A New Route toward 4-Substituted Pyrazino[2,1-*b*]quinazoline-3,6-dione Systems. Total Synthesis of Glyantrypine

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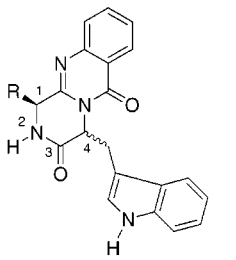
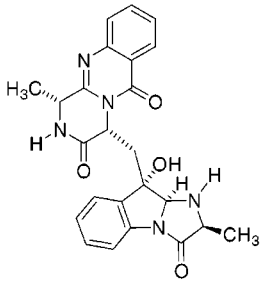
Treatment of sodium *N*-(*o*-azidobenzoyl)aminoacylglycinates **8** with acetic anhydride afforded 1-acetyl-4-(*o*-azidobenzoyl)-2,5-piperazinediones **7**, with complete retention of the stereochemistry. The intramolecular aza Wittig reactions of compounds **7** in the presence of tributylphosphine followed by deacetylation gave 1,2-unsubstituted pyrazino[2,1-*b*]quinazoline-3,6-diones **1**. This route was adapted to the synthesis of both enantiomers of the alkaloid glyantrypine.

Introduction

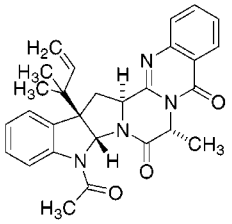
The pyrazino[2,1-*b*]quinazoline-3,6-dione system can be considered as a costrained peptidomimetic and is present in several families of natural products such as the fiscalins,[1] the fumiquinazolines,[2] glyantrypine,[3] and *N*-acetylardeemin.[4] Other natural products, like the asperlicins,[5] vasicinone,[6] and the luotonins,[7] among many others, contain related heteroareno[2,1-*b*]quinazoline substructures. Some of these compounds exhibit very interesting biological properties. For instance, *N*-acetylardeemin is one of the most potent known inhibitors of multidrug resistance to antitumor compounds (MDR), which can be considered as the most important single factor that prevents the success of antitumor chemotherapy in many cancer patients.[8] Because the anti-MDR activity of *N*-acetylardeemin can be ascribed to its pyrazino[2,1-*b*]quinazoline fragment,[9] we became interested in developing new synthetic entries to this ring system. We were particularly interested in the preparation of 1,2-unsubstituted derivatives **1** because of their potential role as starting materials for the synthesis of more complex derivatives with additional rings fused to the 1−2 bond and also to study their anti-MDR properties.



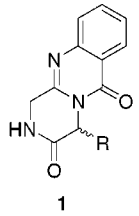
Compuesto	R^1	Conf. C-4
Fiscalin B	iPr	*R*
Glyantrypine	H	Unknown



Fumiquinazoline A



N-Acetylardeemin



1

The currently known syntheses of pyrazino[2,1-*b*]-quinazoline-3,6-dione derivatives can be grouped as follows: (a) Transformation of 4-substituted 2,5-piperazinediones into the corresponding iminoethers[10] or thioiminoethers,[11] followed by cyclocondensation with anthranilic acid or methyl anthranilate. (b) Acylation of 4-substituted 2,5-piperazinediones with *o*-azidobenzoyl chloride, followed by Staudinger reaction with a phosphine to yield the corresponding λ^5-phosphazene and

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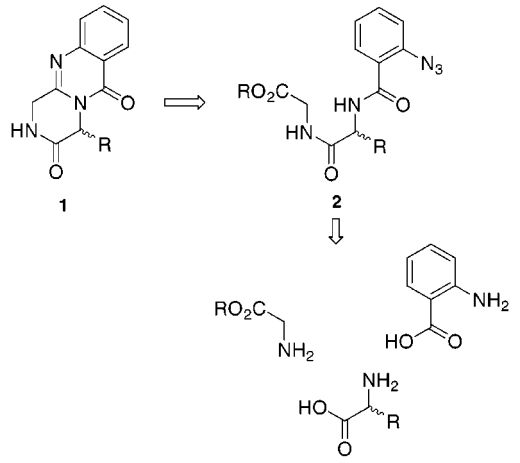
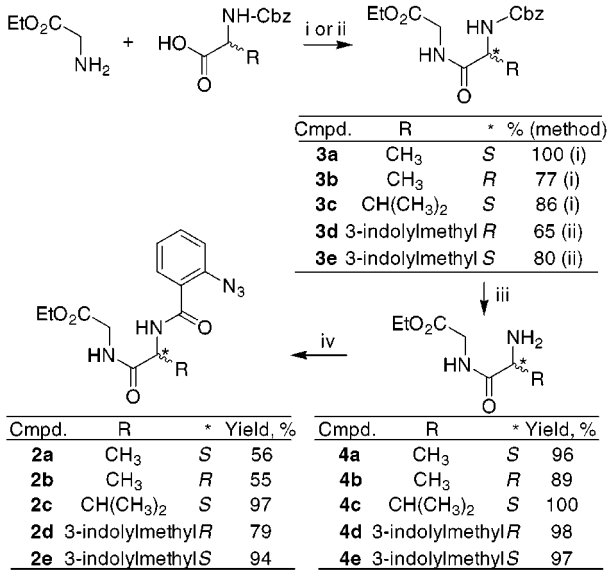
Scheme 1



Scheme 2



Cmpd.	R	*	% (method)
3a	CH_3	*S*	100 (i)
3b	CH_3	*R*	77 (i)
3c	$CH(CH_3)_2$	*S*	86 (i)
3d	3-indolylmethyl	*R*	65 (ii)
3e	3-indolylmethyl	*S*	80 (ii)

Cmpd.	R	*	Yield, %
2a	CH_3	*S*	56
2b	CH_3	*R*	55
2c	$CH(CH_3)_2$	*S*	97
2d	3-indolylmethyl	*R*	79
2e	3-indolylmethyl	*S*	94

Cmpd.	R	*	Yield, %
4a	CH_3	*S*	96
4b	CH_3	*R*	89
4c	$CH(CH_3)_2$	*S*	100
4d	3-indolylmethyl	*R*	98
4e	3-indolylmethyl	*S*	97

subsequent intramolecular aza Wittig cyclization of the latter intermediate.[12,13] These methods lead to 2-substituted derivatives of the desired ring system, and therefore their application to the synthesis of **1** requires troublesome[14] protection and deprotection steps of the starting 2,5-piperazinediones. (c) Cyclization of 4-imino-4*H*-3,1-benzoxazines,[15,16] prepared through cyclodehydration of suitable *o*-acylanthranylamides in the presence of iodine−triphenylphosphine.[17]

Our route to **1** involves the novel retrosynthetic approach summarized in Scheme 1, which is based on the double cyclization of open-chain "tripeptides" **2**, where the anthranilic acid unit is the *N*-terminal residue and bears an azido group as a masked amino function. This strategy allows the use of unprotected glycine derivatives as starting materials and hence leads directly to the target compounds **1**.

Results and Discussion

Starting materials were prepared as shown in Scheme 2. Dipeptides **3** were obtained from ethyl glycinate and the appropriate *N*-Cbz amino acids, using ethyl chloroformate or EDC[18] as the coupling reagent. They were deprotected by catalytic hydrogenation under atmospheric pressure,[19] yielding compounds **4**, which were immediately acylated with *o*-azidobenzoyl chloride to give compounds **2** in good overall yields.

The double cyclization of compounds **2** to the target structures **1** was carried out in two stages, starting from their transformation into 2,5-piperazinedione derivatives. This transformation involves the acylation of an amide group to give an imide, and therefore difficulties were anticipated.[20] Thus, all attempts to cyclize compound **2c** in the presence of a variety of bases, under thermal conditions and under other literature conditions,[21] were unsuccessful. In one of the experiments, exposure of **2c** to an excess of triethylamine in the presence of 4-(dimethylamino)pyridine (DMAP) afforded a small amount (9%) of compound **5**, but this result could not be reproduced. We decided therefore to hydrolyze compounds **2** to the corresponding carboxylic acids **6** and try to activate the carboxylic function. After several failed attempts under varied literature methods,[22−24] we finally achieved moderate success by activation of the carboxylic group through formation of a mixed anhydride in the presence of acetic anhydride at 80 °C. These conditions led also to acetylation of the free nitrogen of the 2,5-piperazinedione structure, affording compounds **7** in ca. 30% yield. During our efforts to improve this result, we found that the sodium salts **8** are soluble in acetic anhydride under our reaction conditions. Their use instead of **6** improved the activation of the carboxylic group and allowed the isolation of compounds **7a**−**c** in 81−97% yields. The efficiency and mildness of the method was confirmed by applying

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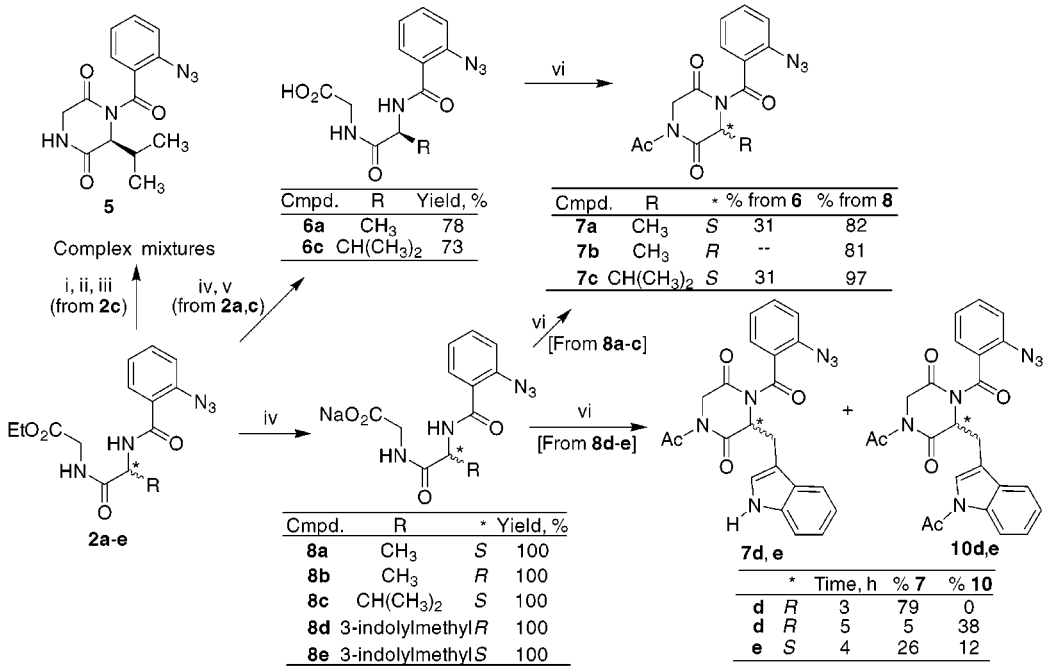
Scheme 3



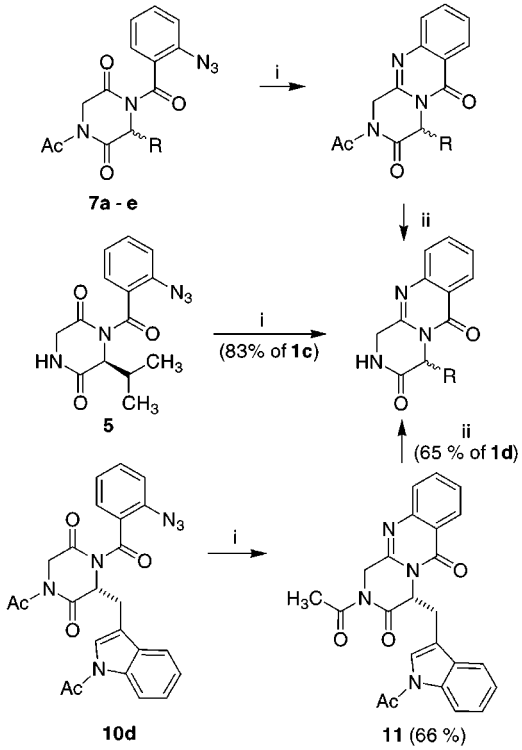
Cmpd.	R	Yield, %
6a	CH_3	78
6c	$CH(CH_3)_2$	73

Cmpd.	R	*	% from **6**	% from **8**
7a	CH_3	*S*	31	82
7b	CH_3	*R*	--	81
7c	$CH(CH_3)_2$	*S*	31	97

Cmpd.	R	*	Yield, %
8a	CH_3	*S*	100
8b	CH_3	*R*	100
8c	$CH(CH_3)_2$	*S*	100
8d	3-indolylmethyl	*R*	100
8e	3-indolylmethyl	*S*	100

	*	Time, h	% **7**	% **10**
d	*R*	3	79	0
d	*R*	5	5	38
e	*S*	4	26	12

Scheme 4



Cmpd.	R	*	Yield, %
9a	CH_3	*S*	78
9b	CH_3	*R*	61
9c	$CH(CH_3)_2$	*S*	93
9d	3-indolylmethyl	*R*	61
9e	3-indolylmethyl	*S*	51

Cmpd.	R	*	Yield, %
1a	CH_3	*S*	66
1b	CH_3	*R*	64
1c	$CH(CH_3)_2$	*S*	71
1d	3-indolylmethyl (-)-glyantrypine	*R*	62
1e	3-indolylmethyl (+)-glyantrypine	*S*	50

it to the synthesis of precursors to both enantiomers of glyantripine, which contain a sensitive tryptophan unit. Thus, treatment of the carboxylic salts **8d**,**e** with acetic anhydride led to mixtures of the corresponding compounds **7d**,**e** and **10d**,**e**, the latter of which was acetylated at the indole nitrogen and was isolated in variable proportions depending on the reaction time (Scheme 3).

The second cyclization to pyrazino[2,1-*b*]quinazoline-3,6-dione derivatives was carried out through a Staudinger−aza Wittig sequence by treatment of compounds **7** with tributylphosphine, which afforded compounds **9** in 51−93% yields. Similarly, the diacetylated derivative **10d** was transformed into compound **11** in 66% yield (Scheme 4). Deacetylation of **9** or **11** to give the target compounds **1** was achieved in good yield by addition of hydrazine hydrate at room temperature. On the other hand, treatment of compound **5** with tributylphosphine led directly to **1c** in 83% yield. Both **1d** and **1e** showed spectral properties identical to those previously described for glyantrypine.[3] Because of the absence of reference data in the literature,[3] we could not use the optical rotation values of our synthetic samples to establish the absolute configuration of natural glyantrypine.

One final issue that needed to be addressed was the integrity of the stereocenter during the series of transformations, particularly during the cyclization step in the presence of acetic anhydride. This was confirmed by the absence of any splitting of the ^{1}H NMR signals of compounds **7d** and **7e** in the presence of 1 equiv of Eu(hfc)$_3$. In a control experiment, a racemic sample prepared by mixing equimolecular amounts of **7d** and **7e** showed a clear separation of most signals under the same conditions.

Experimental Section

All reagents were of commercial quality and were used as received. Solvents 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 aluminum plates coated with silica gel with fluorescent indicator. Separations by flash chromatography were performed on silica gel. Melting points were measured in a hot stage microscope and are uncorrected. Optical rotation values were determined in a polarimeter equipped with a 1 mL cell measuring 10 cm and a thermostated bath, using the emission wavelength of a sodium lamp; concentrations are given in g/100 mL. Infrared spectra were recorded on a FT-IR spectrophotometer, with solid compounds compressed into KBr pellets and liquid compounds examined as films on NaCl disks. NMR spectra were obtained at 250 MHz for ^{1}H and 63 MHz for ^{13}C, with $CDCl_3$ or DMSO-d_6 as solvents (Servicio de Espectroscopía, Universidad Complutense). Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense.

Synthesis of *N*-Cbz Dipeptides. General Procedures. Method A. To a stirred solution of the suitable *N*-Cbz amino acid and triethylamine (1 equiv) in dry $CHCl_3$ (20 mL per g of protected amino acid) was dropwise added ethyl chloroformate (1 equiv) at 0 °C. The solution thus obtained was warmed to room temperature, and a solution of ethyl glycinate hydrochloride (1 equiv) and triethylamine (1 equiv) in dry $CHCl_3$ (20 mL per g of protected amino acid) was added over 30 min. When the addition was complete, the solution was refluxed for 10 min, cooled, and washed with water (3 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated, yielding the analytically pure dipeptides.

Method B. A solution of the *N*-Cbz amino acid, ethyl glycinate hydrochloride (1.1 equiv), and EDC (1.1 equiv) in dry CH_2Cl_2 (25 mL per g of protected amino acid) was stirred at room temperature for 16 h. The suspension was washed sequentially with 1 M aqueous HCl, 1 M aqueous $NaHCO_3$, and water, in volumes equal to that of the CH_2Cl_2 phase; dried (Na_2SO_4); and evaporated, yielding the analytically pure dipeptides.

Ethyl *N*-(Benzyloxycarbonyl)-L-alanylglycinate (3a). Starting from 4.46 g (20 mmol) of *N*-(benzyloxycarbonyl)-L-alanine and using method A, 6.16 g (100%) of **3a** was obtained as a colorless oil that crystallizes from 1:1 AcOEt/Et_2O: mp 96−98 °C; $[\alpha]^{25}_D = +13.3$ (*c* 0.325, $CHCl_3$); IR (KBr) ν 3290, 1732, 1654 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30−7.40 (m, 5H), 6.52 (br. s, 1H), 5.33 (br. s, 1H), 5.10 (AB system, J = 11.7 Hz, 2H), 4.20.4.40 (m, 1H), 4.18 (q, J = 7.0 Hz, 3H), 4.00 (m, 2H), 1.39 (d, J = 7.1 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.6, 169.7 (2 signals), 128.6, 128.4, 128.3, 128.2, 67.2, 61.7, 41.4, 17.3, 14.2 (2 signals). Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.67; H, 6.65; N, 9.03.

Ethyl *N*-(Benzyloxycarbonyl)-D-alanylglycinate (3b). Starting from 3.50 g (15.6 mmol) of *N*-(benzyloxycarbonyl)-D-alanine and using method A, 3.74 g (77%) of **3b** was obtained: mp 95−97 °C; $[\alpha]^{25}_D = -13.2$ (*c* 0.325, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.15; H, 6.74; N, 8.71. Spectral data were identical to those of **3a**.

Ethyl *N*-(Benzyloxycarbonyl)-L-valylglycinate (3c). Starting from 4.0 g (15.9 mmol) of *N*-(benzyloxycarbonyl)-L-valine and using method A, 4.61 g (86%) of **3c** was obtained as white crystals. Starting from 4.0 g (15.9 mmol) of *N*-(benzyloxycarbonyl)-L-valine and using method B, 3.98 g (74%) of **3c** was obtained: mp 143−145 °C; $[\alpha]^{25}_D = +17.1$ (*c* 0.07, $CHCl_3$); IR (KBr) ν 3290, 1748, 1689, 1652 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25−7.40 (m, 5H), 6.42 (br. s, 1H), 5.35 (br. d, J = 8.4 Hz, 1H), 5.05−5.20 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.90−4.15 (m, 3H), 2.17 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.98 and 0.93 (d, J = 6.8 Hz, 3H and d, J = 6.8 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.6, 169.7 (2 signals), 128.6, 128.4, 128.3, 128.2, 67.2, 61.7, 58.2, 41.3, 31.1, 19.3, 14.2. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.76; H, 7.22; N, 8.30.

Ethyl *N*-(Benzyloxycarbonyl)-D-tryptophanylglycinate (3d). Starting from 2.0 g (5.516 mmol) of *N*-(benzyloxycarbonyl)-D-tryptophan and using method B, 1.62 g (65%) of **3d** was obtained as pale yellow crystals: mp 70−72 °C; $[\alpha]^{25}_D = +2.9$ (*c* 0.23, $CHCl_3$); IR (KBr) ν 3314, 1704, 1666 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.60 (d, J = 7.0 Hz, 1H), 7.06−7.34 (m, 9H), 7.01 (s, 1H), 6.33 (br. s, 1H), 4.95−5.15 (m, 2H), 4.40−4.60 (m, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.70−4.95 (m, 2H), 3.25−3.40 (m, 1H), 3.17 (dd, J = 14.4 and 7.2 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.7, 169.5, 156.0, 136.3, 128.6, 128.4, 128.3, 128.2, 127.0, 123.5, 122.3, 119.8, 118.8, 111.4, 110.0, 67.1, 61.6, 55.5, 41.4, 28.5, 14.2. Anal. Calcd for $C_{23}H_{25}N_3O_5$: C, 65.24; H, 5.95; N, 9.92. Found: C, 64.89; H, 5.57; N, 9.93.

Ethyl *N*-(Benzyloxycarbonyl)-L-tryptophanylglycinate (3e). Starting from 0.25 g (0.74 mmol) of *N*-(benzyloxycarbonyl)-L-tryptophan and using method B, 0.25 g (80%) of **3e** was obtained as pale yellow crystals: mp 70−72 °C; $[\alpha]^{25}_D = -3.1$ (*c* 0.215, $CHCl_3$). Anal. Calcd for $C_{23}H_{25}N_3O_5$: C, 65.24; H, 5.95; N, 9.92. Found: C, 64.92; H, 5.86; N, 9.56. Spectral data were identical to those of **3d**.

Deprotection of *N*-Cbz Dipeptides. General Procedure. To a solution of the suitable *N*-Cbz dipeptide **3** in methanol (100 mL) was added 10% Pd−C (0.2 times the weight of protected dipeptide). The suspension was stirred at room temperature for 16 h under a balloon filled with hydrogen. The suspension was filtered through Celite and evaporated, and the residue was crystallized from ethanol.

Ethyl L-Alanylglycinate (4a). Starting from 5.103 g (16.5 mmol) of **3a**, 2.78 g (96%) of **4a** was obtained as pale yellow needles: mp 55−57 °C; $[\alpha]^{25}_D = +8.2$ (*c* 0.535, DMSO); IR (KBr) ν 3329, 2977, 1741, 1661 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72 (br. s, 1H), 4.07 (q, J = 7.3 Hz, 2H), 3.85−3.95 (m, 2H), 3.41 (q, J = 6.8 Hz, 1H), 1.94 (br. s, 2H), 1.21 (d, J = 6.8 Hz, 3H), 1.15 (t, J = 7.3 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 176.0, 170.1, 61.5, 50.7, 41.09, 21.7, 14.6. Anal. Calcd for $C_7H_{14}N_2O_3$: C, 48.26; H, 8.10; N, 16.08. Found: C, 48.60; H, 7.98; N, 15.81.

Ethyl D-Alanylglycinate (4b). Starting from 2.0 g (6.5 mmol) of **3a**, 1.01 g (89%) of **4b** was obtained as pale yellow needles: mp 55−57 °C; $[\alpha]^{25}_D = -7.7$ (*c* 0.535, DMSO). Anal. Calcd for $C_7H_{14}N_2O_3$: C, 48.26; H, 8.10; N, 16.08. Found: C, 48.35; H, 7.72; N, 16.03. Spectral data were identical to those of **4a**.

Ethyl L-Valylglycinate (4c). Starting from 4.61 g (13.7 mmol) of **3c**, 2.73 g (100%) of **4c** was obtained as white needles: mp 140−142 °C; $[\alpha]^{25}_D = +31.6$ (*c* 0.095, DMSO); IR (KBr) ν 3308, 3074, 1746, 1660 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.87 (br. s, 1H), 4.17 (q, J = 7.0 Hz, 2H), 3.90−4.15 (m, 2H), 3.25−3.35 (m, 1H), 2.20−2.40 (m, 1H), 1.59 (br. s, 2H), 1.25 (t, J = 7.0 Hz, 3H), 0.98 and 0.86 (d, J = 6.8 Hz, 3H and d, J = 6.8 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 167.2, 166.0, 59.7, 55.9, 44.0, 32.1, 18.5, 16.9. Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.45; H, 8.97; N, 13.85. Found: C, 52.87; H, 8.81; N, 13.74.

Ethyl D-Tryptophanylglycinate (4d). Starting from 1.201 g (2.84 mmol) of **3d**, 0.8 g (98%) of **4d** was obtained as pale pink needles: mp 90−92 °C; $[\alpha]^{25}_D = +18.0$ (*c* 0.5, DMSO); IR (KBr) ν 3230, 3403, 1735, 1684 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.12 (br. s, 1H), 8.15 (br. s, 2H), 7.70 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.23 (s, 1H), 6.97−7.15 (m, 2H), 4.00−4.15 (m, 3H), 3.80−4.00 (m, 2H),

3.04−3.28 (m, partially overlapped with the water signal, 2H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 169.3, 169.0, 136.2, 127.0, 125.0, 121.0, 118.0, 118.3, 111.3, 106.6, 60.6, 52.4, 40.7, 27.2, 14.0. Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 66.27; H, 6.62; N, 14.52. Found: C, 66.08; H, 6.48; N, 14.32.

Ethyl L-Tryptophanylglycinate (4e). Starting from 1.045 g (2.47 mmol) of **3e**, 0.694 g (97%) of **4e** was obtained as pale pink needles: mp 91−93 °C; $[\alpha]^{25}_D$ = −17.3 (c 0.5, DMSO). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 66.27; H, 6.62; N, 14.52. Found: C, 66.14; H, 6.47; N, 14.26%. Spectral data were identical to those of **4d**.

Acylation of Dipeptides with *o*-Azidobenzoyl Chloride. General Procedure. To a solution of the suitable dipeptide **4** in THF (30 mL) were added Et_3N (1 equiv) and DMAP (0.2 equiv). The solution was stirred at 80 °C for 15 min, under an argon atmosphere, and treated at the same temperature with a solution of *o*-azidobenzoyl chloride[25] (1.2 equiv) in THF (10 mL). The reacting mixture was maintained at 80 °C for a further 3 h and then at room temperature for 16 h (in the case of the indole derivatives **4d**,**e**, the flask was protected from light for the duration of the experiment). The reacting mixture was then filtered and evaporated, and the residue was chromatographed on silica gel, eluting with 6:1 petroleum ether/ethyl acetate.

Ethyl *N*-(*o*-Azidobenzoyl)-L-alanylglycinate (2a). Starting from 3.044 g (17.5 mmol) of **4a**, 3.118 g (56%) of **2a** was obtained as pale brown crystals: mp 88−90 °C; $[\alpha]^{25}_D$ = +9.9 (c 0.21, $CHCl_3$); IR (KBr) ν 3304, 2132, 1747, 1647 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.91 (d, J = 7.5 Hz, 1H), 7.94 (d, J = 7.1 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.15−7.30 (m, 2H), 6.92 (br. s, 1H), 4.70−4.85 (m, 1H), 4.17 (q, J = 7.5 Hz, 2H), 3.95−4.05 (m, 2H), 1.50 (d, J = 7.2 Hz, 3H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.5, 169.7, 164.7, 137.5, 132.8, 132.2, 125.2, 124.4, 118.5, 61.6, 49.5, 41.5, 18.2, 14.2. Anal. Calcd for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93. Found: C, 52.35; H, 5.24; N, 21.57.

Ethyl *N*-(*o*-Azidobenzoyl)-D-alanylglycinate (2b). Starting from 0.95 g (5.46 mmol) of **4b**, 0.963 g (55%) of **2b** was obtained, as white crystals: mp 87−89 °C; $[\alpha]^{25}_D$ = −10.2 (c 0.21, $CHCl_3$); Anal. Calcd for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93. Found: C, 52.34; H, 5.25; N, 21.74. Spectral data were identical to those of **2a**.

Ethyl *N*-(*o*-Azidobenzoyl)-L-valylglycinate (2c). Starting from 1.2 g (6.03 mmol) of **4c**, 2.027 g (97%) of **2c** was obtained as pale brown crystals: mp 98−100 °C; $[\alpha]^{25}_D$ = +1.4 (c 0.12, $CHCl_3$); IR (KBr) ν 3309, 2131, 1748, 1641 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.08 (d, J = 7.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.48 (t, J = 8.2 Hz, 1H), 7.18−7.30 (m, 2H), 6.76 (br. s, 1H), 4.56 (t, J = 7.0 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.95−4.15 (m, 2H), 2.27−2.40 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.8 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.3, 169.6, 164.9, 137.3, 132.7, 132.2, 125.2, 124.5, 118.4, 61.5, 59.2, 41.4, 30.7, 19.4, 18.1, 14.1. Anal. Calcd for $C_{16}H_{21}N_5O_4$: C, 55.32; H, 6.09; N, 20.16. Found: C, 55.67; H, 5.82; N, 19.81.

Ethyl *N*-(*o*-Azidobenzoyl)-D-tryptophanylglycinate (2d). Starting from 0.86 g (2.97 mmol) of **4d**, 1.02 g (79%) of **2d** was obtained as pale brown crystals: mp 57−59 °C; $[\alpha]^{25}_D$ = + 56.3 (c 0.19, $CHCl_3$); IR (KBr) ν 3406, 2131, 1736, 1644 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.00−8.15 (m, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.0 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.00−7.20 (m, 4H), 6.60 (t, J = 5.1 Hz, 1H), 4.97 (q, J = 7.0 Hz, 1H), 3.78−4.02 (m, 2H), 3.91 (t, J = 5.2 Hz, 2H), 3.46 (dd, J = 14.6 and 5.5 Hz, 1H), 3.27 (dd, J = 14.6 and 7.1 Hz, 1H), 1.19 (t, J = 7,0 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.7. 169.5, 164.8, 137.5, 136.2, 132.8, 132.2, 127.6, 125.1, 124.2, 123.6, 122.3, 119.8, 118.9, 118.4, 111.3, 110.5, 61.6, 52.8, 41.6, 27.8, 14.2. Anal. Calcd for $C_{22}H_{22}N_6O_4$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.65; H, 4.97; N, 19.04.

Ethyl *N*-(*o*-Azidobenzoyl)-L-tryptophanylglycinate (2e). Starting from 0.673 g (2.32 mmol) of **4e**, 0.956 g (94%) of **2e** was obtained as pale brown crystals: mp 57−59 °C; $[\alpha]^{25}_D$ = −54.1 (c = 0.2, $CHCl_3$). Anal. Calcd for $C_{22}H_{22}N_6O_4$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.57; H, 4.89; N, 19.57. Spectral data were identical to those of **2d**.

(3*S*)-4-(*o*-Azidobenzoyl)-3-isopropyl-2,5-piperazinedione (5). To a solution of **2c** (0.17 g, 0.5 mmol) in dry THF (25 mL) and under an argon atmosphere were added Et_3N (0.44 mL, 1.5 mmol) and DMAP (6 mg, 0.05 mmol). The solution was stirred at 80 °C for 3 h and then at room temperature for 16 h. The solvent was evaporated, and the residue was chromatographed on silica gel, eluting with 6:1 petroleum ether/ethyl acetate to yield 0.014 g (9%) of compound **5**, as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 (t, J = 7.2 Hz, 1H), 7.15−7.30 (m, 4H), 4.13 and 3.68 (AB quartet, J = 17.4 Hz, 2H), 3.54 (d, J = 3.8 Hz, 1H), 2.15−2.34 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H).

Hydrolysis of Compounds (2). General Procedures. Preparation of Sodium Salts (8). To a solution of the suitable compound **2** in MeOH (15 mL per g of **2**) was added 0.5 N aqueous NaOH (1 equiv), and the solution was heated at 50 °C for 2 h. Evaporation of the solvent afforded the sodium salts **8**.

Sodium *N*-(*o*-Azidobenzoyl)-L-alanylglycinate (8a). Starting from 0.933 g (2.92 mmol) of **2a**, 0.915 g (100%) of **8a** was obtained: mp 101−103 °C; $[\alpha]^{25}_D$ = +17.3 (c 0.185, DMSO); IR (KBr) ν 3352, 2132, 1631, 1600 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.69 (d, J = 7.6 Hz, 1H), 7.60−7.51 (m, 3H), 7.34 (d, J = 7.9 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 4.31−4.50 (m, 1H), 3.38−3.33 (m, 2H), 1.27 (d, J = 7,1 Hz, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 172.1, 168.5, 164.9, 136.7, 131.6, 131.3, 124.8, 122.6, 116.0, 53.1, 43.9, 16.9. Anal. Calcd for $C_{12}H_{12}N_5O_4$-Na: C, 46.01; H, 3.86; N, 22.36. Found: C, 46.12; H, 4.09; N, 21.99.

Sodium *N*-(*o*-Azidobenzoyl)-D-alanylglycinate (8b). Starting from 0.70 g (2.19 mmol) of **2b**, 0.68 g (100%) of **8b** was obtained: mp 101−103 °C; $[\alpha]^{25}_D$ = −17.8 (c 0.185, DMSO). Anal. Calcd for $C_{12}H_{12}N_5O_4Na$: C, 46.01; H, 3.86; N, 22.36. Found: C, 45.96; H, 4.08; N, 21.93%. Spectral data were identical to those of **8a**.

Sodium *N*-(*o*-Azidobenzoyl)-L-valylglycinate (8c). Starting from 1.026 g (2.95 mmol) of **2c**, 1.00 g (100%) of **8c** was obtained: mp 127−129 °C; $[\alpha]^{25}_D$ = +50.0 (c 0.05, DMSO); IR (KBr) ν 3299, 2132, 1632 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.42 (d, J = 7.5 Hz, 1H), 8.31 (s, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.42 (br. s, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 4.25−4.38 (m, 1H), 3.26−3.36 (m, 2H), 2.05−2.25 (m, 1H), 0.89 (d, J = 7.0 Hz, 6H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 176.5, 171.6, 165.1, 136.6, 132.1, 131.8, 125.0, 124.0, 117.6, 59.8, 43.6, 30.6, 19.3, 18.3. Anal. Calcd for $C_{14}H_{16}N_5O_4Na$: C, 49.27; H, 4.73; N, 20.52. Found: C, 48.93; H, 4.89; N, 20.65.

Sodium *N*-(*o*-Azidobenzoyl)-D-tryptophanylglycinate (8d). Starting from 1.02 g (2.35 mmol) of **2d**, 1.00 g (100%) of **8d** was obtained: mp 108−110 °C; $[\alpha]^{25}_D$ = +28.7 (c 0.115, DMSO); IR (KBr) ν 3402, 2131, 1636 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.58 (d, J = 7.9 Hz, 1H), 7.15−7.59 (m, 8H), 7.03 (t, J = 6.9 Hz, 1H), 6.96 (t, J = 6.9 Hz, 1H), 4.59−4.70 (m, 1H), 3.27−2.99 (m, 4H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 170.5, 169.9, 165.1, 136.7, 136.0, 131.5, 129.7, 127.4, 127.3, 124.6, 123.5, 120.7, 119.2, 118.2, 118.1, 111.2, 110.3, 54.4, 44.2, 27.3. Anal. Calcd for $C_{20}H_{17}N_6O_4Na$: C, 56.08; H, 4.00; N, 19.62. Found: C, 55.73; H, 4.32; N, 19.73.

Sodium *N*-(*o*-Azidobenzoyl)-L-tryptophanylglycinate (8e). Starting from 0.367 g (0.84 mmol) of **2e**, 0.360 g (100%) of **8e** was obtained: mp 110−112 °C. $[\alpha]^{25}_D$ = −28.8 (c 0.115, DMSO). Anal. Calcd for $C_{20}H_{17}N_6O_4Na$: C, 56.08; H, 4.00; N, 19.62. Found: C, 55.74; H, 4.40; N, 19.53. Spectral data were identical to those of **8d**.

Preparation of Carboxylic Acids (6). To a solution of the suitable salt **8** in water (15 mL per g of salt) was added 1 N aqueous HCl (1 equiv), and the solution was stirred at room temperature for 15 min and then left to stand for 5 min. The precipitated solid was filtered and dried in vacuo.

***N*-(*o*-Azidobenzoyl)-L-alanylglycine (6a).** Starting from 2.339 g (7.47 mmol) of **8a**, 1.705 g (78%), of **6a** was obtained: mp 105−107 °C; $[\alpha]^{25}_D$ = +29.8 (c = 0.205, DMSO); IR (KBr)

(25) Prepared from anthranilic acid as described in Cledera, P.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **1998**, *54*, 12349.

ν 3322, 2135, 1750, 1634 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.58 (d, J = 7.5 Hz, 1H), 8.25 (t, J = 5.0 Hz, 1H), 7.64−7.50 (m, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.24 (t, J = 6.7 Hz, 1H), 4.39−4.57 (m, 1H), 3.70−3.95 (m, 2H), 1.31 (d, J = 7.5 Hz, 3H) (the CO_2H proton was not detected); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.2, 171.0, 164.7, 136.7, 131.6, 129.9, 127.3, 124.7, 119.4, 48.6, 40.7, 18.2. Anal. Calcd for $C_{12}H_{13}N_5O_4$: C, 49.48; H, 4.50; N, 24.04. Found: C, 49.55; H, 4.49; N, 24.04.

***N*-(*o*-Azidobenzoyl)-L-valylglycine (6c).** Starting from 0.3 g (0.88 mmol) of **8c**, 0.219 g (73%) of **6c** was obtained: mp 48−50 °C; $[\alpha]^{25}_D$ = + 58.18 (*c* 0.055, DMSO); IR (KBr) ν 3307, 2131, 1743, 1632 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.04 (br. s, 1H), 8.18 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.35−7.46 (m, 2H), 7.05−7.29 (m, 2H), 4.68 (t, J = 7.3 Hz, 1H), 3.90−4.18 (m, 2H), 2.13−2.32 (m, 1H), 0.99 (d, J = 7.0 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.2, 171.9, 165.4, 137.6, 132.9, 132.2, 125.2, 124.3, 118.6, 59.3, 41.4, 31.3, 19.4, 18.3. Anal. Calcd for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93. Found: C, 53.01; H, 5.26; N, 21.70.

Cyclizations in the Presence of Acetic Anhydride. General Procedure. A solution of the suitable carboxylic acid **6** or sodium salt **8** in acetic anhydride (2.5 mL per 0.1 g of substrate) was stirred in a bath at 80 °C for 3 h. The solution was evaporated, yielding the virtually pure 2,5-piperazinedione derivatives. Analytical samples were obtained by chromatography on silica gel, eluting with 6:1 petroleum ether/ethyl acetate.

(3*S*)-1-Acetyl-4-(*o*-azidobenzoyl)-3-methyl-2,5-piperazinedione (7a). Starting from 0.6 g (1.90 mmol) of **8a**, 0.49 g (82%) of **7a** was obtained. Starting from 0.2 g (0.687 mmol) of **6a**, 0.065 g (31%) of **7a** was obtained: mp 76−78 °C; $[\alpha]^{25}_D$ = −10.7 (*c* 0.055, $CHCl_3$); IR (KBr) ν 2131, 1692 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.59−7.05 (m, 4H), 5.23 (q, 1H, J = 7.2 Hz), 5.10 and 3.99 (AB quartet, 2H, J = 17.5 Hz), 2.62 (s, 3H), 1.64 (d, J = 7.2 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.6, 168.8, 167.4, 165.5, 141.9, 136.9, 132.3, 129.2, 125.2, 118.4, 55.2, 46.2, 27.1, 18.2. Anal. Calcd for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.16; N, 22.21. Found: C, 52.94; H, 4.16; N, 21.99.

(3*R*)-1-Acetyl-4-(*o*-azidobenzoyl)-3-methyl-2,5-piperazinedione (7b). Starting from 0.58 g (1.85 mmol) of **8b**, 0.47 g (81%) of **7b** was obtained: mp 75−77 °C; $[\alpha]^{25}_D$ = +10.9 (*c* 0.055, $CHCl_3$). Anal. Calcd for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.16; N, 22.21. Found: C, 53.65; H, 4.38; N, 22.20. Spectral data were identical to those of **7a**.

(3*S*)-1-Acetyl-4-(*o*-azidobenzoyl)-3-isopropyl-2,5-piperazinedione (7c). Starting from 1.145 g (3.35 mmol) of **8c**, 1.11 g (97%) of **7c** was obtained. Starting from 0.2 g (0.626 mmol) of **6c**, 0.065 g (31%) of **7c** was obtained: mp 72−74 °C; $[\alpha]^{25}_D$ = −4.24 (*c* 0.165, $CHCl_3$); IR (KBr) ν 2127, 1723 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.54−7.11 (m, 4H), 5.11 and 4.03 (AB quartet, J = 20.0 Hz, 2H), 4.93 (d, J = 10 Hz, 1H), 2.63 (s, 3H), 2.05−2.20 (m, 1H), 1.11 and 1.09 (2 d, 6H, J = 7.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.6, 167.4, 167.3, 166.6, 136.8, 136.5, 132.1, 129.3, 125.3, 118.2, 64.0, 46.5, 31.9, 27.2, 19.7, 19.52. Anal. Calcd for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.40. Found: C, 56.25; H, 5.17; N, 20.21.

(3*R*)-1-Acetyl-4-(*o*-azidobenzoyl)-3-(3-indolylmethyl)-2,5-piperazinedione (7d) and (3*R*)-1-Acetyl-4-(*o*-azidobenzoyl)-3-(1-acetyl-3-indolylmethyl)-2,5-piperazinedione (10d). Starting from 0.195 g (0.452 mmol) of **8d**, 0.150 g (79%) of **7d** was obtained after a 3 h reaction. Starting from 0.22 g (0.51 mmol) of **8d**, 0,010 g (5%) of **7d** and 0.063 g (38%) of **10d** were obtained after a 5 h reaction followed by chromatography on silica gel, eluting with 6:1 petroleum ether/ethyl acetate.

7d: mp 53−55 °C; $[\alpha]^{25}_D$ = −39.2 (*c* 0.12, $CHCl_3$); IR (KBr) ν 3405, 2131, 1712 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.03−7.55 (m, 8H), 6.93 (s, 1H), 5.40−5.50 (m, 1H), 4.27 and 2.16 (AB quartet, J = 19.5 Hz, 1H), 3.77 (dd, J = 14.9 and 5.2 Hz, 1H), 3.57 (dd, J = 14.9 and 5.1 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.3, 168.9, 167.9, 136.7, 136.1, 132.0, 128.8, 128.1, 126.7, 125.2, 123.2, 120.5, 118.5, 118.4, 111.7, 108.3, 60.3, 46.1, 29.4, 27.3. Anal. Calcd for $C_{22}H_{18}N_6O_4$: C, 61.39; H, 4.22; N, 19.52. Found: C, 61.09; H, 4.35; N, 19.33.

10d: mp 59−61 °C; $[\alpha]^{25}_D$ = −8.6 (*c* 0.145, $CHCl_3$); IR (KBr) ν 2131, 1711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.45 (d, J = 7.1 Hz, 1H), 6.95−7.50 (m, 8H), 5.40−5.50 (m, 1H), 4.55 and 2.80 (AB quartet, J = 19.5 Hz, 2H); 3.64 (dd, J = 14.9 and 5.2 Hz, 1H), 3.49 (dd, J = 14.9 and 6.1 Hz, 1H), 2.51 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.9 (2 signals), 168.2, 167.3, 166.8, 163.5, 136.5, 135.5, 132.0, 129.3, 128.6 (2 signals), 126.1, 125.6, 125.1, 123.9, 118.3, 116.8, 114.8, 59.1, 46.0, 28.7, 26.9, 23.8. Anal. Calcd. for $C_{24}H_{20}N_6O_5$: C, 61.01; H, 4.27; N, 17.79. Found: C, 60.75; H, 4.23; N, 17.42.

(3*S*)-1-Acetyl-4-(*o*-azidobenzoyl)-3-(3-indolylmethyl)-2,5-piperazinedione (7e) and (3*S*)-1-Acetyl-4-(*o*-azidobenzoyl)-3-(1-acetyl-3-indolylmethyl)-2,5-piperazinedione (10e). Starting from 0.203 g (0.5 mmol) of **8e**, 0.057 g (26%) of **7e** and 0.029 g (12%) of **10e** were obtained after a 4 h reaction followed by chromatography on silica gel, eluting with 6:1 petroleum ether/ethyl acetate.

7e: mp 54−56 °C; $[\alpha]^{25}_D$ = +39.6 (*c* 0.145, $CHCl_3$). Anal. Calcd for $C_{22}H_{18}N_6O_4$: C, 61.39; H, 4.22; N, 19.52. Found: C, 61.14; H, 4.35; N, 19.74. Spectral data were identical to those of **7d**.

10e: mp 60−62 °C; $[\alpha]^{25}_D$ = +8.9 (*c* 0.145, $CHCl_3$). Anal. Calcd for $C_{24}H_{20}N_6O_5$: C, 61.01; H, 4.27; N, 17.79. Found: C, 61.17; H, 4.22; N, 17.28. Spectral data were identical to those of **10d**.

Aza Wittig Cyclizations. General Procedure. A solution of the suitable 2,5-piperazinedione derivative and tributylphosphine (1.1 equiv) in dry toluene (20 mL) was stirred at room temperature for 3 h. After evaporation, the residue was chromatographed on silica gel, eluting with 2:1 petroleum ether/ethyl acetate.

(4*S*)-2-Acetyl-4-methyl-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (9a). Starting from 0.063 g (0.2 mmol) of **7a**, 0.042 g (78%) of **9a** was obtained: mp 126−128 °C; $[\alpha]^{25}_D$ = −2.2 (*c* 0.135, $CHCl_3$); IR (KBr) ν 1698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.31 (d, J = 7.5 Hz, 1H), 7.83−7.44 (m, 3H), 5.60−5.75 (m, 1H), 5.60 and 4.44 (AB quartet, J = 17.5 Hz, 2H), 2.60 (s, 3H), 1.71 (d, J = 6.9 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.7, 169.2, 168.0, 150.4 (2 signals), 135.7, 128.6, 127.6, 127.0, 120.4, 44.8, 31.0, 25.6, 19.6. Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.60. H, 4.79; N, 15.23.

(4*R*)-2-Acetyl-4-methyl-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (9b). Starting from 0.200 g (0.07 mmol) of **7b**, 0.104 g (61%) of **9b** was obtained: mp 127−129 °C; $[\alpha]^{25}_D$ = +2.2 (*c* 0.135, $CHCl_3$). Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.64. H, 4.72; N, 15.16. Spectral data were identical to those of **9a**.

(4*S*)-2-Acetyl-4-isopropyl-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (9c). Starting from 0.150 g (0.438 mmol) of **7c**, 0.122 g (93%) of **9c** was obtained: mp 62−64 °C; $[\alpha]^{25}_D$ = −7.3 (*c* 0.055, $CHCl_3$); IR (KBr) ν 1688 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.26 (d, J = 7.5 Hz, 1H), 7.85−7.47 (m, 3H), 5.61 and 4.50 (AB quartet, J = 17.5 Hz, 2H), 5.36 (d, J = 10.0 Hz, 1H), 2.61 (s, 3H), 2.15−2.35 (m, 1H), 1.15 and 1.00 (d, J = 6.5 Hz, 3H and d, J = 6.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.6, 167.3, 160.6, 148.1, 146.1, 135.1, 127.7, 127.3, 127.3, 120.3, 62.6, 45.4, 31.2, 27.3, 19.7, 19.6. Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 63.91; H, 5.45; N, 14.40.

(4*R*)-2-Acetyl-4-(3-indolylmethyl)-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (9d). Starting from 0.035 g (0.081 mmol) of **7d**, 0.019 g (61%) of **9d** was obtained: mp 56−58 °C; $[\alpha]^{25}_D$ = −210 (*c* 0.02, $CHCl_3$); IR (KBr) ν 3399, 1708, 1684 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.33 (d, J = 7.5 Hz, 1H), 8.11 (s, 1H), 7.77 (t, J = 7.1 Hz, 1H), 7.49−7.58 (m, 2H), 7.23−7.31 (m, 2H), 7.11 (t, J = 6.9 Hz, 1H), 6.90 (t, J = 7.1 Hz, 1H), 6.69 (d, J = 2.5 Hz, 1H), 5.78−5.85 (m, 1H), 4.82 and 2.63 (AB quartet, J = 17.5 Hz, 2H), 3.75 (dd, J = 15.0 and 2.5 Hz, 1H), 3.63 (dd, J = 15.0 and 7.5 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3, 164.4, 162.3, 148.3, 147.3, 137.0, 135.0, 126.0, 127.3, 127.1, 126.8, 123.0 (2 signals), 120.3, 120.1, 117.9, 111.5, 107.6, 58.6, 45.1, 27.9, 27.1. Anal. Calcd for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50. Found: C, 68.33; H, 4.40; N, 14.41.

(4*S*)-2-Acetyl-4-(3-indolylmethyl)-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (9e). Starting from 0.1 g (0.23 mmol) of **7e**, 0.046 g (51%) of **9e** was obtained: mp 56−58 °C; $[\alpha]^{25}_D$ = +206 (*c* 0.02, $CHCl_3$). Anal. Calcd for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50. Found: C, 68.47; H, 5.01; N, 14.29. Spectral data were identical to those of **9d**.

(4*R*)-2-Acetyl-4-(1-acetyl-3-indolylmethyl)-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (11). Starting from 0.048 g (0.101 mmol) of **10d**, 0.029 g (66%) of **11** was obtained: mp 62−64 °C; $[\alpha]^{25}_D$ = − 30.0 (*c* 0.01, $CHCl_3$); IR (KBr) ν 1711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.1 Hz, 1H), 8.28 (d, *J* = 7.1 Hz, 1H), 7.78 (t, *J* = 7.1 Hz, 1H), 7.53−7.63 (m, 2H), 7.23−7.36 (m, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.04 (s, 1H), 5.82−5.92 (m 1H), 4.82 and 3.46 (AB quartet, *J* = 17.5 Hz, 2H), 3.10−3.50 (m, 2H), 2.52 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.2, 168.1, 160.2 (2 signals), 147.6, 147.2, 135.8, 135.4, 124.4, 127.2, 126.9, 126.2, 124.2, 124.1, 120.2, 118.2, 117.9, 111.6, 107.3, 57.7, 40.9, 27.1, 24.0 and 23.9. Anal. Calcd for $C_{24}H_{20}N_4O_4$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.74; H, 4.76: N, 12.82.

(4*R*)-4-Isopropyl-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione (1c). Starting from 0.014 g (0,046 mmol) of **5**, 0.010 g (83%) of **1c** was obtained, as an oil (see data below).

Deacetylations with Hydrazine. General Procedure. 80% Hydrazine hydrate (2 equiv) was added to a solution of the starting acetyl derivative in DMF (20 mL). The solution was stirred at room temperature for 3 h, poured on ice water (20 mL), and extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated.

(4*S*)-4-Methyl-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione (1a). Starting from 0.055 g (0.20) mmol of **9a**, 0.030 g (66%) of **1a** was obtained, as an oil: $[\alpha]^{25}_D$ = +35.0 (*c* 0.185, DMSO); IR (KBr) ν 3281, 1682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.5 Hz, 1H), 7.90−6.90 (m, 4H), 5.40 (q, *J* = 7.1 Hz, 1H), 4.63 (d, *J* = 15.0 Hz, 1H) and 4.23 (dd, *J* = 15.0 and 4.8 Hz, 2H), 1.62 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.3, 160.3, 147.8, 147.2, 134.9, 127.4, 127.0 (2 signals), 120.3, 45.08, 29.2, 17.0. Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.60; H, 5.14; N, 18.54.

(4*R*)-4-Methyl-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione (1b). Starting from 0.057 g (0.21) mmol of **9b**, 0.031 g (64%) of **1b** was obtained, as an oil: $[\alpha]^{25}_D$ = −35.0 (*c* 0.185, DMSO). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.66; H, 5.07; N, 18.35. Spectral data were identical to those of **1a**.

(4*S*)-4-Isopropyl-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]-quinazoline-3,6-dione (1c). Starting from 0.166 g (0.56 mmol) of **9c**, 0.100 g (71%) of **1c** was obtained, as an oil. $[\alpha]^{25}_D$ = +50.0 (*c* 0.01, DMSO); IR (KBr) ν 3241, 1683 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.5 Hz, 1H), 7.79−7.46 (m, 3H), 6.73 (br. s, 1H), 5.25 (d, *J* = 7.5 Hz, 1H), 4.70 (d, *J* = 17.1 Hz, 1H), 4.43 (dd, *J* = 17.1 and 5.3 Hz, 2H), 2.10−2.40 (m, 1H) 1.06 and 0.94 (d, *J* = 7.5 Hz, 3H and d, *J* = 6.7 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.1, 160.8, 148.6, 147.0, 134.9, 127.3, 127.2, 126.9, 120.3, 60.8, 45.4, 31.8, 19.9 and 18.9. Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.75; H, 5.71; N, 16.63.

(4*R*)-4-(3-Indolylmethyl)-1,2,3,4-tetrahydro-5*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione (1d) [(−)-Glyantrypine]. Starting from 0.030 g (0.077 mmol) of **9d**, 0.016 g (62%) of **1d** was obtained. Starting from 0.023 g (0.053 mmol) of **11d**, 0.012 g (65%) of **1d** was obtained: mp 86−88 °C; $[\alpha]^{25}_D$ = −150.5 (*c* 0.105, DMSO); IR (KBr) ν 3273, 1683 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.34 (s, 1H), 8.20 (d, *J* = 10.0 Hz, 1H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.50−7,62 (m, 2H), 7.20−7.35 (m, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 2.5 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 5.25 (t, *J* = 6.0 Hz, 1H), 3.80 (dd, *J* = 17.2 and 5.1 Hz), 3.33−3.42 (m, 2H), 3.04 (d, *J* = 17.2 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.5, 159.8, 149.2, 146.9, 135.9, 134.6, 127.0, 126.6, 126.5, 126.2, 124.3, 121.1, 119.8, 118.5, 117.7, 111.3, 107.7, 56.4, 43.7, 26.4. Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.73; H, 4.94; N, 16.57.

(4*S*)-4-(3-Indolylmethyl)-1,2,3,4-tetrahydro-5*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione (1e) [(+)-Glyantrypine]. Starting from 0.023 g (0.059 mmol) of **9e**, 0.010 g (50%) of **1e** was obtained: mp 86−87 °C; $[\alpha]^{25}_D$ = +150.1 (*c* 0.105, DMSO). Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.55; H, 5.18; N, 16.93. Spectral data were identical to those of **1d** and those found in ref 3.

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