44.5, 33.3, 24.5, 20.2.

3.6. Addition of diethyl malonate sodium enolate to 2a

To a stirred suspension of HNa (1.7 mmol) in 2 mL of dry THF at 0°C was added, under argon, diethyl malonate (1.7 mmol). The resulting solution was stirred at 0°C for 30 min and **2a** (0.59 mmol) in dry THF (5 mL) was added. The resulting solution was allowed to stir for 4 h at 0°C and overnight at room temperature. Then the mixture was poured in saturated NH_4Cl solution, extracted with diethyl ether and dried over Na_2SO_4. Concentration of the resulting extracts and chromatography separation (EtOAc/Hexane 1:1, silica gel) gave the products.

3.6.1. (+)-(1*S*,4*S*)-Diethyl-1(2,4-dimethyl-3,6-dioxo-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazolinyl)-methylmalonate (*cis*-12). It was obtained (EtOAc/Hexane 1:1, silica gel) as a white solid; yield: 82%. (Found: C, 60.85, H, 6.19; N, 9.87. $C_{21}H_{25}N_3O_6$ requires: C, 60.71, H, 6.06, N, 10.11); mp 88–90°C; $[\alpha]^{25}_D$=+78 (*c* 0.15, $CHCl_3$); ν_{max} (KBr): 1746, 1668, 1606 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.25 (dd, 1H, *J*=7.9 and 1.1 Hz), 7.77 (m, 1H), 7.59 (d, 1H, *J*=7.6 Hz), 7.47 (m, 1H), 5.30 (q, 1H, *J*=7.2 Hz), 4.47 (dd, 1H, *J*=11.5 and 4.3 Hz), 4.25 (m, 2H), 3.93–3.63 (m, 3H), 3.15 (s, 3H), 2.67 (m, 1H), 2.32 (m, 1H), 1.77 (d, 3H, *J*=7.2 Hz), 1.31 (t, 3H, *J*=7.2 Hz), 1.07 (t, 3H, *J*=7.2 Hz); δ_C (63 MHz, $CDCl_3$) 168.7, 168.4, 167.3, 160.3, 149.2, 146.8, 134.6, 127.4, 127.2, 126.9, 120.5, 62.2, 61.9, 61.4, 52.4, 48.6, 33.1, 32.9, 18.9, 14.2, 13.9; EIMS *m/z* (rel. intensity) 415 (M^+, 23), 256 (100).

3.6.2. (+)-(1*R*,4*S*)-Diethyl-1(2,4-dimethyl-3,6-dioxo-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazolinyl)-methylmalonate (*trans*-12). It was obtained (EtOAc/Hexane 1:1, silica gel) as a colorless oil; yield: 10%. (Found: C, 60.93, H, 5.92; N, 9.96. $C_{21}H_{25}N_3O_6$ requires: C, 60.7l, H, 6.06, N, 10.11); $[\alpha]^{25}_D$=+58 (*c* 0.35, $CHCl_3$); ν_{max} (KBr): 1725, 1668, 1608 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.25 (dd, 1H, *J*=7.9 and 1.0 Hz), 7.74 (m, 1H), 7.60 (d, 1H, *J*=8.1 Hz), 7.48 (m, 1H), 5.25 (q, 1H, *J*=6.9 Hz), 4.69 (dd, 1H, *J*=7.3, 2.9 Hz), 4.15–3.88 (m, 4H), 3.55 (dd, 1H, *J*=8.1, 5.4 Hz), 3.11 (s, 3H), 2.94 (ddd, 1H, *J*=14.5, 8.1 and 3.9 Hz), 2.66 (ddd, 1H, *J*=14.5, 7.3, 5.4 Hz), 1.63 (d, 3H, *J*=6.9 Hz), 1.22–1.09 (m, 6H); δ_C (63 MHz, $CDCl_3$) 168.8, 168.7, 167.7, 160.35 148.9, 146.7, 134.8, 127.4, 127.3, 126.9, 120.7, 62.2, 61.9, 58.7, 52.4, 52.2, 47.9, 32.0, 31.6, 19.6, 14.0, 13.9.

3.7. (±)-(1*S**,4*S**)-2,4-Dimethyl-1-phenylthiomethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione (13)

To a stirred suspension of NaPhS (1.7 mmol) in 5 mL of dry THF at 0°C was added, under argon, **2a** (0.59 mmol) in dry THF (5 mL). The resulting solution was allowed to stir for 4 h at 0°C and overnight at room temperature. Then the mixture was poured in saturated NH_4Cl solution, extracted with diethyl ether and dried over Na_2SO_4. Concentration of the resulting extracts and chromatography separation (EtOAc/Hexane 1:2, silica gel) gave **13** as a white solid; yield: 52%. (Found: C, 65.32, H, 5.37; N, 11.38. $C_{20}H_{19}N_3O_2S$ requires: C, 65.73, H, 5.24, N, 11.49); mp 132–134°C; ν_{max} (KBr): 1663, 1600 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.21 (d, 1H, *J*=7.9 Hz), 7.73 (t, 1H, *J*=7.0 Hz), 7.58 (d, 1H, *J*=8.1 Hz), 7.45 (m, 1H), 7.34 (d, 2H, *J*=7.4 Hz), 7.21–7.09 (m, 3H), 5.25 (q, 1H, *J*=7.1 Hz), 4.72 (t, 1H, *J*=6.1 Hz), 3.67–3.51 (m, 2H), 3.07 (s, 3H), 1.80 (d, 3H,. *J*=7.1 Hz); δ_C (63 MHz, $CDCl_3$) 167.2, 160.3, 149.1, 147.1, 134.8, 134.3, 130.2, 129.3, 128.8, 127.3, 127.2, 127.1, 126.8, 120.4, 62.9, 52.5, 40.1, 34.3, 29.8, 19.6. EIMS *m/z* (rel. intensity) 365 (M^+, 11), 255 (100), 242 (32).

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