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Synthesis of 5-*N*-Acetylardeemin *seco*-Analogues

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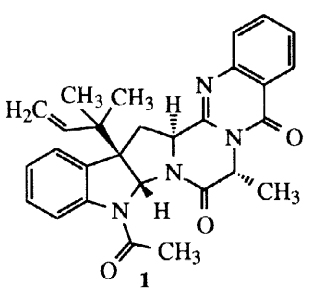
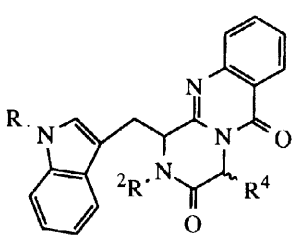
Abstract: Piperazinediones derived from ethyl *N*-indolylmethyl- glicinate or L-alaninate and different α-amino esters were cyclized with anthranilic acid in two steps with retention of configuration of the stereocenters to afford compounds which are analogues of 5-*N*-acetylardeemin, a MDR reversal agent.

The multidrug resistance (MDR) phenomenon is characterized by the overexpression of a transport membrane protein, the glycoprotein-170, which acts by exporting antitumour drugs out of the cell, thus lowering the active intracellular concentrations below the therapeutic levels.[1] Agents capable of inhibiting such protein could be useful in combination with anticancer drugs, substrates of that transport, by reversing this resistance. Among different compounds so far studied as multidrug resistance reversal agents, our group is actually interested in the study of analogues of the fungal metabolite 5-*N*-acetylardeemin (**1**).[2] Thus, we have reported stereocontrolled synthesis for simpler analogues of **1** such as **2** and other 1,2,4-trialkyl- and 1,1,2,4-tetraalkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones,[3] some of which have shown an interesting activity as MDR reversal agents. Here we report the synthesis of compounds **3** and their acetyl derivates **4**, which are isomers of **2** and can be considered as ardeemin *seco*-analogues.



1



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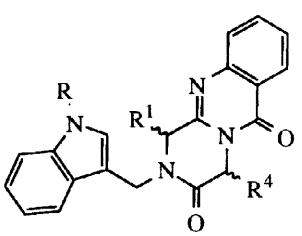

3 R= H
4 R =$COCH_3$

The retrosynthetic analysis of **3** (Scheme 1) pointed to the *N*-(3-indolylmethyl)-α-amino esters **7** as starting materials.

Gramine (**5a**) and gramine methyl salts (**5b**), which have been frequently used to alkylate *C*-nucleophiles,[4] were here used as indolylmethyl electrophiles to obtain compounds **7** by *N*-alkylation of ethyl glycinate (**6a**) and ethyl *L*-alaninate (**6b**) hydrochlorides with moderate yields (Scheme 2). Even with large excess of the amino ester **6a**, **7a** was accompanied by the *N,N*-dialkylester **7c**, and a chromatographic separation was needed. Steric effects prevented the dialkylation of **6b**, and **7b** was the single reaction product in

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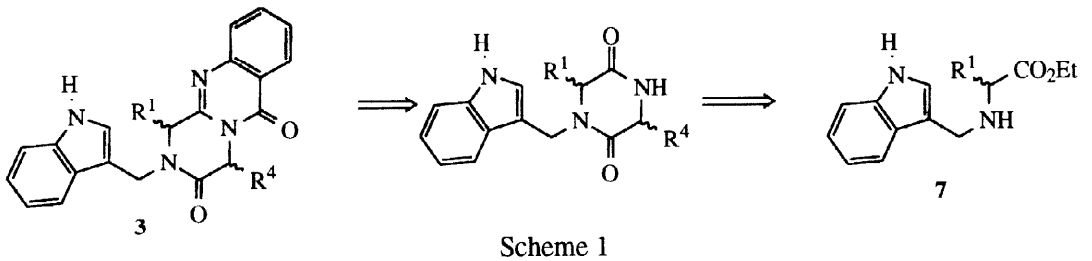
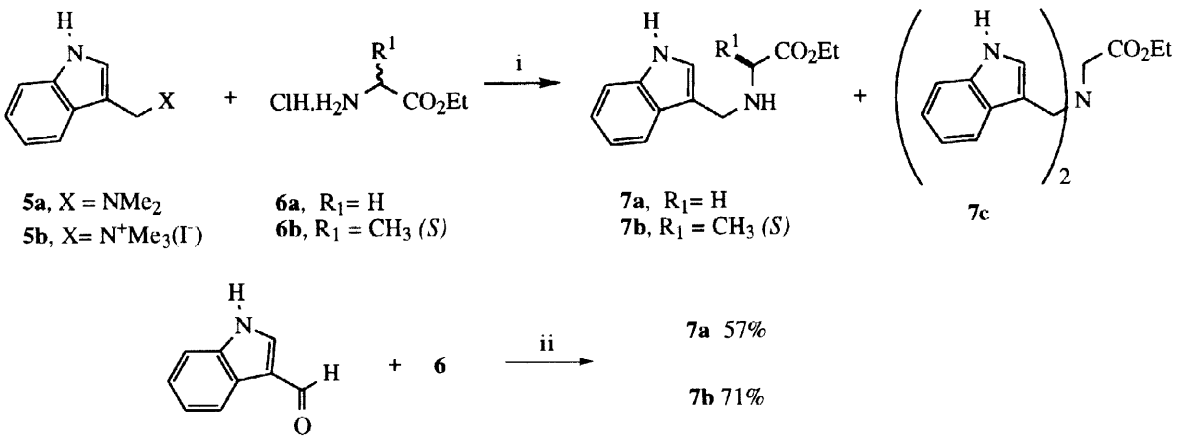
this case. The methylene protons of this compound are diastereotopic and appear as an AB-system with a geminal coupling of 12.8 Hz.



Scheme 1

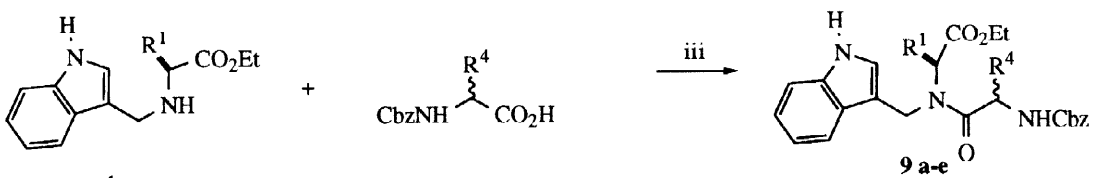
Better yields of compounds **7a** and **7b** were obtained by reductive amination of indole-3-carboxaldehyde with compounds **6** in the presence of sodium cyanoborohydride.



i = Et_3N, THF, reflux, 48 h. ii = $NaBH_3CN$, MeOH, 48 h.

Scheme 2

EDC mediated coupling[5] of **7a** or **7b** and the corresponding Cbz-amino acids **8** proceeded in good yields to afford dipeptide derivatives **9** as mixtures of *s-Z*/*s-E* rotamers, as evidenced by the complexity of their ^1H NMR spectra, and the duplicity of the clearly separated signals N-H and H-4 of indole nucleus and NH of the carbamate function (Scheme 3).

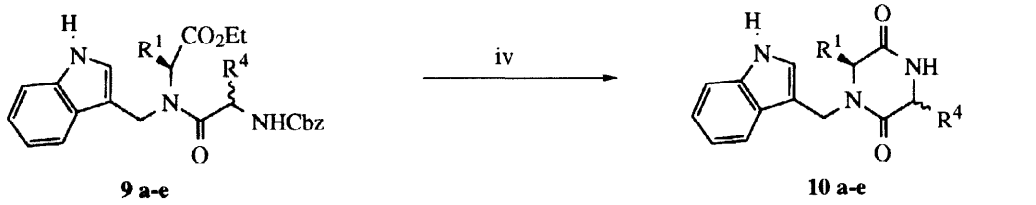


iii= EDC, CH_2Cl_2, 24 h.

Compound	R^1	R^4	Yield%
9a	H	$CH_3(S)$	85
9b	H	$CH_3(R)$	73
9c	H	^iPr (S)	73
9d	$CH_3(S)$	H	75
9e	$CH_3(S)$	$CH_3(S)$	82

Scheme 3

Removal of the Cbz group of **9** by hydrogenolysis was followed by spontaneous cyclization to afford piperazinediones **10** in excellent yields (Scheme 4). The most significant of their ^{1}H and ^{13}C NMR data are the signals of the methylene protons of the indolylmethyl substituent, which appear very close when R^1 = H (**10a-c**) and very different in the methyl derivatives (**10d-e**), thus reflecting the restricted conformational freedom that imposes that methyl group to the *N*-indolylmethyl substituent.



9 a-e **10 a-e**

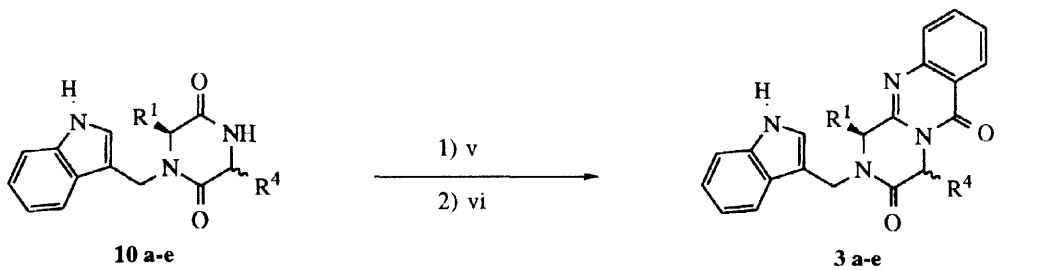
iv= H_2/Pd-C, MeOH, 20 psi, 3 h.

Compound	R^1	R^4	Yield%
10a	H	$CH_3(S)$	91
10b	H	$CH_3(R)$	91
10c	H	$^{i}Pr\ (S)$	97
10d	$CH_3(S)$	H	90
10e	$CH_3(S)$	$CH_3(S)$	91

Scheme 4

The cyclization does not affect the stereochemistry of stereocenters. The enantiomeric purity of compounds **10a** and **10b** was confirmed by comparing significant signals (aromatic and methyl protons) of the ^{1}H-NMR spectra of their complexes with Eu(hfc)$_3$ as chiral reagent with that of an equimolar mixture of **10a** and **10b** in $CDCl_3$.

The reaction of **10a** with anthranilic acid to give **3a** was first tried in thionyl chloride following Kametani's procedure for the synthesis of pyrazino[2,1-*b*]quinazolinone derivatives from amides,[6] but this method did not work with **10a** and other piperazinediones. However, this annulation was accomplished in two steps by first transforming compounds **10** to their corresponding iminoethers following Fukuyama's conditions,[7] and then, heating a mixture of crude iminoethers with an excess of anthranilic acid, which furnished compounds **3a-3e** in moderate yields and with retention of configuration in all stereocenters (Scheme 5).



10 a-e **3 a-e**

v = $Et_3O^+FB_4^-$, CH_2Cl_2, Na_2CO_3, 24 h.
vi = anthranilic acid, 140 °C, 2 h.

Compound	R^1	R^4	Yield%
3a	H	$CH_3(S)$	30
3b	H	$CH_3(R)$	30
3c	H	$^{i}Pr\ (S)$	19
3d	$CH_3(S)$	H	16
3e	$CH_3(S)$	$CH_3(S)$	16

Scheme 5

Compounds **3** were characterized by their analytical and spectroscopic data. ^{1}H NMR Signals corresponding to indole and quinazoline aromatic protons were assigned taking into account literature data of related compound ardeemin.[2b] Chemical shifts of the two methylene protons in the indolylmethyl substituent differ about 0.6 ppm in the C-1 unsubstituted compounds **3a-3c**, and about 1.1 ppm in the 1-methylderivatives **3d** and **3e**. The restricted rotation around the *N*-CH_2 bond in these compounds places the most deshielded of these protons nearly coplanar to the carbonyl group at C-3. The similarity of the chemical shift values assigned to the H-4 proton in compounds **3a** and **3e** with that of the same proton in 2,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**11**),[8] confirms that the C-4 methyl group has a pseudoaxial configuration, being the H-4 proton deshielded by the anisotropic effect of the quasi-coplanar carbonyl group at C-6. However, both methylene protons at C-1 of **3a**, resonate as a singlet (δ = 4.40 ppm), while they appear as an AB system (δ = 4.85 and 4.36 ppm) in compound **11** (Figure 1). This different behaviour reflects that steric 1,2-diequatorial interactions between the hydrogen atoms at C-1 and the *N*-indolylmethyl substituent in **3a**, are lower than in the *N*-methyl analogue **11**, making possible a fast chair-boat equilibrium in the pyrazine ring of **3a**. Similar assumptions can be applied to **3b**. In the C-1 methyl derivative **3d**, the methylene protons at C-4 resonate as two well differentiated doublets (δ = 5.26 and 4.59 ppm), showing an anchored boat conformation for the pyrazine ring. Finally, the 1,4-dimethylderivative **3e** showed the same locked boat conformation (δ H-1 and H-4 = 4.65 and 5.53 ppm, respectively).

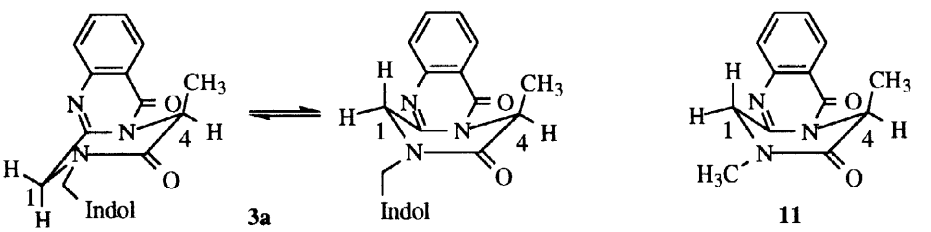
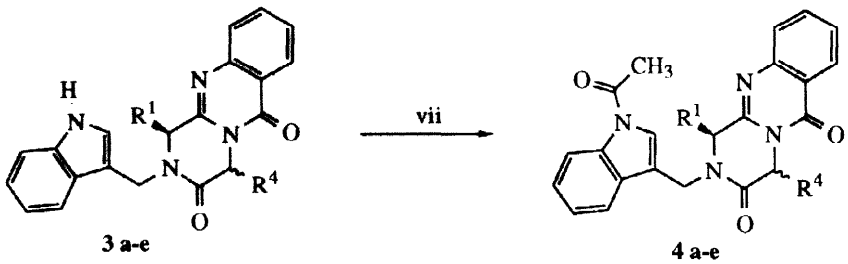


Figure 1

Some additional ^{1}H NMR experiments were performed to confirm that the above described condensation between iminoethers and anthranilic acid is stereochemically controlled. The enantiomeric purity was determined with **3a**, **3b** and an equimolar mixture of both enantiomers in the presence of (+)-Eu(hfc)$_3$. On the other hand, the expected *cis*-stereochemistry of compound **3e** was confirmed by NOE experiments. Thus, irradiation of the methyl doublet at δ = 1.68 ppm produced enhancement of the signals assigned to H-4 and the other methyl group, while when the sample was irradiated at the frequency of resonance of this last methyl group (δ = 1.58 ppm), enhancement of the signals corresponding to H-1 and the C-4 methyl protons, were also observed. These data allow us to conclude that condensation of iminoethers with anthranilic acid takes place without epimerization of the stereogenic centers.

Finally, compounds **3** were acetylated in good yields to provide *N*-acetylardeemin analogues **4** with more conformational freedom.



3 a-e

4 a-e

vii = acetic anhydride, 160 °C, 7 h.

Compound	R^1	R^4	Yield%
4a	H	$CH_3(S)$	75
4b	H	$CH_3(R)$	75
4c	H	^iPr (*S*)	69
4d	$CH_3(S)$	H	72
4e	$CH_3(S)$	$CH_3(S)$	74

Scheme 6

ACKNOWLEDGEMENTS

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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. The expression "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 indicador (Scharlau Cf 530). Separations by flash chromatography were performed on silica gel (SDS 60 ACC). Melting points were measured on a Reichert 723 hot stage microsope or in open capillary tubes using a Büchi immersion apparatus, and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Paragon 1000 (FT-IR) spectrophotometer, with solid compounds compressed into KBr pellets and liquids compounds placed between two NaCl disks. NMR spectra were obtained on a Bruker AC-250 (250 MHz for ^1H, 63 MHz for ^{13}C) spectrometer (Servicio de Espectroscopía, Universidad Complutense), with $CDCl_3$ or DMSO-d_6 as solvents. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer.

N-(3-indolylmethyl)-α-amino esters (7).

a) By alkylation reactions.

A suspension of **5a** or **5b**[9] (11.40 mmol), **6a** or **6b** (45.80 mmol) and triethylamine (114.60 mmol) in THF (80 ml), was refluxed for 48 hours and, after cooling, triethylamine hydrocloride was removed by filtration. The filtrate was concentrated under vacuum, and the residue was chromatographied on silica gel eluting with ethyl acetate to yield ethyl *N,N*-bis(3-indolylmethyl) glicinate **7c** (15% from **5a** and 20% from **5b**) and ethyl *N*-(3-indolylmethyl) glicinate **7a** (42% from **5a** and 55% from **5b**) or ethyl *N*-(3-indolylmethyl)-L-alaninate **7b** (39% from **5a**).

b) By reductive amination of indole-3-carboxaldehyde.

A solution of indole-3-carboxaldehyde (2.9 g, 20 mmol), **6a** or **6b** hydrocloride (50 mmol), and $NaBH_3CN$ (1.28, 20 mmol) int methanol (50 ml) was stirred for 24 hours at room temperature. The methanol was removed "in vacuo", and the residue was dissolved in 2N HCl (10 ml) and extracted with ether. The aqueous solution was neutralized with K_2CO_3 solution, then, saturated with NaCl and extracted with chloroform. The combined organic layers were dried (Na_2SO_4) and concentrated to yield **7a** (2.56 g, 51%) or **7b** (3.57 g, 71%), which could be used for next reactions without further purification.

Data for **7a**: Mp 64-65 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.38 (broad s, 1H, NH indole), 7.75 (d, 1H, J= 7.1 Hz, $C_{4'}$-H), 7.36 (d, 1H, J= 7.4 Hz, $C_{7'}$-H), 7.25-7.10 (m, 3H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 4.20 (q, 2H, J= 7.2 Hz, $OC\underline{H}_2CH_3$), 4.04 (s, 2H, indole-$C\underline{H}_2$-N), 3.40 (s, 2H, $NC\underline{H}_2CO$), 1.25 (t, 3H, J= 7.2 Hz, $OCH_2C\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 172.75 (CO), 136.45 ($C_{7a'}$), 127.17 ($C_{3a'}$), 122.95 ($C_{2'}$), 122.25 ($C_{5'}$), 119.74 ($C_{4'}$), 118.86 ($C_{6'}$), 113.43 ($C_{3'}$), 111.41 ($C_{7'}$), 61.02 ($O\underline{C}H_2CH_3$), 49.84 ($N\underline{C}H_2CO$), 44.01 (indole-$\underline{C}H_2$-N), 14.33 ($OCH_2\underline{C}H_3$) ppm. IR (KBr) ν: 3403 (NH), 3297 (NH), 1731 (C=O), 1372 (C-O), 743 cm^{-1}. Anal. calcd. for $C_{13}H_{16}N_2O_2$: C, 66.79; H, 6.81; N, 11.77. Found: C, 67.04; H, 6.89; N, 12.06.

Data for **7b**: Mp. 65-67 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.13 (broad s, 1H, NH indole), 7.75 (d, 1H, J= 7.6 Hz, $C_{4'}$-H), 7.36 (d, 1H, J= 7.3 Hz, $C_{7'}$-H), 7.25-7.10 (m, 3H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 4.20 (q, 2H, J= 7.1Hz, $OC\underline{H}_2CH_3$), 4.01, 3.89 (AB system, 2H, J= 12.8 Hz, indole-$C\underline{H}_2$-N), 3.47 (q, 1H, J= 7.0 Hz, $C\underline{H}CH_3$), 1.34 (d, 3H, J= 7.0 Hz, $CHC\underline{H}_3$) 1.25 (t, 3H, J= 7.1 Hz, $OCH_2C\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 176.00 (CO), 136.45 ($C_{7a'}$), 127.17 ($C_{3a'}$), 123.46 ($C_{2'}$), 122.25 ($C_{5'}$), 119.74 ($C_{4'}$), 118.86 ($C_{6'}$), 113.43 ($C_{3'}$), 111.41 ($C_{7'}$), 61.02 ($O\underline{C}H_2CH_3$), 56.19 ($\underline{C}H$-CH_3), 43.08 (indole-$\underline{C}H_2$-N), 19.25 (CH-$\underline{C}H_3$), 14.39 (O-CH_2-$\underline{C}H_3$) ppm. IR (KBr) ν: 3400 (NH), 3294 (NH), 1724 (C=O), 743 cm^{-1}. Anal. calcd. for $C_{14}H_{18}N_2O_2$: C, 68.29; H, 7.31; N, 11.38. Found: C, 67.87; H, 7.38; N, 11.27.

Data for **7c**: ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.38 (broad s, 2H, NH indole), 7.76 (d, 2H, J= 7.5 Hz, $C_{7'}$-H), 7.36 (d, 2H, J= 8.1 Hz, $C_{4'}$-H), 7.25-7.10 (m, 6H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 4.25- 4.09 (m, 6H, $OC\underline{H}_2CH_3$ and indole-$C\underline{H}_2$-N), 3.40 (s, 2H, $NC\underline{H}_2CO$), 1.25 (t, 3H, J= 7.2 Hz, $OCH_2C\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 172.07 (CO), 136.22 ($C_{7a'}$), 127.68 ($C_{3a'}$), 124.04 ($C_{2'}$), 122.13 ($C_{5'}$), 120.04 ($C_{4'}$), 119.56 ($C_{6'}$), 113.24 ($C_{3'}$), 112.73 ($C_{7'}$), 60.12 ($O\underline{C}H_2CH_3$), 53.39 ($N\underline{C}H_2CO$), 49.20 (indole-$\underline{C}H_2$-N), 14.37 ($OCH_2\underline{C}H_3$) ppm. IR (KBr) ν: 3403 (NH), 1731 (C=O), 743 cm^{-1}.

Synthesis of dipeptides (9).

General procedure. A solution of **7a** or **7b** (2.15 mmol), the corresponding compound **8** (2.36 mmol) and EDC (0.618 g, 3.22 mmol) in dichloromethane was stirred for 24 hours at room temperature. The reaction mixture was extracted consecutively with 1N HCl, 1N $NaHCO_3$ solutions and water. The organic layer was dried (Na_2SO_4) and concentrated to yield **9** as an oil, which was used without further purification. NMR signals of both conformers, when were clearly identified, are given.

Data for **9a**: Yield, 0.75 g (85%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.71 and 8.60 (2 broad s, 1H, N-H indole), 7.55-7.49 (2d, 1H, J= 7.8 Hz, $C_{4'}$-H), 7,40-7.05 (m, 9H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H $C_{7'}$-H, $C_6\underline{H}_5$), 5.89 (m, 1H, CHN$\underline{H}$CO), 5.20-3.77 (m, $OC\underline{H}_2C_6H_5$, $OC\underline{H}_2CH_3$, indole-$C\underline{H}_2$-N, N-$C\underline{H}_2$-CO, $C\underline{H}CH_3$),

1.48 and 1.36 (2d, J= 6.8 Hz, 3H, CHC<u>H</u>3), 1.20 (m, 3H, OCH2C<u>H</u>3) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 173.40 and 173.21 (<u>C</u>OOEt), 169.39 and 169.21 (<u>C</u>O amide), 155.85 and 155.75 (CO carbamate), 136.67, 136.48, 136.31, 128.94, 128.65, 128.24, 126.89, 126.432, 124.93, 124.00, 122.70, 122.57, 120.20, 120.03, 119.24, 118.47 (<u>C</u>6H5, C2', C3a', C4', C5', C6', C7a'), 111.78 and 111.49 (C7'), 110.27 and 109.65 (C3'), 66.94 (<u>C</u>H2C6H5), 61.77 and 61.32 (O<u>C</u>H2CH3), 53.38 (<u>C</u>HCH3), 47.57 and 47.38 (N<u>C</u>H2COOEt), 43.89 and 41.13 (indole-<u>C</u>H2-N), 19.40 and 19.24 (CH<u>C</u>H3), 14.19 and 14.06 (OCH2<u>C</u>H3) ppm. IR (KBr) ν: 3413 (NH), 3297 (NH), 1734 (C=O), 1710 (C=O), 1648 (C=O), 743 cm^{-1}. Anal. calcd. for $C_{24}H_{27}N_3O_5$: C, 65,90; H, 6.17; N, 9.61. Found: C, 66.07; H, 6.18; N, 9.77.

Data for **9b**: Yield, 0.68 g (73%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.71 and 8.60 (2 broad s, 1H, N-H indole), 7.55-7.49 (2d, 1H, J= 7.8 Hz, C4'-H), 7,40-7.05 (m, 9H, C2'-H, C5'-H, C6'-H C7'-H, C6<u>H</u>5), 5.89 (m, 1H, CHN<u>H</u>CO), 5.20-3.77 (m, O<u>C</u>H2C6H5, O<u>C</u>H2CH3, indole-C<u>H</u>2-N, N-C<u>H</u>2-CO, C<u>H</u>CH3), 1.48 and 1.36 (2d, J= 6.8 Hz, 3H, CHC<u>H</u>3), 1.20 (m, 3H, OCH2C<u>H</u>3) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 173.40 and 173.21 (<u>C</u>OOEt), 169.39 and 169.21 (<u>C</u>O amide), 155.85 and 155.75 (CO carbamate), 136.67, 136.48, 136.31, 128.94, 128.65, 128.24, 126.89, 126.432, 124.93, 124.00, 122.70, 122.57, 120.20, 120.03, 119.24 and 118.47 (<u>C</u>6H5, C2', C3a', C4', C5', C6', C7a'), 111.78 and 111.49 (C7'), 110.27 and 109.65 (C3'), 66.94 (<u>C</u>H2C6H5), 61.77 and 61.32 (O<u>C</u>H2CH3), 53.38 (<u>C</u>HCH3), 47.57 and 47.38 (N<u>C</u>H2COOEt), 43.89 and 41.13 (indole-<u>C</u>H2-N), 19.40 and 19.24 (CH<u>C</u>H3), 14.19 and 14.06 (OCH2<u>C</u>H3) ppm. IR (KBr) ν: 3413 (NH), 3297 (NH), 1734 (C=O), 1710 (C=O), 1648 (C=O), 743 cm^{-1}. Anal. calcd. for $C_{24}H_{27}N_3O_5$: C, 65,90; H, 6.17; N, 9.61. Found: C, 66.09; H, 6.20; N, 9.56.

Data for **9c**: Yield, 0.73 g (73%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.55 and 8.51 (2 broad s, 1H, N-H indole), 7.57-7.48 (2d, 1H, J= 7.8 Hz, C4'-H), 7.40-7.00 (m, 9H, C2'-H, C5'-H, C6'-H C7'-H, C6<u>H</u>5), 5.65 (m, 1H, CHN<u>H</u>CO), 5.10-3.77 (m, O<u>C</u>H2C6H5, O<u>C</u>H2CH3, indole-C<u>H</u>2-N, N-C<u>H</u>2-CO, C<u>H</u>CH3), 1.18-0.85 (m, 9H, CH(C<u>H</u>3)2, OCH2C<u>H</u>3) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 172.40 (<u>C</u>OOEt), 169.22 and 168.95 (<u>C</u>O amide), 156.39 and 156.20 (CO carbamate), 136.67, 136.48, 136.31, 128.42, 127.99, 127.90, 127.80, 126.71, 126.36, 124.64, 123.87, 122.46, 122.37, 120.03, 119.24, 119.07, 118.30 (<u>C</u>6H5, C2', C3a', C4', C5', C6', C7a'), 111.43 and 111.19 (C7'), 110.33 (C3'), 66.83 and 66.77 (<u>C</u>H2C6H5), 61.57 and 61.04 (O<u>C</u>H2CH3), 56.08 and 55.75 (<u>C</u>HCH(CH3)2), 47.57 and 47.38 (N<u>C</u>H2COOEt), 43.92 and 40.79 (indole-<u>C</u>H2-N), 31.71 and 31.45 (<u>C</u>H(CH3)2), 19.40 and 19.24 (CH<u>C</u>H3), 14.19 and 14.06 (OCH2<u>C</u>H3) ppm. IR (KBr) ν: 3413 (NH), 3313 (NH), 1744 (C=O), 1710 (C=O), 1639 (C=O), 743 cm^{-1}.

Data for **9d**: Yield, 0.65 g (75%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.26 and 8.12 (2 broad s, 1H, N-H indole), 7.64-7.48 (2d, 1H, J= 7.8 Hz, C4'-H), 7.40-7.00 (m, 9H, C2'-H, C5'-H, C6'-H C7'-H, C6<u>H</u>5), 5.94 and 5.73 (2 broad s, 1H, CHN<u>H</u>CO), 5.20-5.00 (m, 2H, O<u>C</u>H2C6H5), 4.75-4.05 (7H O<u>C</u>H2CH3, indole-C<u>H</u>2-N, N-C<u>H</u>2-CO, C<u>H</u>CH3), 1.49-1.35 (2 d, 3H, J=7.1 Hz, CHC<u>H</u>3), 1.19-1.11 (m, 3H, OCH2C<u>H</u>3) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 171.36 (<u>C</u>OOEt), 168.60 (<u>C</u>O amide), 156.27 (CO carbamate), 136.48, 136.35, 128.65, 128.43, 128.01, 127.88, 125.76, 126.36, 122.95, 122.60, 119.90, 118.28 (<u>C</u>6H5, C2', C3a', C4', C5', C6', C7a'), 111.51 (C7'), 110.73 (C3'), 66.80 (<u>C</u>H2C6H5), 61.20 (O<u>C</u>H2CH3), 54.81 (<u>C</u>HCH3), 42.93 (indole-<u>C</u>H2-N), 42.57 (indole-<u>C</u>H2-N), 14.57 (CH<u>C</u>H3), 14.04 (OCH2<u>C</u>H3) ppm. IR (KBr) ν: 3413 (NH), 3336 (NH), 1734 (C=O), 1720 (C=O), 1648 (C=O), 743 cm^{-1}.

Data for **9e**: Yield, 0.76 g (82%).^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.43 and 8.36 (2 broad s, 1H, N-H indole), 7.64-7.52 (2d, 1H, J= 7.8 Hz, C4'-H), 7.40-7.00 (m, 9H, C2'-H, C5'-H, C6'-H C7'-H, C6<u>H</u>5), 5.94 and 5.73 (2 d, J= 7.7 Hz, 1H, CHN<u>H</u>CO), 5.20-5.00 (m, 2H, O<u>C</u>H2C6H5), 4.75-4.05 (6H,

$OC\underline{H}_2CH_3$, indole-$C\underline{H}_2$-N, N-$C\underline{H}(CH_3)$-COO, $C\underline{H}CH_3$), 1.49-1.35 (m , 6 H, $CHC\underline{H}_3$), 1.24-1.13 (m, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 173.11 (COOEt), 171.56 (CO amide), 157.27 (CO carbamate), 136.38, 136.29, 128.39, 127.96, 127.80, 123.36, 122.35, 119.67, 118.11 (C_6H_5, $C_{2'}$, $C_{3a'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{7a'}$), 111.44 ($C_{7'}$), 111.26 ($C_{3'}$), 66.58 ($CH_2C_6H_5$), 61.09 (OCH_2CH_3), 54.11 ($CHCH_3$), 47.56 ($CHCH_3$), 42.57 (indole-CH_2-N), 19.24 ($CHCH_3$), 14.33 ($CHCH_3$), 13.99 (OCH_2CH_3) ppm. IR (KBr) ν: 3413 (NH), 3326 (NH), 1734 (C=O), 1720 (C=O), 1650 (C=O), 745 cm^{-1}.

3-Alkyl- and 3,6-dialkyl-1-(3-indolylmethyl)-2,5-piperazinediones (10).

General procedure. To a solution of **9** (0.5 g) in methanol (50 ml), palladium on activated carbon (Pd 10 %, 0.25 g) was added. The suspension was mechanically stirred in a hydrogenation flask at 20 psi, and the progress of the reaction was monitored by thin layer chromatography. At the completion of hydrogenolysis (2-3 hours), the catalyst was removed by filtration through celite, and the solvent evaporated under reduced pressure to leave a residue identified as piperazinediones **10**, which can be purified by column chromatography on silica gel eluting with ethyl acetate.

Data for **10a**: Yield, 0.26 g (91%). Mp 78-81 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.45 (broad s, 1H, N-H indole), 7.66 (d, 1H, J= 7.8 Hz, $C_{4'}$-H), 7.38 (d, 1H, J= 8.0 Hz, $C_{7'}$-H), 7.22-7.10 (m, 3H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 6.18 (broad s, 1H, N_4-H), 4.79, 4.76 (AB system, 2H, J= 14.7 Hz, indole-$C\underline{H}_2$-N), 4.09 (m, 1H, C_3-H), 3.83 (s, 2H, C_6-H), 1.52 (d, 3H, J= 7.0 Hz, C_3-$C\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 166.21 y 166.17 (C_2, C_5), 136.22 ($C_{7a'}$), 127.68 ($C_{3a'}$), 124.04 ($C_{2'}$), 122.13 ($C_{5'}$), 120.04 ($C_{4'}$), 119.56 ($C_{6'}$), 111.32 ($C_{3'}$), 109.83 ($C_{7'}$), 51.15 (C_3), 48.43 (C_6), 40.85 (indole-$C\underline{H}_2$-N), 20.22 ($C_3C\underline{H}_3$) ppm. IR (KBr) ν: 3403 (NH), 3259 (NH), 1682 (C=O), 1647 (C=O), 742 cm^{-1}. Anal. calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.87; N, 16.34. Found: C, 65.20; H, 6.06; N, 16.42.

Data for **10b**: Yield, 0.26 g (91%). Mp 78-81 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.18 (broad s, 1H, N-H indole), 7.67 (d, 1H, J= 7.6 Hz, $C_{4'}$-H), 7.40 (d, 1H, J= 8.0 Hz, $C_{7'}$-H), 7.24-7.09 (m, 3H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 6.04 (broad s, 1H, N_4-H), 4.79, 4.76 (AB system, 2H, J= 14.7 Hz, indole-$C\underline{H}_2$-N), 4.13 (m, 1H, C_3-H), 3.82 (s, 2H, C_6-H), 1.50 (d, 3H, J= 7.0 Hz, C_3-$C\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 166.21 y 166.17 (C_2, C_5), 136.22 ($C_{7a'}$), 127.68 ($C_{3a'}$), 124.53 ($C_{2'}$), 122.13 ($C_{5'}$), 120.04 ($C_{4'}$), 119.56 ($C_{6'}$), 111.32 ($C_{3'}$), 109.83 ($C_{7'}$), 51.15 (C_3), 48.43 (C_6), 40.85 (indole-$C\underline{H}_2$-N), 20.22 ($C_3C\underline{H}_3$) ppm. IR (KBr) ν: 3403 (NH), 3259 (NH), 1682 (C=O), 1647(C=O), 742 cm^{-1}. Anal. calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.87; N, 16.34. Found: C, 61.53; H, 6.03; N, 16.35.

Data for **10c**: Yield, 0.28 g (93%). Mp, 223-225 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.23 (broad s, 1H, indole-NH), 7.71 (d, 1H, J= 7.7 Hz, $C_{4'}$-H), 7.37 (d, 1H, J= 8.0 Hz, $C_{7'}$-H), 7.20-7.09 (m, 3H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 6.15 (broad s, 1H, N_4-H), 4.90, 4.71 (AB system, 2H, J= 14.5 Hz, indole-$C\underline{H}_2$-N), 3.91 (m, 1H, C_3-H), 3.85 (s, 2H, C_6-H), 2.47 (m, 1H, C_3-$C\underline{H}(CH_3)_2$), 1.00 (d, 3H, J= 7,1 Hz, C_3-$CH(C\underline{H}_3)_2$), 0.82 (d, 3H, J= 6.8 Hz, C_3-$CHCH_3)_2$) ppm.^{13}C-RMN (63 MHz, $CDCl_3$) δ: 166.30 y 165.25 (C_2, C_5), 136.22 ($C_{7a'}$), 127.68 ($C_{3a'}$), 124.75 ($C_{2'}$), 122.85 ($C_{5'}$), 120.34 ($C_{4'}$), 119.18 ($C_{6'}$), 111.37 ($C_{3'}$), 110.08 ($C_{7'}$), 60.97 (C_3), 48.27 (C_6), 40.81 (indole-$C\underline{H}_2$-N), 33.04 ($C_3C\underline{H}(CH_3)_2$), 18.99 y 16.14 ($C_3CH(C\underline{H}_3)_2$) ppm. IR (KBr) ν: 3403 (NH), 3259 (NH), 1682 (C=O), 1647 (C=O), 742 cm^{-1}. Anal. calcd. for $C_{16}H_{19}N_3O_2$: C, 67.36; H, 6.66; N, 14.73. Found: C, 67.42; H, 6.43; N, 14.53.

Data for **10d**: Yield, 0.29 g (97%). Mp, 72-75 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.34 (broad s, 1H, NH indole), 7.62 (d, 1H, J= 7.8 Hz, C_4'-H), 7.35 (d, 1H, J= 7.9 Hz, C_7'-H), 7.24-7.10 (m, 3H, C_2'-H, C_5'-H, C_6'-H), 6.18 (broad s, 1H, N_4-H), 5.37, 4.21 (AB system, 2H, J= 14.9 Hz, indole-C$\underline{H}_2$-N), 4.02-3.86 (m, 3H, C_3-H_2 y C_6-H), 1.39 (d, 3H, J= 7.1 Hz, C_6-CH_3) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 169.34 y 166.40 (C_2, C_5), 136.29 (C_{7a}'), 127.68 (C_{3a}'), 124.53 (C_2'), 122.71 (C_5'), 120.25 (C_4'), 119.10 (C_6'), 111.37 (C_3'), 110.08 (C_7'), 54.20 (C_6), 45.00 (C_3), 40.81 (indole-$\underline{C}H_2$-N), 17.55 ($C_6\underline{C}H_3$) ppm. IR (KBr) ν: 3404 (NH), 3249 (NH), 1676 (C=O), 1654 (C=O), 743 cm^{-1}. Anal. calcd. for $C_{14}H_{15}N_3O_2$: C, 65.57; H, 5.87; N, 16.34. Found: C, 65.67; H, 6.14; N, 16.44.

Data for **10e**: Yield, 0.29 g (95 %). Mp, 62-64 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.21 (broad s, 1H, N-H indole), 7.63 (d, 1H, J= 7.6 Hz, C_4'-H), 7.36 (d, 1H, J= 7.9 Hz, C_7'-H), 7.17-7.07 (m, 3H, C_2'-H, C_5'-H, C_6'-H), 6.18 (broad s, 1H, N_4-H), 5.56, 4.08 (AB system, 2H, J= 14.8 Hz, indole-C$\underline{H}_2$-N), 4.11 (m, 1H, C_3-H), 3.92 (q, 1H, J= 7.0 Hz, C_6-$\underline{H}$), 1.55 (d, 3H, J= 7.0 Hz, C_6-C$\underline{H}_3$), 1.53 (d, 3H, J= 7.0 Hz, C_3-C$\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 169.34 y 166.40 (C_2, C_5), 136.29 (C_{7a}'), 127.68 (C_{3a}'), 124.54 (C_2'), 122.76 (C_5'), 120.30 (C_4'), 119.20 (C_6'), 111.37 (C_3'), 110.08 (C_7'), 53.45 (C_6), 51.79 (C_3), 40.81 (indole-$\underline{C}H_2$-N), 22.48 ($C_3\underline{C}H_3$), 19.14 ($C_6\underline{C}H_3$) ppm. IR (KBr) ν: 3403 (NH), 3264 (NH), 1679 (C=O), 1648 (C=O), 743 cm^{-1}. Anal. calcd. for $C_{15}H_{17}N_3O_2$: C, 66.42; H, 6.27; N, 15.49. Found: C, 66.68; H, 6.46; N, 15.50.

2-(3-Indolylmethyl)-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione derivatives (3). ***a) General synthesis of iminoethers.***

To a solution of piperazinediones **10** (3.5 mmol) in dichloromethane (20 ml), triethyloxonium tetrafluoroborate (7 mmol) and anhydrous sodium carbonate (14 mmol) were added. After stirring the mixture at room temperature in argon atmosphere for 24 hours, it was poured into ice water, and the aqueous phase was extracted with chloroform or dichloromethane. The organic layers were dried (Na_2SO_4), and the solvent evaporated under reduced presssure. The crude iminoethers thus obtained were used for further reactions, but samples for analytical purposes were obtained by chromatography on silica gel eluting with dichloromethane.

b) Synthesis of compounds (3).

A mixture of the above iminoethers (0.35 mmol) and anthranilic acid (0.7 mmol) was heated at 140 °C for 2 hours under argon stream. After cooling, the melt was treated with aqueous ammonia and extracted with chloroform. The organic layers was dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographied in silica gel eluting with dichloromethane.

Data for **3a**: Yield, 41 mg (30%). Mp, 105-107 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.26 (d, 1H, J= 7.9 Hz, C_7-H), 8.18 (broad s, 1H, indole-NH), 7.75-7.63 (m, 2H, C_4'-H, C_9-H), 7.55 (d, 1H, J= 8.0 Hz, C_{10}-H), 7.46 (t, 1H, J= 8.0 Hz, C_8-H), 7.39 (d, 1H, J= 8.0 Hz, C_7'-H), 7.21-7.09 (m, 3H, C_2'-H, C_5'-H, C_6'-H), 5.53 (q, 1H, J= 7.1 Hz, C_4-H), 5.22, 4.62 (AB system, 2H, J= 14.7 Hz, indole-C$\underline{H}_2$-N), 4.39 (s, 2H, , C_1-H), 1.55 (d, 3H, J= 7.1 Hz, C_4-C$\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 167.19 (C_3) y 160.00 (C_6), 148.42 (C_{11a}), 147.25 (C_{10a}), 136.50 (C_{7a}'), 134.85 (C_9), 127.27, 127.01, 126.88, 124.57, 122.95, 120.48, 119.28 (C_2', C_{3a}', C_4', C_5' , C_6', C_{6a}, C_7, C_8, C_{10}) 111.48 (C_7'), 110.06 (C_3'), 52.44 (C_4), 48.74 (C_1), 41.09 (indole-$\underline{C}H_2$-N), 17.17 (C_4-$\underline{C}H_3$) ppm. IR (KBr) ν: 3304, 1662, 1608, 745 cm^{-1}. Anal. calcd. for $C_{21}H_{18}N_4O_2$: C, 70.39; H, 5.02; N, 15.64. Found: C, 70.12; H, 4.87; N, 15.25.

Data for **3b**: Yield, 41 mg (30%). Mp, 105-107 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.26 (d, 1H, J= 7.9 Hz, C_7-H), 8.18 (broad s, 1H, indole-NH), 7.75-7.63 (m, 2H, $C_{4'}$-H, C_9-H), 7.55 (d, 1H, J= 8.0 Hz, C_{10}-H), 7.46 (t, 1H, J= 8.0 Hz, C_8-H), 7.39 (d, 1H, J= 8.0 Hz, $C_{7'}$-H), 7.21-7.09 (m, 3H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 5.53 (q, 1H, J= 7.1 Hz, C_4-H), 5.22, 4.62 (AB system, 2H, J= 14.7 Hz, indole-C$\underline{H}_2$-N), 4.40 (d, 2H, C_1-H), 1.55 (d, 3H, J= 7.1 Hz, C_4-C$\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 167.19 (C_3) y 160.00 (C_6), 148.42 (C_{11a}), 147.25 (C_{10a}), 136.50 ($C_{7a'}$), 134.85(C_9), 127.27, 127.01, 126.88, 124.57, 122.95, 120.48, 119.28 ($C_{2'}$, $C_{3a'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, C_{6a}, C_7, C_8, C_{10}) 111.48 ($C_{7'}$), 110.06 ($C_{3'}$), 52.44 (C_4), 48.74 (C_1), 41.09 (indole-$\underline{C}H_2$-N), 17.17 (C_4-CH_3) ppm. IR (KBr) ν: 3316, 1661, 1607, 745 cm^{-1}. Anal. calcd. for $C_{21}H_{18}N_4O_2$: C, 70.39; H, 5.02; N, 15.64. Found: C, 70.13; H, 4.77; N, 15.35.

Data for **3c**: Yield, 26 mg (16%). Mp, 92-94 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.27 (d, 1H, J= 7.9 Hz, C_7-H), 8.22 (broad s, 1H, indole-NH), 7.76-7.70 (m, 2H, $C_{4'}$-H, C_9-H), 7.56 (d, 1H, J= 8.0 Hz, C_{10}-H), 7.47 (t, 1H, J= 8.0 Hz, C_8-H), 7.39 (d, 1H, J= 7.9 Hz, $C_{7'}$-H), 7.24-7.14 (m, 3H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 5.36 (d, 1H, J= 7.8 Hz, C_4-H), 5.26, 4.57 (AB system, 2H, J= 14.6, indole-C$\underline{H}_2$-N), 4.47, 4.40 (AB system, 2H, J= 17.4 Hz, C_1-H), 2.17 (m, 1H, C_4-C$\underline{H}$(CH_3)$_2$), 1.05, 1.02 (2 d, 6H, J= 7.0 Hz, C_4-CH(C$\underline{H}_3$)$_2$ diastereotopics) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 165.60 (C_3) y 160.00 (C_6), 151.87 (C_{11a}), 146.90 (C_{10a}) 136.53 ($C_{7a'}$), 134.84 (C_9), 127.27, 127.23, 126.78, 124.62, 122.88, 120.35, 119.37 ($C_{2'}$, $C_{3a'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, C_{6a}, C_7, C_8, C_{10}), 111.22 ($C_{7'}$), 110.23 ($C_{3'}$), 61.18 (C_4), 49.96 (C_1), 40.95 (indole-$\underline{C}H_2$-N), 32.11 (C_4-$\underline{C}$H(CH_3)$_2$), 19.75, 18.38 (C_4-CH($\underline{C}H_3$)$_2$) ppm. IR (KBr) ν: 3407 (NH), 1662 (C=O), 1607, 746 cm^{-1}. Anal. calcd. for $C_{23}H_{22}N_4O_2$: C, 71.50; H, 5.69; N, 14.50. Found: C, 69.22; H, 5.93; N, 12.18.

Data for **3d**: Yield, 23 mg (16%). Mp, 107-109 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.25 (d, 1H, J= 7.8 Hz, C_7-H), 8.19 (broad s, 1H, indole-NH), 7.74-7.68 (m, 2H, $C_{4'}$-H, C_9-H), 7.51 (d, 1H, J= 8.1 Hz, C_{10}-H), 7.45 (t, 1H, J= 8.1 Hz, C_8-H), 7.37 (d, 1H, J= 7.9 Hz, $C_{7'}$-H), 7.24-7.09 (m, 3H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 5.36, 4.12 (AB system, 2H, J= 18.3 Hz, indole-C$\underline{H}_2$-N), 5.26, 4.59 (AB system, 2H, J= 14.8 Hz, C_4-$\underline{H}$), 4.65 (q, 1H, J= 7.1 Hz, C_1-$\underline{H}$), 1.45 (d, 3H, J= 7.1 Hz, C_1-C$\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 165.51 (C_3), 160.39 (C_6), 151.94 (C_{11a}), 146.90 (C_{10a}), 136.33 ($C_{7a'}$), 134.71(C_9), 127.27, 126.83, 126.81, 124.39, 122.78, 120.34, 119.14 ($C_{2'}$,$C_{3a'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, C_{6a}, C_7, C_8, C_{10}), 111.27 ($C_{7'}$), 110.25 ($C_{3'}$), 55.60 (C_1), 44.58 (C_4), 39.10 (indole-$\underline{C}H_2$-N), 19.18 (C_1-$\underline{C}H_3$) ppm. IR (KBr) ν: 3350 (NH), 1656 (C=O), 749 cm^{-1}. Anal. calcd. for $C_{21}H_{18}N_4O_2$: C,70.39; H, 5.02; N, 15.64. Found: C, 69.89; H, 5.50; N, 13.46.

Data for **3e**:Yield, 21 mg (16%). Mp, 120-122 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.25 (d, 1H, J= 7.8 Hz, C_7-H), 8.19 (broad s, 1H, indole-NH), 7.74-7.68 (m, 2H, $C_{4'}$-H, C_9-H), 7.51 (d, 1H, J= 8.1 Hz, C_{10}-H), 7.45 (t, 1H, J= 8.1 Hz, C_8-H), 7.37 (d, 1H, J= 7.9 Hz, $C_{7'}$-H), 7.24-7.09 (m, 3H, $C_{2'}$-H, $C_{5'}$-H, $C_{6'}$-H), 5.41 (q, 1H, J= 7.1 Hz, C_4-H), 5.56, 4.37 (AB system, 2H, J= 14.9 Hz, indole-C$\underline{H}_2$-N), 4.67 (q, 1H, J= 7.1 Hz, C_1-$\underline{H}$), 1.78 (d, 3H, J= 7.1 Hz, C_4-C$\underline{H}_3$), 1.68 (d, 3H, J= 7.1 Hz, C_1-C$\underline{H}_3$) ppm. ^{13}C-RMN (63 MHz, $CDCl_3$) δ: 165.58 (C_3), 159.58 (C_6), 152.12 (C_{11a}), 146.90 (C_{10a}), 136.32 ($C_{7a'}$), 134.65 (C_9), 127.76, 126.56, 126.44, 126.02, 125.89, 121.37, 119.76, 118.94, 118.52 ($C_{2'}$, $C_{3a'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, C_{6a}, C_7, C_8, C_{10}), 111.56 ($C_{7'}$), 108.75 ($C_{3'}$), 54.04 (C_1), 51.74 (C_4), 37.90 (indole-$\underline{C}H_2$-N), 20.95 (C_4-$\underline{C}H_3$), 18.41 (C_1-$\underline{C}H_3$) ppm. IR (KBr) ν: 3418 (NH), 1662 (C=O), 1609, 749 cm^{-1}. Anal. calcd. for $C_{22}H_{20}N_4O_2$: C, 70.96; H, 5.37; N, 15.05. Found: C, 70.86; H, 5.59; N, 14.87.

2-(1-Acetyl-3-indolylmethyl)-2,4-dihydro-1*H*-pirazino[2,1-*b*]quinazoline-3,6-dione derivatives (4).

A solution of compounds **3** (0.56 mmol) and pyridine (1.12 mmol) in acetic anhydride (25 ml) was refluxed at 160 ºC for 4 hours. Evaporation of the solvent gave a residue which was chromatographied in silica gel eluting with a gradient of ethyl acetate/methanol from (1:0) to (1:1) to afford **4**.

Data for **4a**: Yield, 170 mg (76%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.39 (d, 1H, J= 7.9 Hz, $C_{2'}$-H), 8.24 (d, 1H, J= 7.7 Hz, $C_{7'}$-H), 7.74-7.24 (m, aromatics 7H), 5.53 (q, 1H, J= 7.1 Hz, C_4-H), 5.11, 4.60 (AB system, 2H, J= 14.7 Hz, indole-C$\underline{H}_2$N), 4.3 (s, 2H, C_1-H), 2.63 (s, 3H, CH_3-CO), 1.54 (d, 3H, J= 7.1 Hz, C_4-C$\underline{H}_3$) ppm. IR (KBr) ν: 3409, 3299, 3056, 1733, 1656, 1607, 744 cm^{-1}. MS m/e 400 (M^+), 358, 280, 229, 130 (100%), 102, 60.

Data for **4b**: Yield, 167 mg (75%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.33 (d, 1H, J= 7.9 Hz, $C_{2'}$-H), 8.17 (d, 1H, J= 7.9 Hz, $C_{7'}$-H), 7.70-7.08 (m, aromatics 7H), 5.51 (q, 1H, J= 7.2 Hz, C_4-H), 5.06, 4.58 (AB system, 2H, J= 14.6 Hz, indole-C$\underline{H}_2$-N), 4.42 (s, 2H, C_1-H), 2.59 (s, 3H, CH_3-CO), 1.51 (d, 3H, J= 7.1 Hz, C_4-C$\underline{H}_3$) ppm. IR (KBr) ν: 3446, 2977, 2932, 1670, 754 cm^{-1}.

Data for **4c**: Yield, 146 mg (69%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.43 (d, 1H, J= 7.9 Hz, $C_{2'}$-H), 8.22 (d, 1H, J= 6.9 Hz, $C_{7'}$-H), 7.76-7.20 (m, aromatics 7H), 5.37 (d, 1H, J= 7.8 Hz, C_4-H), 5.22, 5.17, 4.58, 4.36 (2 AB system, 4H, indole-C$\underline{H}_2$-N and C_1-H), 2.66 (s, 3H, CH_3-CO), 2.20 (m, 1H, C_4-C$\underline{H}$(CH_3)$_2$), 1.05, 1.03 (2 d, 6H, J= 6.9 Hz, C_4-CH(C$\underline{H}_3$)$_2$) ppm. IR (KBr) ν: 3409, 2990, 2922, 1729, 1672, 1609, 743 cm^{-1}.MS m/e 428 (M^+), 327, 285, 268, 130 (100%), 191, 83.

Data for **4d**: Yield, 164 mg (72%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.38 (d, 1H, J= 7.9 Hz, $C_{2'}$-H), 8.24 (d, 1H, J= 7.7 Hz, $C_{7'}$-H), 7.73-7.24 (m, aromatics 7H), 5.39, 4.24 (AB system, 2H, J= 18.3 Hz, indole-C$\underline{H}_2$-N), 5.21, 4.52 (AB system, 2H, J= 19.7 Hz, C_4-H), 4.65 (q, 1H, J= 6.9 Hz, C_1-H), 2.64 (s, 3H, CH_3-CO), 1.50 (d, 3H, J= 6.9 Hz, C_1-C$\underline{H}_3$) ppm. IR(KBr) ν: 3445, 2980, 2927, 1673, 1609, 755 cm^{-1}.

Data for **4e**: Yield, 166 mg (74%). ^{1}H-NMR: (250 MHz, $CDCl_3$) δ: 8.37 (d, 1H, J= 7.9 Hz, $C_{2'}$-H), 8.24 (d, 1H, J= 7.8 Hz, $C_{7'}$-H), 7.73-7.10 (m, aromatics 7H), 5.54-3.64 (m, 4H, indole-C$\underline{H}_2$-N, C_4-H, C_1-H), 2.63 (s, 3H, CH_3-CO), 1.74-1.56 (m, 6H, C_4-C$\underline{H}_3$, C_1-C$\underline{H}_3$) ppm. IR (KBr) ν: 3401, 2984, 2933, 1662, 1604, 750 cm^{-1}.

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