Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 2762–2771
Tetrahedron
www.elsevier.com/locate/tet

Atom-efficient synthesis of 2,6-diazacyclophane compounds through alcoholysis/reduction of 3-nitroarylmethylene-2,5-piperazinediones

Juan Francisco González, Elena de la Cuesta, Carmen Avendaño*

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

Received 4 October 2007; received in revised form 9 January 2008; accepted 11 January 2008
Available online 16 January 2008

Abstract

Readily available cyclic dehydrodipeptides are convenient starting materials for atom-efficient synthesis of different compounds. A one-pot ring-opening/alcoholysis/hydrolysis process with 3-nitroarylmethylene-2,5-piperazinediones yielded *N*-3-nitroarylpyruvoylamino esters, which gave the corresponding amines by reduction of the nitro group. In the case of 2-nitroaryl compounds, an intramolecular reductive amination afforded *N*-indole-2-carbonylamino esters, while the intermolecular reductive amination of 3- and 4-nitroaryl derivatives allowed the synthesis of 2,6-diazacyclophanes. The amino compounds may be coupled with amino acids to get peptide-like derivatives.

Keywords: Cyclic dehydrodipeptides; Methanolysis; Azacyclophanes; Peptide-like compounds; Indoles; α-Ketoamides

1. Introduction

3-Arylmethylene-2,5-piperazinediones may be obtained by cyclization of *N*-haloacetyldehydroamino esters[1] and, most generally, by an aldol-type reaction between an aromatic aldehyde and *N*-acetyl or *N*,*N*′-diacetyl-2,5-piperazinediones.[2] Many of these compounds and their 3,6-bis-arylmethylene derivatives are natural products with interesting biological activity,[3] and they are also versatile synthetic reagents used as chiral templates in the synthesis of α-amino acids[4] and as starting materials to antitumor antibiotics of the saframycins family.[5]

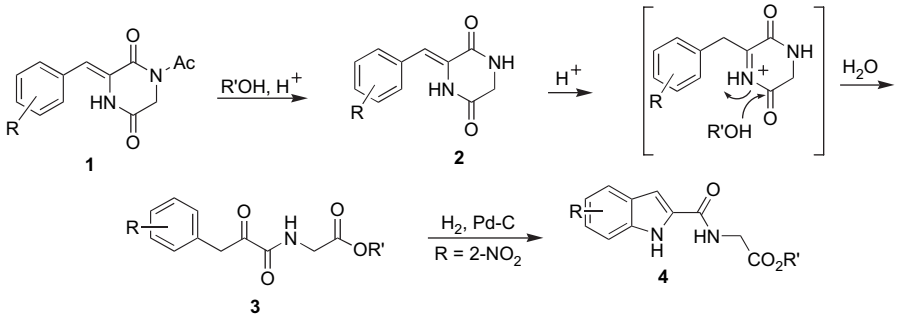
In the development of a synthetic procedure to obtain pyrazino[1,2-*b*]isoquinolines[6] we observed that compounds **1** are unstable in acidic alcohol solutions, giving first the *N*-deacetyl derivatives **2** and, later, compounds **3**. This one-pot three-step process implies protonation of the enamine portion of **2**, ring-opening of *N*-acyliminium cations by addition of alcohol, and imine hydrolysis in the reaction workup, being the reversal of other methods applied for the synthesis of cyclic dehydrodipeptides.[7] Related literature precedents of this acid-promoted alcoholysis are the acid hydrolysis of 3-benzylidene-2,5-piperazinediones[8] and azlactones[9] to give *N*-pyruvoylamino acids and 3-arylpyruvic acids, respectively. In the initial report of this transformation, we gave an account of its extension to nitroarylmethylene derivatives that could give through reductive processes other structures, such as **4** (Scheme 1).[10]

The α-ketoamide function generated in compounds **3** is present in natural products such as the immunosuppressive macrocyclic polyketides FK506 and rapamycin[11] and the antitumor antibiotic lankacidin,[12] being also an important moiety of transition-state protease inhibitors.[13] This function is usually prepared by strategies that imply the Dess–Martin periodinane oxidation of α-hydroxyamides, oxidation of α-cyanoketones, or amidation of α-keto acids.[14–17] On the other hand, the indole-2-carboxamide generated in compounds **4** is an important moiety of biologically active compounds such as reverse transcriptase inhibitors, peptide-like compounds, and antitumor agents.[18]

Given the ready access to compounds **1** and the novelty of their one-pot transformation to compounds **3** and **4**, a more detailed optimization study exploration of more diverse structures was planned. We disclose here full details of our investigation.

* Corresponding author. Tel.: +34913941821; fax: +34913941822.
E-mail address: avendano@farm.ucm.es (C. Avendaño).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.01.047



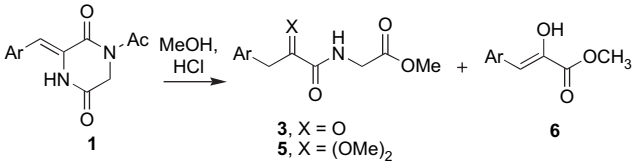
Scheme 1.

2. Results and discussion

The success of the ring-opening reaction of compounds **1** in the previously studied examples[10] required to avoid the precipitation of compounds **2**, whose solubility is highly dependent on the kind of the aryl substituent and the nature of the alcohol employed. The best results were obtained for benzylic alcohol, but the esters thus obtained (**3**, R′=Bn) were usually unstable when a subsequent catalytic reduction of the nitro groups was required, giving the corresponding carboxylic acids (R′=H). Since improvement of yields with methanol (**3**, R′=Me) were envisaged in high diluted solutions assisted by microwave irradiation,[19] the methanolysis of compounds **1a**–**1h**, obtained by aldol-type condensation of 1,4-diacetylpiperazine-2,5-dione and commercial aldehydes, was performed under thermal and/or microwave-assisted reaction conditions. A detailed study of these reactions allowed the isolation in some cases of the secondary products **5** and **6** (Table 1).

With the exception of compounds **1a** and **1h**, the yields of the methanolysis products **3** were more satisfactory in MW-assisted reactions (method C), varying from 50 to 90%. Dimethyl ketals **5c** and **5f** and methyl 3-arylpyruvoyl esters **6** were also isolated. Compounds **6** exists exclusively as enol forms in $CDCl_3$ solution, and are the products of a second acid-promoted methanolysis of compounds **3**, which is favored by the electron-withdrawing effect of the ketone into the amide function.[20] All compounds **3** exist as keto forms, with the exception of **3g**, in which the enol tautomer is exclusive perhaps because it is stabilized through intramolecular hydrogen bonding (Fig. 1).

Table 1
Methanolysis of compounds **1**



Entry	Ar in **1**	Method[a]	Products (% yield)
1	2-NO_2-Phenyl	A	**3a** (59)[10]
2		C	**3a** (51)
3	3-NO_2-Phenyl	A	**3b** (8)[10]
4		C	**3b** (54)+**6b** (13)
5	4-NO_2-Phenyl	C	**3c**[10] (63)[b]+**5c** (7)
6	2,4-$(NO_2)_2$-Phenyl	C	**3d** (90)
7	1-NO_2-2-Naphthyl	B	**3e** (33)+**6e** (34)
8		C	**3e** (60)+**6e** (10)
9	4-(4-NO_2-Phenoxy)phenyl	B	**3f** (41)+**5f** (20)
10		C	**3f** (63)+**5f** (8)
11	6-(3-NO_2-Phenyl)-2-pyridyl	B	**3g**[c] (50)+**6g** (10)
12		C	**3g**[c] (61)+**6g** (24)
13	3-NO_2-2-Thienyl	B	**3h** (70)+**6h** (28)
14		C	**3h** (38)+**6h** (25)

[a] Method A: reflux time 2.5 h, 0.12 M solutions of compounds **1** in methanol containing 10% (v/v) of concd HCl; method B: reflux time 12 h, 0.03 M solutions of compounds **1** in methanol containing 10% (v/v) of concd HCl; method C: microwave irradiation time 5 min, 130 °C, 0.003 M solutions of compounds **1** in methanol containing 10% (v/v) of concd HCl.

[b] The corresponding benzyl ester was obtained in 50% yield under reflux conditions.

[c] As the enol tautomer.

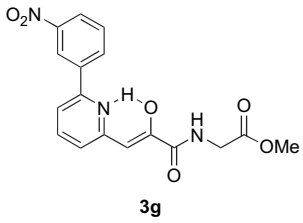
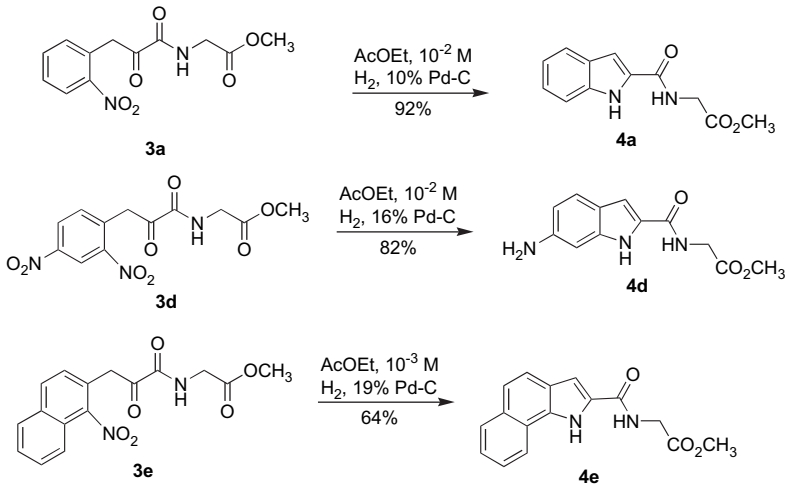


Figure 1.

Catalytic hydrogenation of the *o*-nitro group of compounds **3a**, **3d**, and **3e** in ethyl acetate solutions afforded methyl *N*-indole-2-carbonylamino esters **4a**,[10] **4d**, and **4e** through a Reissert-type synthesis (Scheme 2). This approach to compounds **4** differs from the most common N-acylation of amino esters with 2-indolecarbonyl chloride[21] or the palladium-mediated carbonylation of 2-iodoindoles in the presence of an amine.[22]

Catalytic reduction of the nitro group in *m*- and *p*-nitrocompounds **3f** and **3g** under similar reaction conditions gave the corresponding aminoaryl derivatives **7f** and **7g** that exists, as compound **3g**, exclusively as the enol form. Compounds **3b** and **3c** gave mixtures of the expected amino compounds **7b** and **7c**, that were rather unstable and characterized by their ^{1}H NMR spectra, with traces of other two new products (**8** and **9**). Structures of compounds **8** and **9** were assigned by ^{13}C NMR and ^{1}H NMR spectra that showed the disappearing of the ketone signal and the presence of a $-CH-CH_2-$ portion characterized by a double doublet one-proton signal

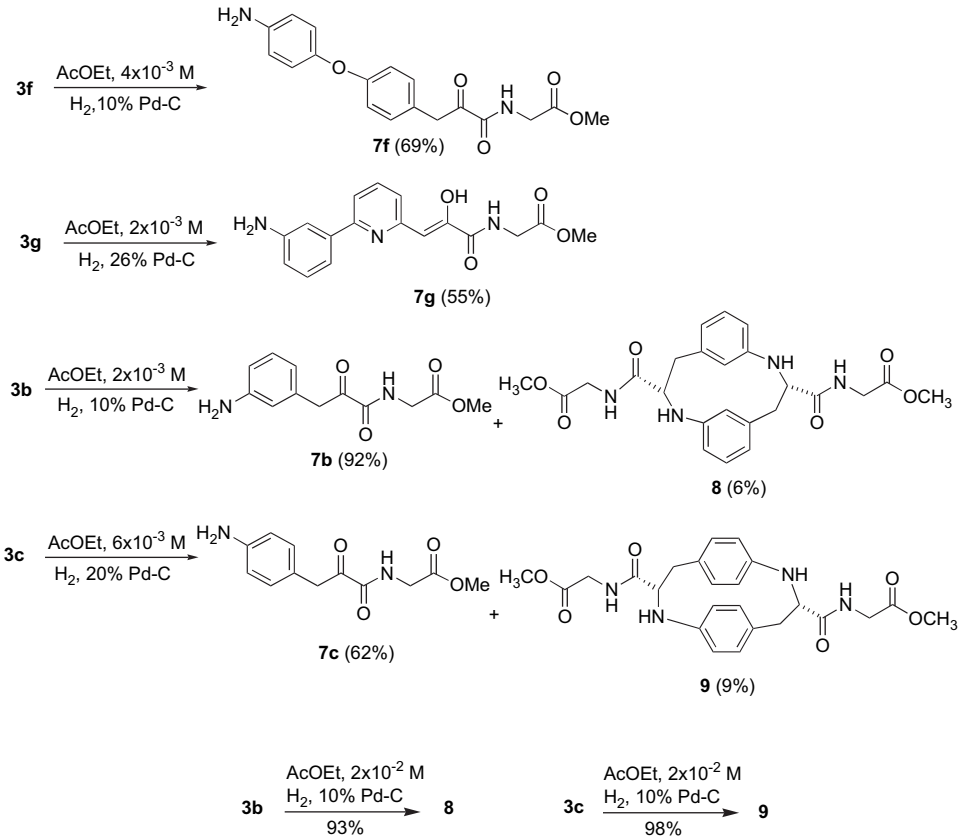


Scheme 2.

coupled to two benzylic methylene protons. These new products were identified as metacyclophane and paracyclophane derivatives, which are formed through an intermolecular reductive amination. As it was expected, they were nearly quantitatively obtained by performing the reduction of **3b** and **3c** at higher concentrations (Scheme 3). No traces of other cyclophanes were observed in the reduction of the rest of nitroderivatives studied here.

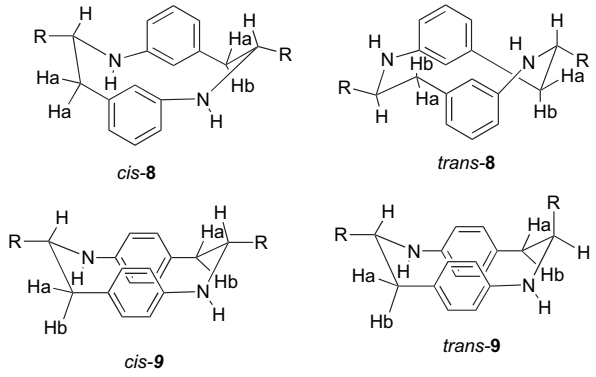
Cyclophanes are important compounds in macrocyclic and supramolecular chemistry mainly because of the rigid framework of their large cavities, primarily defined by aromatic units, which are ready to accommodate charged or neutral guest molecules.[23]

In order to determine the relative stereochemistry of cyclophanes **8** and **9**, after an initial semiempirical study using PM3 parameter set, we performed ab initio calculations using the 3-21G(d) basis set at the Hartree–Fock (HF) density functional level in the gas phase.[24] A representation of both possible diastereoisomers of metacyclophane **8** showed that the two benzene rings are disposed quasi-parallel but not superimposed



Scheme 3.

while in paracyclophane **9** the two benzene rings are parallel and nearly superposed. The two tethers adopt in the cis-isomer of compound **8** a boat-like conformation, while in the trans-isomer they adopt a distorted chair-like conformation with the two side-chains equatorially disposed in both cases. In the two diastereoisomers of **9** the two tethers adopt a boat-like conformation, but, while the two side-chains are equatorially disposed in the *cis*-isomer, in the trans-isomer one is equatorial and the other is axial (Fig. 2). The calculated heat of formation values showed that the cis-isomers are more stable than the trans-isomers (ΔH=3.7 kcal mol^{-1} for **8** and 1.2 kcal mol^{-1} for **9**), and also that *cis*-**8** is more stable than *cis*-**9** (ΔH=6.8 kcal mol^{-1}) (Fig. 2). These data support a cis-stereochemistry for both compounds.



Calculated H-C-C-Ha and H-C-C-Hb dihedral angles	
cis-**8**	170.7°/128.1° and 145.3°/97.8°
cis-**9**	177.7°/61.6° and 172.2°/56.6°
trans-**8**	175.1°/59.0° and 158.2°/85.2°
trans-**9**	175.9°/60.5° and 69.2°/45.8°

Figure 2. Side view of cis- and trans-diastereoisomer of metacyclophane (**8**) and paracyclophane (**9**).

Aminoaryl compounds **7b** and **4d** were coupled with *N*-Boc-protected amino acids, under standard HOAt–EDC–NMO mediated conditions, to give compounds **10**–**14** (Table 2).

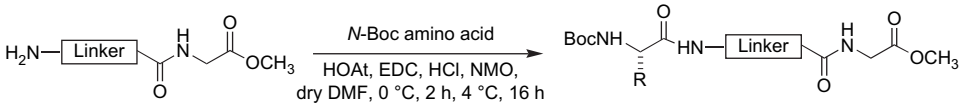
In conclusion, cyclic dehydrodipeptides **1**, easily obtained by aldol-type condensation of 1,4-diacetylpiperazine-2,5-dione and aromatic aldehydes, are convenient starting materials for a one-pot atom-efficient synthesis of *N*-3-arylpyruvoylamino esters **3** and a great array of structurally diverse compounds. 2-Nitroaryl derivatives allow the synthesis of *N*-indole-2-carbonylamino esters **4** through intramolecular reductive amination. Reduction of the nitro groups in compounds **3** afford the corresponding *N*-aminoarylpyruvoylamino esters **7** or aminoindolecarbonylamino esters **4** that may be coupled with amino acids to give peptide-like compounds **10**–**14**. Alternatively, the intermolecular reductive amination of *m*- or *p*-nitroaryl compounds **3b** and **3c** has been revealed as a simple and very efficient route for the synthesis of 2,6-diazacyclophanes **8** and **9**.

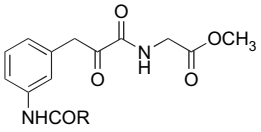
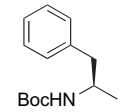
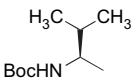
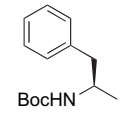
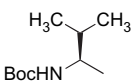
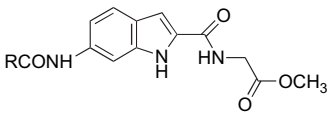
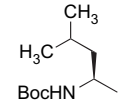
3. Experimental

3.1. General

The reagents used were of commercial origin (Aldrich, Fluka) and were employed without further purification. Solvents (SDS, Scharlau) were purified and dried by standard procedures.

Table 2
Coupling reactions of compounds **7b** and **4d** with *N*-Boc-protected amino acids



Product	R	Yield
		**10**[10], 76%
		**11**, 71%
		**12**, 71%
		**13**, 42%
		**14**, 43%

Reactions were monitored by thin-layer chromatography, using Macherey-Nagel or Merck plates with fluorescent indicator. Separations by flash liquid chromatography were performed using silica gel from SDS 60 ACC (230–400 mesh) or Merck (60, 40–63 μm) and aluminum oxide from Merck (90, 70–230 mesh).

Melting points are uncorrected, and were determined using a Hoffler hot stage microscope. Spectroscopic data were obtained with the following instruments: IR, Perkin–Elmer Paragon 1000 FT-IR; NMR, Bruker AC-250 (250 MHz for ^{1}H and 63 MHz for ^{13}C), Varian Unity 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) or Varian Unity Inova 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C). Combustion elemental analyses were obtained by the Servicio de Microanálisis Elemental, Universidad Complutense, using a Perkin–Elmer 2400 CHN and a Leco CHNS 932 microanalyzer.

3.2. Condensation procedure

To a solution of *N*,*N*′-diacetyl-2,5-piperazinedione (10 mmol) in anhydrous THF (100 mL), under Ar atmosphere, were added the corresponding aldehyde (11 mmol) and 1 equiv of a 1 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol. The reaction was stirred at room temperature for 5 h. After the addition of an aqueous solution of ammonium chloride (30 mL) and concentration of the solvent the condensation product precipitated. The filtrate was first washed with water (30 mL) and then with hexane (30 mL) and the crude residue was purified by flash column chromatography.

3.2.1. 1-Acetyl-3-(3-nitrophenylmethylene)-2,5-piperazinedione (*1b*)

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **1b** (94% yield) as a yellow solid. Mp 159–160 °C; IR (film) ν 1694, 1634 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.48 (br s, 1H), 8.33 (s, 1H), 8.27 (d, J=7.8 Hz, 1H), 7.76 (d, J=7.9 Hz, 1H), 7.68 (dd, J=7.9 and 7.8 Hz, 1H), 7.21 (s, 1H), 4.52 (s, 2H), 2.70 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.2 (C), 163.2 (C), 159.3 (C), 148.7 (C), 134.3 (CH), 134.1 (C), 130.5 (CH), 127.5 (C), 123.7 (CH), 123.4 (CH), 116.8 (CH), 45.9 (CH_2), 27.2 (CH_3). Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.62; H, 3.77; N, 14.35.

3.2.2. 1-Acetyl-3-(4-nitrophenylmethylene)-2,5-piperazinedione (*1c*)

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **1c** (92% yield) as a yellow solid. Mp 210–211 °C (lit[25] 212–214 °C); IR (film) ν 1693, 1633 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.34 (d, J=8.4 Hz, 2H), 8.02 (br s, 1H), 7.61 (d, J=8.4 Hz, 2H), 7.21 (s, 1H), 4.57 (s, 2H), 2.70 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.3 (C), 162.3 (C), 159.1 (C), 147.6 (C), 139.0 (C), 129.4 (CH), 127.9 (C), 124.7 (CH), 116.4 (CH), 46.1 (CH_2), 27.3 (CH_3). Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.72; H, 3.64; N, 14.48.

3.2.3. 1-Acetyl-3-(2,4-dinitrophenylmethylene)-2,5-piperazinedione (*1d*)

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **1d** (98% yield) as a yellow solid. Mp 239–240 °C; IR (film) ν 1695, 1633 cm^{-1}; ^{1}H NMR (250 MHz, acetone-d_6) δ 8.91 (m, 1H), 8.66 (d, J=8.0 Hz, 1H), 8.13 (d, J=8.0 Hz, 1H), 7.36 (s, 1H), 4.22 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (63 MHz, acetone-d_6) δ 173.6 (C), 164.6 (C), 161.0 (C), 158.7 (C), 150.7 (C), 138.2 (C), 134.5 (CH), 129.4 (CH), 127.6 (C), 121.7 (CH), 113.4 (CH), 47.4 (CH_2), 27.7 (CH_3). Anal. Calcd for $C_{13}H_{10}N_4O_7$: C, 46.71; H, 3.02; N, 16.76. Found: C, 46.52; H, 2.94; N, 16.54.

3.2.4. 1-Acetyl-3-(1-nitro-2-naphthylmethylene)-2,5-piperazinedione (*1e*)

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **1e** (99% yield) as a yellow solid. Mp 276–277 °C; IR (film) ν 1706, 1694 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.32 (br s, 1H), 8.10 (d, J=8.5 Hz, 1H), 7.98 (m, 1H), 7.85 (m, 1H), 7.72 (m, 2H), 7.49 (d, J=8.5 Hz, 1H), 7.22 (s, 1H), 4.44 (s, 2H), 2.84 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.3 (C), 162.9 (C), 158.6 (C), 147.6 (C), 133.6 (C), 132.0 (C), 129.6 (CH), 129.2 (CH), 128.5 (CH), 128.2 (CH), 124.7 (C), 124.1 (CH), 122.6 (C), 121.9 (CH), 113.4 (CH), 46.0 (CH_2), 27.3 (CH_3). Anal. Calcd for $C_{17}H_{13}N_3O_5$: C, 60.18; H, 3.86; N, 12.38. Found: C, 59.93; H, 3.73; N, 12.06.

3.2.5. 1-Acetyl-3-(4-(4-nitrophenoxy)phenylmethylene)-2,5-piperazinedione (*1f*)

The crude residue was purified by flash column chromatography (3:7 hexane/EtOAc) to provide compound **1f** (98% yield) as a yellow solid. Mp 186–188 °C; IR (film) ν 1681, 1621 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.27 (d, J=16.5 Hz, 2H), 8.13 (br s, 1H), 7.50 (d, J=11.0 Hz, 2H), 7.20 (d, J=16.5 Hz, 2H), 7.20 (s, 1H), 7.11 (d, J=11.0 Hz, 2H), 4.56 (s, 2H), 2.69 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.7 (C), 163.0 (C), 162.1 (C), 159.8 (C), 155.6 (C), 143.2 (C), 130.7 (CH), 129.2 (C), 126.0 (CH), 125.6 (C), 121.0 (CH), 117.8 (CH), 117.8 (CH), 46.0 (CH_2), 27.2 (CH_3). Anal. Calcd for $C_{19}H_{15}N_3O_6$: C, 59.84; H, 3.96; N, 11.02. Found: C, 59.75; H, 3.64; N, 10.87.

3.2.6. 1-Acetyl-3-(6-(3-nitrophenyl)-2-pyridylmethylene)-2,5-piperazinedione (*1g*)

The crude residue was purified by flash column chromatography (3:7 hexane/EtOAc) to provide compound **1g** (93% yield) as a yellow solid. Mp 250–251 °C; IR (film) ν 1693, 1633 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.63 (t, J=1.7 Hz, 1H), 8.29 (m, 1H), 8.24 (m, 1H), 7.96 (m, 1H), 7.93 (m, 1H), 7.80–7.60 (m, 2H), 6.84 (s, 1H), 4.26 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.6 (C), 163.1 (C), 159.6 (C), 154.9 (C), 153.8 (C), 148.9 (C), 140.1 (C), 139.7 (CH), 133.3 (CH), 132.0 (C), 131.2 (CH), 127.0 (CH), 124.7 (CH), 121.6 (CH), 121.1 (CH), 109.3 (CH), 46.9 (CH_2), 27.5 (CH_3). Anal. Calcd for $C_{18}H_{14}N_4O_5$: C, 59.02; H, 3.85; N, 15.29. Found: C, 58.83; H, 3.61; N, 15.01.

*3.2.7. 1-Acetyl-3-(3-nitro-2-thienylmethylene)-2,5-piperazinedione (**1h**)*

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **1h** (96% yield) as an orange solid. Mp 178–179 °C; IR (film) ν 1709, 1698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.97 (d, J=9.8 Hz, 1H), 7.25 (d, J=9.8 Hz, 1H), 4.60 (s, 2H), 2.69 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.0 (C), 170.7 (C), 165.8 (C), 162.5 (C), 159.0 (C), 141.6 (C), 129.1 (CH), 128.7 (CH), 110.1 (CH), 47.1 (CH_2), 26.7 (CH_3). Anal. Calcd for $C_{11}H_9N_3O_5S$: C, 44.74; H, 3.07; N, 14.23. Found: C, 44.53; H, 2.94; N, 14.02.

3.3. Acid-promoted methanolysis: method A

A 0.12 M solution of the corresponding compound **1** in methanol containing 10% (v/v) of concd HCl was refluxed for 2.5 h. Then, the solvent was distilled in vacuo to dryness, and the solid residue was purified by flash column chromatography.

3.4. Acid-promoted methanolysis: method B

A 0.03 M solution of the corresponding compound **1** in methanol containing 10% (v/v) of concd HCl was refluxed for 12 h. Then, the solvent was distilled in vacuo to dryness, and the solid residue was purified by flash column chromatography.

3.5. Acid-promoted methanolysis: method C

The microwave instrument used in this experiment was the CEM Discover. A 0.003 M solution of the corresponding compound **1** in methanol containing 10% (v/v) of concd HCl was placed in a MW test tube (10 mL) containing a magnetic stirring bar. The sealed tube was irradiated at 130 °C for 5 min. After cooling to room temperature, the solution was filtered and the solvent evaporated in vacuo. EtOAc (50 mL) was added to the residue, the organic solution was washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography.

*3.5.1. Methyl N-(3-(2-nitrophenyl)pyruvoyl)glycinate (**3a**)*

The crude residue was purified by flash column chromatography (6:4 hexane/EtOAc) to provide compound **3a** (method A, 59% yield) as a yellow solid. Mp 91–93 °C; IR (film) ν 1750, 1732, 1694 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.17 (d, J=7.4 Hz, 1H), 7.64 (d, J=7.4 Hz, 1H), 7.51 (d, J=7.4 Hz, 1H), 7.48 (br s, 1H), 7.32 (d, J=7.4 Hz, 1H), 4.63 (s, 2H), 4.14 (d, J=5.7 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 193.2 (C), 169.1 (C), 159.7 (C), 148.3 (C), 133.8 (CH), 133.6 (CH), 129.4 (C), 128.7 (CH), 125.4 (CH), 52.5 (CH_3), 42.5 (CH_2), 41.0 (CH_2). Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.32; H, 4.12; N, 9.89.

*3.5.2. Methyl N-(3-(3-nitrophenyl)pyruvoyl)glycinate (**3b**)*

The crude residue was purified by flash column chromatography (6:4 hexane/EtOAc) to provide compound **3b** (method C, 54% yield) as a yellow solid. Mp 80–81 °C; IR (film) ν 1750, 1688 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.18 (m, 1H), 7.57 (m, 2H), 7.38 (m, 2H), 4.39 (s, 2H), 4.14 (d, J=5.7 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 193.4 (C), 168.4 (C), 159.2 (C), 148.1 (C), 134.2 (C), 136.1 (CH), 129.5 (CH), 124.8 (CH), 122.5 (CH), 52.7 (CH_3), 42.6 (CH_2), 41.0 (CH_2). Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.24; H, 4.08; N, 9.91.

*3.5.3. Methyl N-(3-(2,4-dinitrophenyl)pyruvoyl)glycinate (**3d**)*

The crude residue was purified by flash column chromatography (4:6 hexane/EtOAc) to provide compound **3d** (method C, 90% yield) as a yellow solid. Mp 51–52 °C; IR (film) ν 1784, 1692 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.06 (d, J=3.4 Hz, 1H), 8.51 (dd, J=8.4 and 3.4 Hz, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.42 (t, J=5.6 Hz, 1H), 4.82 (s, 2H), 4.18 (d, J=5.6 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 192.0 (C), 168.9 (C), 159.2 (C), 148.6 (C), 147.4 (C), 136.2 (C), 135.0 (CH), 127.7 (CH), 120.9 (CH), 52.7 (CH_3), 42.7 (CH_2), 41.1 (CH_2). Anal. Calcd for $C_{12}H_{11}N_3O_8$: C, 44.32; H, 3.41; N, 12.92. Found: C, 43.97; H, 3.02; N, 12.73.

*3.5.4. Methyl N-(3-(1-nitro-2-naphthyl)pyruvoyl)glycinate (**3e**)*

The crude residue was purified by flash column chromatography (7:3 hexane/EtOAc) to provide compound **3e** (method C, 60% yield) as a brown solid. Mp 100–101 °C, IR (film) ν 1750, 1691 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.01 (d, J=8.5 Hz, 1H), 7.95 (dd, J=7.3 and 2.3 Hz, 1H), 7.88 (dd, J=8.5 and 1.2 Hz, 1H), 7.64 (m, 2H), 7.46 (t, J=5.7 Hz, 1H), 7.37 (d, J=8.5 Hz, 1H), 4.52 (s, 2H), 4.15 (d, J=5.7 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 192.9 (C), 169.0 (C), 159.4 (C), 147.9 (C), 133.2 (C), 131.5 (CH), 128.9 (CH), 128.7 (CH), 128.1 (CH), 127.4 (CH), 124.8 (C), 124.3 (C), 121.9 (CH), 52.6 (CH_3), 41.0 (CH_2), 40.5 (CH_2). Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.93; H, 3.94; N, 8.23.

*3.5.5. Methyl N-(3-(4-(4-nitrophenoxy)phenyl)pyruvoyl)-glycinate (**3f**)*

The crude residue was purified by flash column chromatography (7:3 hexane/EtOAc) to provide compound **3f** (method C, 63% yield) as a yellow solid. Mp 107–108 °C; IR (film) ν 1753, 1689 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.13 (d, J=7.1 Hz, 2H), 7.37 (t, J=5.6 Hz, 1H), 6.98 (d, J=7.1 Hz, 2H), 6.95 (d, J=6.9 Hz, 2H), 4.18 (s, 2H), 4.04 (d, J=5.6 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.6 (C), 169.1 (C), 159.8 (C), 163.1 (C), 153.9 (C), 142.6 (C), 131.7 (CH), 129.5 (CH), 129.5 (C), 120.7 (CH), 117.1 (CH), 52.7 (CH_3), 42.4 (CH_2), 41.0 (CH_2). Anal. Calcd for $C_{18}H_{16}N_2O_7$: C, 58.06; H, 4.33; N, 7.52. Found: C, 57.87; H, 4.11; N, 7.43.

*3.5.6. Methyl N-(3-(6-(3-nitrophenyl)-2-pyridyl)pyruvoyl)-glycinate (**3g**)*

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **3g** (method C, 61% yield) as a yellow solid. Mp 94–96 °C; IR (film) ν 1748,

1674 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.63 (t, J=2.0 Hz, 1H), 8.27 (d, J=8.2 Hz, 1H), 8.15 (dd, J=7.8 and 1.6 Hz, 1H), 7.80 (t, J=7.8 Hz, 1H), 7.66 (t, J=8.0 Hz, 1H), 7.54 (dd, J=7.8 and 0.8 Hz, 1H), 7.42 (t, J=5.5 Hz, 1H), 7.20 (d, J=7.8 Hz, 1H), 6.60 (s, 1H), 4.15 (d, J=5.5 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.9 (C), 163.1 (C), 157.3 (C), 153.9 (C), 151.9 (C), 148.8 (C), 139.4 (C), 138.8 (CH), 132.4 (CH), 130.3 (CH), 124.2 (CH), 123.1 (CH), 121.7 (CH), 118.6 (CH), 100.3 (CH), 52.5 (CH_3), 41.1 (CH_2). Anal. Calcd for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76. Found: C, 56.95; H, 4.07; N, 11.49.

3.5.7. Methyl N-(3-(3-nitro-2-thienyl)pyruvoyl)glycinate (**3h**)

The crude residue was purified by flash column chromatography (EtOAc) to provide compound **3h** (method B, 70% yield) as a brown solid. Mp 124–125 °C; IR (film) ν 1747, 1681 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.84 (d, J=4.1 Hz, 1H), 7.53 (m, 1H), 6.94 (d, J=4.1 Hz, 1H), 4.53 (s, 2H), 4.15 (d, J=5.7 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 191.9 (C), 169.0 (C), 159.1 (C), 143.6 (C), 141.8 (C), 128.4 (CH), 127.3 (CH), 52.7 (CH_3), 41.0 (CH_2), 37.9 (CH_2). Anal. Calcd for $C_{10}H_{10}N_2O_6S$: C, 41.96; H, 3.52; N, 9.79. Found: C, 41.77; H, 3.38; N, 9.45.

3.5.8. Methyl N-(2,2-dimethoxy-3-(4-nitrophenyl)propanoyl)-glycinate (**5c**)

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **5c** (method C, 7% yield) as a yellow solid. Mp 126–127 °C; IR (film) ν 1754, 1688 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.90 (d, J=8.7 Hz, 2H), 7.14 (d, J=8.7 Hz, 2H), 6.85 (d, J=5.6 Hz, 1H), 3.70 (d, J=5.6 Hz, 2H), 3.49 (s, 3H), 3.16 (s, 6H) 3.08 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.5 (C), 168.3 (C), 146.9 (C), 142.5 (C), 130.9 (CH), 123.3 (CH), 102.4 (C), 52.4 (CH_3), 50.1 (CH_3), 40.6 (CH_2), 38.8 (CH_2). Anal. Calcd for $C_{14}H_{18}N_2O_7$: C, 51.53; H, 5.56; N, 8.59. Found: C, 51.39; H, 5.42; N, 8.38.

3.5.9. Methyl N-[2,2-dimethoxy-3-(4-(4-nitrophenoxy)-phenyl)propanoyl]glycinate (**5f**)

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **5f** (method C, 8% yield) as a yellow oil. IR (film) ν 1755, 1682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.19 (d, J=5.5 Hz, 2H), 7.24 (d, J=4.6 Hz, 2H), 7.07 (t, J=5.5 Hz, 1H), 7.02 (d, J=5.5 Hz, 2H), 6.98 (d, J=4.6 Hz, 2H), 3.95 (d, J=5.5 Hz, 2H), 3.74 (s, 6H), 3.74 (s, 3H), 3.23 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.7 (C), 168.7 (C), 163.4 (C), 153.4 (C), 142.5 (C), 131.9 (C), 131.8 (CH), 125.9 (CH), 120.2 (CH), 116.9 (CH), 102.8 (C), 52.4 (CH_3), 49.9 (CH_3), 40.6 (CH_2), 38.1 (CH_2). Anal. Calcd for $C_{20}H_{22}N_2O_8$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.22; H, 5.03; N, 6.41.

3.5.10. Methyl 2-hydroxy-3-(3-nitrophenyl)-2-propenoate (**6b**)

The crude residue was purified by flash column chromatography (8:2 hexane/EtOAc) to provide compound **6b** (method C, 13% yield) as a yellow solid. Mp 90–91 °C; IR (film) ν 3410, 1704, 1530 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.56 (t, J=2.0 Hz, 1H), 8.05 (ddd, J=8.2, 2.3, and 1.2 Hz, 1H), 7.96 (td, J=7.8 and 1.2 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 6.66 (d, J=1.5 Hz, 1H), 6.47 (d, J=1.1 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.4 (C), 148.8 (C), 141.3 (C), 136.1 (C), 135.8 (CH), 129.7 (CH), 124.7 (CH), 122.8 (CH), 108.8 (CH), 54.1 (CH_3). Anal. Calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.61; H, 3.96; N, 5.97.

3.5.11. Methyl 2-hydroxy-3-(1-nitro-2-naphthyl)-2-propenoate (**6e**)

The crude residue was purified by flash column chromatography (7:3 hexane/EtOAc) to provide compound **6e** (method B, 34% yield) as a yellow solid. Mp 96–97 °C; IR (film) ν 1698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.43 (d, J=8.8 Hz, 1H), 7.99 (d, J=8.8 Hz, 1H), 7.72 (m, 1H), 7.65 (m, 1H), 7.62–7.57 (m, 2H), 6.84 (d, J=1.2 Hz, 1H), 6.56 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9 (C), 142.1 (C), 138.2 (C), 132.9 (C), 130.2 (CH), 128.7 (CH), 127.9 (CH), 127.6 (CH), 126.1 (CH), 124.3 (C), 123.5 (C), 121.8 (CH), 102.2 (CH), 53.8 (CH_3). Anal. Calcd for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.31; H, 3.92; N, 4.87.

3.5.12. Methyl 2-hydroxy-3-(6-(3-nitrophenyl-2-pyridyl)-2-propenoate (**6g**)

The crude residue was purified by flash column chromatography (7:3 hexane/EtOAc) to provide compound **6g** (method C, 24% yield) as a yellow solid. Mp 140–141 °C; IR (film) ν 1714 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.62 (t, J=2.0 Hz, 1H), 8.23 (m, 2H), 7.84 (t, J=7.9 Hz, 1H), 7.62 (t, J=8.0 Hz, 1H), 7.61 (dd, J=7.9 and 0.8 Hz, 1H), 7.22 (dd, J=7.9 and 0.8 Hz, 1H), 6.61 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.0 (C), 156.8 (C), 152.3 (C), 151.6 (C), 148.7 (C), 139.3 (C), 138.9 (CH), 132.5 (CH), 130.3 (CH), 124.3 (CH), 123.1 (CH), 121.7 (CH), 119.1 (CH), 104.2 (CH), 52.7 (CH_3). Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.77; H, 3.85; N, 9.06.

3.5.13. Methyl 2-hydroxy-3-(3-nitro-2-thienyl)-2-propenoate (**6h**)

The crude residue was purified by flash column chromatography (7:3 hexane/EtOAc) to provide compound **6h** (method B, 28% yield) as a yellow solid. Mp 168–169 °C; IR (film) ν 1694 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.89 (d, J=4.3 Hz, 1H), 7.14 (d, J=4.3 Hz, 1H), 6.97 (br s, 1H), 6.78 (s, 1H), 3.97 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.7 (C), 144.2 (C), 141.0 (C), 136.2 (C), 128.5 (CH), 127.2 (CH), 104.4 (CH), 53.7 (CH_3). Anal. Calcd for $C_8H_7NO_5S$: C, 41.92; H, 3.08; N, 6.11. Found: C, 41.76; H, 2.83; N, 6.02.

3.6. Catalytic reduction of compounds **3**

A 10^{-2}–10^{-3} M solution of compounds **3** in EtOAc with a 10–26% Pd–C was hydrogenated at room temperature for 5 h. After filtration over Celite and evaporation of the solvent

under reduced pressure, the solid residue was purified by flash column chromatography.

*3.6.1. Methyl N-(1H-indole-2-carbonyl)glycinate (**4a**)*

A 10^{-2} M solution of **3a** in EtOAc with a 10% Pd–C was used. The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **4a** (92% yield) as a white solid. Mp 197–198 °C; IR (film) ν 3367, 3274, 1737 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.61 (d, J=8.0 Hz, 1H), 7.47 (d, J=8.2 Hz, 1H), 7.22 (dd, J=8.2 and 1.1 Hz, 1H), 7.10 (s, 1H), 7.06 (d, J=8.0 Hz, 1H), 4.14 (s, 2H), 3.66 (s, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 169.9 (C), 162.3 (C), 136.2 (C), 129.4 (C), 126.7 (C), 123.1 (CH), 120.7 (CH), 119.1 (CH), 110.0 (CH), 102.8 (CH), 50.6 (CH_3), 39.8 (CH_2). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.97; H, 5.11; N, 11.93.

*3.6.2. Methyl N-(1H-6-aminoindole-2-carbonyl)glycinate (**4d**)*

A 10^{-2} M solution of **3d** in EtOAc with a 16% Pd–C was used. The crude residue was purified by flash column chromatography (2:8 hexane/EtOAc) to provide compound **4d** (82% yield) as a brown solid. Mp 52–53 °C; IR (film) ν 1748 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.96 (br s, 1H), 8.64 (d, J=5.7 Hz, 1H), 7.26 (d, J=8.5 Hz, 1H), 6.94 (s, 1H), 6.50 (s, 1H), 6.44 (d, J=8.5 Hz, 1H), 5.06 (br s, 2H), 4.01(d, J=5.7 Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 170.9, 162.0, 146.3, 138.8, 128.1, 122.0, 119.1, 111.7, 103.9, 94.4, 51.9, 40.3. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 57.98; H, 5.04; N, 16.75.

*3.6.3. Methyl N-(1H-benzo[g]indole-2-carbonyl)glycinate (**4e**)*

A 10^{-3} M solution of **3e** in EtOAc with a 19% Pd–C was used. The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **4e** (64% yield) as an orange solid. Mp 200–201 °C; IR (film) ν 1748 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.18 (d, J=8.2 Hz, 1H), 7.95 (d, J=7.3 Hz, 1H), 7.70 (d, J=8.2 Hz, 1H), 7.57 (m, 3H), 7.10 (s, 1H), 6.72 (br s, 1H), 4.36 (d, J=5.0 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.4 (C), 164.1 (C), 132.2 (C), 131.6 (C), 130.0 (C), 128.8 (C), 125.9 (CH), 125.3 (CH), 123.8 (C), 122.0 (CH), 121.8 (CH), 120.9 (CH), 120.5 (CH), 104.6 (CH), 52.6 (CH_3), 41.4 (CH_2). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.94; H, 4.83; N, 9.76.

*3.6.4. Methyl N-(3-(3-aminophenyl)pyruvoyl)glycinate (**7b**)*

A 2×10^{-3} M solution of **3b** in EtOAc with a 10% Pd–C was used. The crude residue was purified by flash column chromatography (4:6 hexane/EtOAc) to provide compound **7b** (92% yield) as a yellow oil. IR (film) ν 1748, 1682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 1H), 7.13 (m, 1H), 7.04 (m, 2H), 4.05 (s, 2H), 4.10 (s, 2H), 3.98 (s, 3H).

*3.6.5. Methyl N-(3-(4-aminophenyl)pyruvoyl)glycinate (**7c**)*

A 6×10^{-3} M solution of **3c** in EtOAc with a 20% Pd–C was used. The crude residue was purified by flash column chromatography (2:8 hexane/EtOAc) to provide compound **7c** (62% yield) as a yellow oil. IR (film) ν 3352, 1746, 1679 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.06 (d, J=8.2 Hz, 2H), 6.67 (d, J=8.2 Hz, 2H), 4.12 (s, 2H), 4.09 (s, 2H), 3.80 (s, 3H).

*3.6.6. Methyl N-[3-(4-(4-aminophenoxy)phenyl)pyruvoyl]-glycinate (**7f**)*

A 4×10^{-3} M solution of **3f** in EtOAc with a 10% Pd–C was used. The crude residue was purified by flash column chromatography (2:8 hexane/EtOAc) to provide compound **7f** (69% yield) as a yellow solid. Mp 87–88 °C; IR (film) ν 1748, 1682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.45 (t, J=6.1 Hz, 1H), 7.17 (d, J=7.5 Hz, 2H), 6.90 (m, 4H), 6.70 (d, J=8.6 Hz, 2H), 4.19 (s, 2H), 4.11 (d, J=6.1 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9 (C), 173.9 (C), 169.2 (C), 158.2 (C), 148.3 (C), 142.7 (C), 131.4 (CH), 125.6 (C), 121.7 (CH), 117.7 (CH), 116.7 (CH), 53.1 (CH_3), 42.3 (CH_2), 41.0 (CH_2). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.89; H, 4.96; N, 8.02.

*3.6.7. Methyl N-[3-(6-(3-aminophenyl)pyridyl)pyruvoyl]-glycinate (**7g**)*

A 2×10^{-3} M solution of **3g** in EtOAc with a 26% Pd–C was used. The crude residue was purified by flash column chromatography (aluminum oxide, H_2O) to provide **7g** (55% yield) as a yellow oil. IR (film) ν 1741, 1671 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.52 (d, J=8.0 Hz, 1H), 7.34 (m, 2H), 7.15 (d, J=8.0 Hz, 1H), 6.84 (d, J=7.8 Hz, 1H), 6.60 (s, 1H), 4.23 (d, J=5.5 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.5 (C), 156.8 (C), 152.2 (C), 143.3 (C), 147.7 (C), 139.3 (CH), 138.2 (C), 130.6 (CH), 130.0 (CH), 122.0 (CH), 117.2 (CH), 114.5 (C), 113.1 (CH), 97.9 (CH), 52.3 (CH_3), 41.6 (CH_2). Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.13; H, 5.08; N, 12.43.

*3.6.8. Methyl [2,6-diaza-1,5-bis(1,3)dibenzenacyclododecaphane]-3,7-bisylenecarbonyl glycinate (**8**)*

A 2×10^{-2} M solution of **3b** in EtOAc with a 10% Pd–C was used. The crude residue was purified by flash column chromatography EtOAc to provide compound **8** (98% yield) as an orange oil. IR (film) ν 1748, 1652 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.26 (t, J=5.5 Hz, 1H), 7.07 (dd, J=5.6 and 3.1 Hz, 1H), 6.65 (d, J=7.6 Hz, 1H), 6.57 (s, 1H), 6.55 (m, 1H), 4.29 (dd, J=8.8 and 3.7 Hz, 1H), 4.02 (d, J=5.6 Hz, 2H), 3.76 (s, 3H), 3.13 (dd, J=13.4 and 8.8 Hz, 1H), 2.76 (dd, J=13.4 and 3.7 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.5 (C), 170.2 (C), 146.5 (C), 138.2 (C), 129.5 (CH), 119.8 (CH), 116.2 (CH), 113.8 (CH), 72.7 (CH), 52.3 (CH_3), 40.7 (CH_2), 40.6 (CH_2). Anal. Calcd for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.22; H, 5.87; N, 11.75.

*3.6.9. Methyl [2,6-diaza-1,5-bis(1,4)dibenzenacyclotetradecaphan]-3,7-bisylenecarbonyl-glycinate (**9**)*

A 2×10^{-2} M solution of **3c** in EtOAc with a 10% Pd–C was used. The crude residue was purified by flash column chromatography EtOAc to provide compound **9** (98% yield) as an

orange oil. IR (film) ν 3374, 1742, 1667 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.06 (d, J=8.3 Hz, 2H), 7.05 (m, 1H), 6.68 (d, J=8.3 Hz, 2H), 4.30 (dd, J=8.6 and 4.1 Hz, 1H), 4.08 (d, J=5.5 Hz, 2H), 3.78 (s, 3H), 3.17 (dd, J=14.1 and 4.1 Hz, 1H), 2.81 (dd, J=14.1 and 8.6 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.0 (C), 170.1 (C), 145.4 (C), 130.4 (CH), 126.0 (C), 115.5 (CH), 72.9 (CH), 52.3 (CH_3), 40.7 (CH_2), 39.8 (CH_2). Anal. Calcd for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.31; H, 5.92; N, 11.69.

3.7. N-Acylation of amino compounds

To a solution of the corresponding *N*-Boc-L-amino acid (0.34 mmol), 1-hydroxy-7-azabenzotriazole (HOAt) (0.37 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride (0.41 mmol) and the amino derivatives **7b** and **4d** (0.34 mmol) in anhydrous DMF (20 mL) under Ar atmosphere at 0 °C, was added 4-methylmorpholine (NMM) (1.02 mmol). After being stirred at 0 °C for 2 h, the reaction mixture was kept in a freezer overnight (16 h) and it was then warmed at room temperature. EtOAc (80 mL) was added and the organic solution was washed with 5% H_3PO_4 (20 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried with sodium sulfate, filtered, and concentrated. An analytical sample was obtained through flash chromatography.

3.7.1. Methyl N-(3-(3-tert-butoxycarbonyl-L-valylamino-phenyl)pyruvoyl)glycinate (**11**)

The crude residue was purified by flash column chromatography (3:7 hexane/EtOAc) to provide compound **11** (71% yield) as a yellow oil. IR (film) ν 1748, 1662 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.47 (m, 2H), 7.39 (s, 1H), 7.25 (m, 1H), 6.98 (d, J=3.8 Hz, 1H), 4.19 (s, 2H), 4.11 (d, J=3.0 Hz, 2H), 4.07 (m, 1H), 3.75 (s, 3H), 2.22 (m, 1H), 1.47 (s, 9H), 1.06 (d, J=7.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.7 (C), 170.2 (C), 169.2 (C), 160.0 (C), 156.2 (C), 137.8 (C), 133.3 (C), 129.1(CH), 125.8 (CH), 122.7 (CH), 118.9 (CH), 80.3 (C), 59.9 (CH), 52.5 (CH_3), 42.9 (CH_2), 41.0 (CH_2), 30.6 (CH), 28.3 (CH_3), 19.4 (CH_3). Anal. Calcd for $C_{22}H_{31}N_3O_7$: C, 58.78; H, 6.95; N, 9.35. Found: C, 58.63; H, 6.36; N, 9.02.

3.7.2. Methyl N-(1H-6-tert-butoxycarbonyl-L-phenylalanyl-aminoindole-2-carbonyl)glycinate (**12**)

The crude residue was purified by flash column chromatography (4:6 hexane/EtOAc) to provide compound **12** (71% yield) as a brown solid. Mp 118–119 °C; IR (film) ν 3420, 1644 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.12 (br s, 1H), 9.02 (br s, 1H), 7.86 (m, 1H), 7.35 (m, 1H), 7.18 (m, 6H), 6.67 (s, 1H), 6.61 (m, 1H), 6.54 (br s, 1H), 4.68 (t, J=5.9 Hz, 1H), 4.18 (d, J=4.3 Hz, 2H), 3.70 (s, 3H), 3.10 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.3 (C), 170.8 (C), 162.3 (C), 156.8 (C), 137.3 (C), 136.9 (C), 134.6 (C), 129.3 (CH), 128.4 (CH), 126.5 (CH), 124.0 (C), 121.7 (CH), 114.1 (CH), 103.1 (CH), 103.4 (CH), 77.5 (C), 57.7 (CH), 53.0 (CH_3), 41.4 (CH_2), 38.4 (CH_2), 28.2 (CH_3). Anal. Calcd for $C_{26}H_{30}N_4O_6$: C, 63.15; H, 6.11; N, 11.33. Found: C, 62.91; H, 6.01; N, 11.16.

3.7.3. Methyl N-(1H-6-tert-butoxycarbonyl-L-valylamino-indole-2-carbonyl)glycinate (**13**)

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **13** (42% yield) as a yellow solid. Mp 112–113 °C; IR (film) ν 3292, 1746, 1668 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.35 (br s, 1H), 8.68 (br s, 1H), 7.74 (s, 1H), 7.25 (d, J=8.5 Hz, 1H), 7.13 (br s, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.71 (s, 1H), 6.64 (s, 1H), 4.19 (d, J=5.4 Hz, 2H), 4.00 (d, J=6.7 Hz, 1H), 3.74 (s, 3H), 2.10 (m, 1H), 1.14 (s, 9H), 0.97 (d, J=6.7 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.2 (C), 170.7 (C), 161.8 (C), 156.7 (C), 136.6 (C), 134.7 (C), 131.2 (C), 124.1 (C), 121.9 (CH), 114.3 (CH), 103.1 (CH), 102.9 (CH), 80.0 (C), 61.3 (CH), 52.6 (CH_3), 41.2 (CH_2), 30.6 (CH), 28.3 (CH_3), 19.4 (CH_3). Anal. Calcd for $C_{22}H_{30}N_4O_6$: C, 59.18; H, 6.77; N, 12.55. Found: C, 58.95; H, 6.52; N, 12.23.

3.7.4. Methyl N-(1H-6-tert-butoxycarbonyl-L-leucylamino-indole-2-carbonyl)glycinate (**14**)

The crude residue was purified by flash column chromatography (1:1 hexane/EtOAc) to provide compound **14** (43% yield) as a yellow solid. Mp 122–123 °C, IR (film) ν 3305, 1744, 1673 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.64 (br s, 1H), 8.95 (br s, 1H), 7.80 (s, 1H), 7.26 (d, J=8.7 Hz, 1H), 7.23 (br s, 1H), 6.72 (d, J=8.7 Hz, 1H), 6.70 (s, 1H), 5.86 (br s, 1H), 4.33 (m, 1H), 4.27 (d, J=5.3 Hz, 2H), 3.85 (s, 3H), 1.61 (m, 2H), 1.40 (s, 9H), 1.25 (m, 1H), 1.01 (d, J=6.3 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.6 (C), 171.3 (C), 161.9 (C), 159.5 (C), 136.8 (C), 135.0 (C), 129.7 (C), 124.0 (C), 121.8 (CH), 114.2 (CH), 103.2 (CH), 102.8 (CH), 80.2 (C), 54.1 (CH), 52.6 (CH_3), 41.2 (CH_2), 40.6 (CH_2), 28.4 (CH_3), 23.1 (CH), 16.4 (CH_3). Anal. Calcd for $C_{23}H_{32}N_4O_6$: C, 59.99; H, 7.00; N, 12.17. Found: C, 59.82; H, 6.86; N, 11.94.

Acknowledgements

This work was supported by CICYT (CTQ2006-10930/BQU project) and Comunidad Autónoma de Madrid (Group 920234).

References and notes

1. Shin, C.; Masaki, M.; Ohta, M. *J. Org. Chem.* **1967**, *32*, 1860–1863.
2. Gallina, C.; Liberatori, A. *Tetrahedron Lett.* **1973**, 1135–1136.
3. Kamei, H.; Oka, M.; Hamagishi, Y.; Tomita, K.; Konishi, M.; Oki, T. *J. Antibiot.* **1990**, *43*, 1018–1020.
4. Oba, M.; Terauchi, T.; Owari, Y.; Imai, Y.; Motoyama, I.; Nishiyama, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1275–1281.
5. Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712–3713.
6. González, J. F.; de la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.* **2007**, *15*, 112–118.
7. Li, W.-R.; Peng, S.-Z. *Tetrahedron Lett.* **1998**, *39*, 7373–7376.
8. Dominy, B. W.; Lawton, R. G. *J. Org. Chem.* **1969**, *34*, 2013–2014.
9. Baskar, B.; Pandian, N. G.; Priya, K.; Chadha, A. *Tetrahedron* **2005**, *61*, 12296–12306.
10. González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron Lett.* **2006**, *47*, 6711–6714.
11. Schreiber, S. L. *Science* **1991**, *251*, 283–287.

12. Kende, A. S.; Liu, K.; Kaldor, I.; Dorey, G.; Koch, K. *J. Am. Chem. Soc.* **1995**, *117*, 8258–8270.
13. Chen, K. X.; Njoroge, F. G.; Arasappan, A.; Venkatraman, S.; Vibulbhan, B.; Yang, W.; Parekh, T. N.; Pichardo, J.; Prongay, A.; Cheng, K.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan, V. *J. Med. Chem.* **2006**, *49*, 995–1005.
14. Han, W.; Hu, Z.; Jiang, X.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 711–713.
15. Sun, D. X.; Liu, L.; Heinz, B.; Kolykhalov, A.; Lamar, J.; Johnson, R. B.; Wang, Q. M.; Yip, Y.; Chen, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4333–4338.
16. Yang, Z.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2002**, *4*, 1103–1105.
17. Nakamura, M.; Inoue, J.; Yamada, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2807–2810.
18. Kobayashi, E.; Okamoto, A.; Asada, N.; Okabe, M.; Nagamura, S.; Asai, A.; Saito, H.; Gosni, K.; Hirata, T. *Cancer Res.* **1994**, *54*, 2404–2410.
19. Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
20. Tavares, F. X.; Boncek, V.; Deaton, D. N.; Hassell, A. M.; Long, S. T.; Miller, A. B.; Payne, A. A.; Miller, L. R.; Shewchuk, L. M.; Wells-Knecht, K.; Willard, D. H., Jr.; Wright, L. L.; Zhou, H.-Q. *J. Med. Chem.* **2004**, *47*, 588–599.
21. Johnson, J. R.; Andreen, J. H.; Holley, A. D. *J. Am. Chem. Soc.* **1947**, *69*, 2370–2372.
22. Herbert, J. M.; Mcneill, A. H. *Tetrahedron Lett.* **1998**, *39*, 2421–2424.
23. Vögtle, F. *Cyclophane Chemistry*; Wiley: Chichester, UK, 1993.
24. Young, D. *Computational Chemistry*; Wiley Interscience: New York, NY, 2001; Appendix A.A.1.6, p 330.
25. Katritzky, A. R. *J. Heterocycl. Chem.* **1988**, *25*, 591–597.