Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 8171–8176

TETRAHEDRON

Synthesis and convenient functionalisation of pyridazinofurocoumarins: nitrogenated isosters of potent DNA inhibitors

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Received 3 June 2003; revised 11 August 2003; accepted 20 August 2003

Abstract—Pyridazino[3,4-*h*]psoralens and pyridazino[3,4-*j*]angelicins are prepared in good yield from resorcinols through a direct, easy and generally applicable synthetic route. The key step in this route is the inverse electron-demand Diels–Alder reaction between linear or angular furocoumarins and 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine to give the dicarboxymethylated tetracycles. The ester group in the *peri* position with respect to the oxygen in the furan ring can be regioselectively transformed to give primary or secondary amides. Similarly, the two ester groups in the tetracycle can be transformed in a high-efficiency process to give bis-amides that can be either symmetrical (from the same amine) or unsymmetrical (from two different amines).

1. Introduction

Furocoumarins form a group of natural or synthetic compounds that are of great pharmacological interest. One of the most important applications of these compounds is in the field of photochemotherapy, where furocoumarins are capable of undergoing photoaddition with thymine units present in DNA. However, the most effective compounds in this class are associated with side-effects, mainly related to their ability to stabilize bridging bonds between the strands of the DNA helix.[1] One of the most promising strategies to obtain monofunctional furocoumarins efficiently involves incorporating one of the reactive double bonds in a benzene nucleus by forming benzofurocoumarins (Chart 1). This approach results in molecules that have a high propensity for intercalation and photoreaction with DNA and also helps to overcome some of the negative phototoxic effects.[2,3]

With this information in mind, it was decided to investigate the effect of introducing nitrogen atoms into the polycyclic skeleton on the basis that this could increase the stability of the complex formed by the interaction of the molecule with DNA.[4] This aim could be achieved by replacing the fourth benzene ring in the benzofurocoumarin system with a pyridazine, which would be attached to the furan ring through its 4,5-bond. We have previously obtained tetracyclic skeletons of this type through inverse electron-demand Diels–Alder reactions between a furocoumarin and the particularly reactive compound 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine.[5] However, for the current target it is necessary to easily and conveniently functionalise one or both positions adjacent to the nitrogen atoms of the pyridazine ring. This aspect is important because equivalent positions are substituted with different chains in a range of tricyclic and tetracyclic compounds that are known to intercalate with DNA.[6]

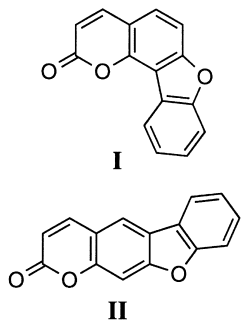

Chart 1. Tetracyclic skeleton of a benzo[*j*]angelicin **I** and a benzo[*h*]-psoralen **II**.

Chains bearing an amide function are amongst the most widely used in this type of intercalating anticancer compound. For this reason, the diene chosen for the Diels–Alder reaction with linear and angular furocoumarins was the 3,6-dicarboxymethyl-substituted tetrazine. It was then planned to investigate the possible amidation of one or both ester groups in the resulting tetracycles. Pyrrolidine

Keywords: furocoumarins; DNA inhibitors; Diels–Alder reaction.
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0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.08.051

was used as an example of a secondary amine and dimethylaminoethylamine was used as a primary amine on the basis that the resulting side-chains are themselves interesting objectives.[7,8]

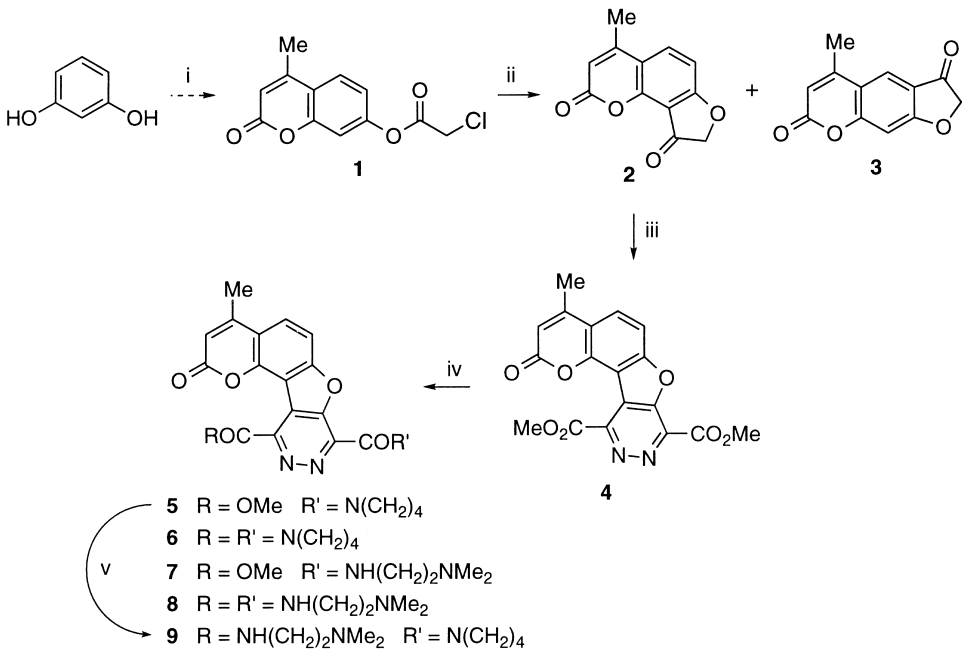
2. Results and discussion

Attachment of a pyridazine to a furan through a Diels–Alder reaction with a tetrazine[9] requires the dienophile to be a furan with a good leaving group in position 3—otherwise ring opening occurs rather than aromatization of the resulting pyridazine.[10,11] For this reason, we chose to synthesise the desired pyridazinofurocoumarins from the appropriate precursor furocoumarin-6-ones.[12,13] These compounds were obtained in good yields from resorcinols in three steps: (a) Pechmann reaction with ethyl acetate in sulfuric acid, (b) acylation of the resulting 7-hydroxycoumarins with acetyl chloride and (c) a tandem Fries rearrangement/cyclization of the chloroacetate. This procedure gave a good overall yield (60%) of the angular furocoumarin **2** from resorcinol. However, the isomeric product **3** was obtained in only 5% yield because the rearrangement of chloroacetate **1** occurred mainly at position 8 of the furocoumarins (Scheme 1).[13]

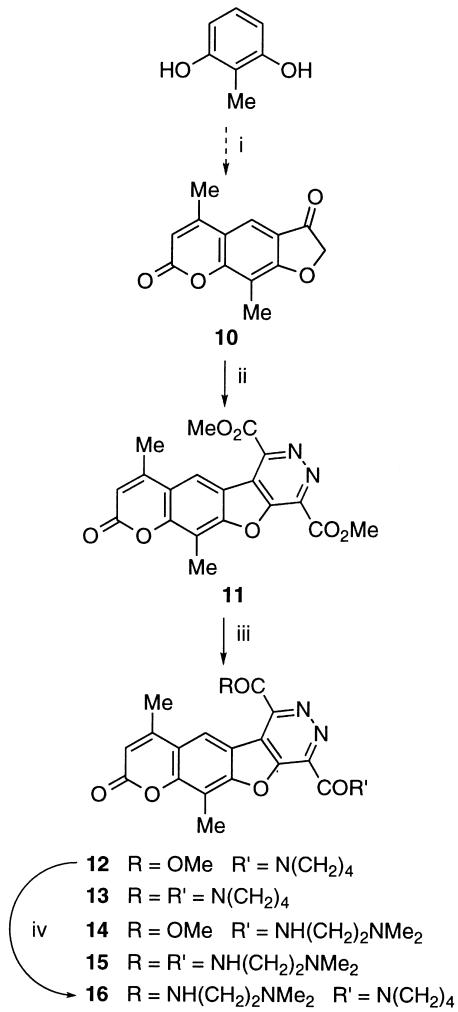
We recently reported a regioselective synthesis of dihydrofuro[3,2-*g*]coumarin-6-one.[14] However, given that the final outcome of the subsequent reaction is independent of the presence or absence of a methyl group in position 8 of the coumarin nucleus, it was decided to synthesise the linear dimethylated furocoumarin **10**. This compound can be prepared in a straightforward manner that provides reasonable quantities of material from 2-methylresorcinol (48% overall yield) through the same reaction scheme as described for the preparation of compound **2** from resorcinol (Scheme 2).[12]

The inverse electron-demand Diels–Alder reactions of furocoumarins **2** and **10** with 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine[15] were performed in dichloromethane heated to 100°C in a sealed tube in the presence of *p*-toluenesulfonic acid. This method proved satisfactory for the preparation of the tetracycles **4** and **11** (69 and 74% yield, respectively). This route also allowed the introduction of the two carboxymethyl groups in the positions contiguous to the nitrogen atoms in the ring (i.e. positions 1 and 4 of the tetracycle), a situation that offers the possibility of further substitution. Given that side-chains bearing a carboxamide group are among the most interesting in terms of the pharmacological properties of these compounds, it was decided to investigate amidation of the pyridazinofurocoumarins **4** and **11**, both of which are key intermediates. Transformation of one of the ester groups gives rise to monoamides through reaction with primary or secondary amines. On the other hand, diamides can be obtained that are either symmetrical, by reacting the intermediate twice with the same amine, or unsymmetrical, by sequential reaction with two different amines.

In the most simple tricyclic pyridazino[4,5-*b*]benzo[*b*]furan systems there is a regioselectivity that favours formation of the carboxamide on the carboxymethyl group in the *peri* position with respect to the oxygen of the furan ring. This reaction is performed using magnesium chloride as a catalyst and works best with secondary amines.[16] The regioselectivity is particularly marked in the case of 8-methyl-1,4-bis(methoxycarbonyl)pyridazino[4,5-*j*]angelicin (**4**), where the use of 1.5 equiv. of the pyrrolidine with 1 equiv. of **4** gives monocarboxamide **5** in 92% yield.



Scheme 1. *Reagents and conditions*: (i) (a) $CH_3COCH_2CO_2Et$, H_2SO_4, rt, (b) $ClCOCH_2Cl$, DMAP, dioxane, reflux; (ii) $AlCl_3$, 120°C; (iii) 3,6-bis-(methoxycarbonyl)-1,2,4,5-tetrazine, *p*-TsOH, CH_2Cl_2, 100°C; (iv) amine, $MgCl_2$, CH_2Cl_2, rt; (v) *N*,*N*-dimethyletilenediamine, $MgCl_2$, CH_2Cl_2, rt.



Scheme 2. *Reagents and conditions*: (i) (a) $CH_3COCH_2CO_2Et$, H_2SO_4, rt, (b) $ClCOCH_2Cl$, DMAP, dioxane, reflux, (c) $AlCl_3$, 120°C; (ii) 3,6-bis-(methoxycarbonyl)-1,2,4,5-tetrazine, *p*-TsOH, CH_2Cl_2, 100°C; (iii) amine, $MgCl_2$, CH_2Cl_2, rt; (iv) *N*,*N*-dimethyletilenediamine, $MgCl_2$, CH_2Cl_2, rt.

The synthesis of the dicarboxamides was also a target in this study and amidation reactions with large excesses of amine (5 equiv.) were performed on **4** and **11**. The use of this method always gave acceptable yields of the 4-monocarboxamides, i.e. substituted in the *peri* position with respect to the oxygen of the furan ring, and the dicarboxamides, although the proportions of these products ranged considerably. The same reaction conditions were used in each case: The reaction mixture contained magnesium chloride in dichloromethane and was stirred for three hours at room temperature. The overall yields (monoamide and diamide) were in the range 74–90% and it appeared that the diamide was formed more easily with linear substrates.

The possibility of obtaining unsymmetrical dicarboxamides was also explored and compounds **9** and **16** were obtained in yields of around 70%. The method used in the preparation of these compounds was similar to that used for the amidation of the monocarboxamide precursors **5** and **12**, respectively.

3. Conclusions

A convenient procedure has been developed for the synthesis of angular and linear pyridazinofurocoumarins with carboxamide chains at C4 or C1 and C4. The route involves only a small number of steps starting from resorcinols. The Diels–Alder reaction of 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine with dihydrofurocoumarinones is the key step in this approach to attach the pyridazine ring to the furan nucleus. The mild amidation conditions allow the regioselective substitution of C4 methoxycarbonyl, the synthesis of C1 and C4 dicarboxamides using an excess of amine, and the synthesis of unsymetrical dicarboxamides through sequential treatment with two different amines. These advantages make this route an easy and general method to prepare a wide range analogues for pharmacological evaluation.

4. Experimental

4.1. General

Melting points were determined in capillary tubes using a Büchi 510 apparatus and are uncorrected. IR spectra were recorded using a Perkin–Elmer 1640FT spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts are given as δ values, *J* in Hz). Mass spectra were obtained using a Hewlett Packard 5988A spectrometer. Elemental analyses were performed using a Perkin–Elmer 240B microanalyser. Silica gel (Merck 60, 230–400 mesh) was used for flash chromatography (FC). Analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm).

4.2. 8-Methyl-1,4-bis(methoxycarbonyl)pyridazino[4,5-*j*]angelicin (4)

A mixture of 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine (1.98 g, 10 mmol),[15] furocoumarinone **2** (2.376 g, 11 mmol) and *p*-TsOH (172 mg, 1 mmol) in CH_2Cl_2 (50 mL) was heated at 100°C in a sealed tube for 8 h until the red colour of the tetrazine had disappeared. The solvent was removed under vacuum and the residue was purified by flash chromatography using CH_2Cl_2/AcOEt (9:1) as eluent; yield: 2.54 g (69%); mp 240–242°C (from dioxane). IR (KBr) 1737, 1654, 1616, 1389, 1200, 1161, 1045 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.28 (d, 1H, *J*=8.7 Hz, H-7), 8.07 (d, 1H, *J*=8.7 Hz, H-6), 6.58 (s, 1H, H-9), 4.23 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 165.1, 162.0, 158.8, 158.3, 154.5, 154.3, 151.1, 149.2, 139.5, 130.6, 119.6, 117.0, 113.7, 109.7, 106.8, 54.3, 53.7, 19.2. EI-MS *m*/*z* (%) 369 (10), 368 (M^+, 22), 337, 310, 252 (33), 251 (100), 222, 221 (63), 58 (12). Anal. calcd for $C_{18}H_{12}N_2O_7$: C, 58.70; H, 3.28; N, 7.61. Found: C, 58.74; H, 3.25; N, 7.55.

4.3. 6,10-Dimethyl-1,4-bis(methoxycarbonyl)pyridazino-[4,5-*h*]psoralen (11)

This compound was prepared from **10** (2.3 g) in an

analogous manner to **4** from **2**. The crude product was purified by flash chromatography using CH_2Cl_2/AcOEt (95:5) as eluent; yield 2.83 g (74%); mp 280–282°C (from dioxane). IR (KBr) 1756, 1723, 1439, 1380, 1370, 1288, 1244, 1214, 1176, 1094, 1064 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.30 (s, 1H, H-11), 6.58 (s, 1H, H-9), 4.23 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 2.55 (s, 6H, $2CH_3$). EI-MS *m/z* (%) 382 (M^+, 23), 325, 324 (75), 323, 266, 265 (100), 264 (65). Anal. calcd for $C_{19}H_{14}N_2O_7$: C, 59.69; H, 3.69; N, 7.33. Found: C, 59.74; H, 3.62; N, 7.41.

4.4. General procedure for amidation of dimethoxycarbonylpyridazinofurocoumarins 4 and 11 with pyrrolidine

To the corresponding dimethoxycarbonylpyridazinofurocoumarin (1 mmol) in dry CH_2Cl_2 (10 mL) was added anhydrous $MgCl_2$ (3 mmol) and the mixture was stirred for 5 min at room temperature. Pyrrolidine (5 mmol) was added and the mixture was stirred for 3 h at room temperature. The mixture was acidified with 0.5 M HCl (15 mL) and extracted with CH_2Cl_2. The organic phase was washed, dried over $NaSO_4$, the solvent evaporated under reduced pressure, and the residue purified by flash chromatography (SiO_2) using CH_2Cl_2/*i*-PrOH (97:3) as eluent.

4.4.1. 8-Methyl-1-methoxycarbonyl-4-pyrrolidincarbonylpyridazino[4,5-*j*]angelicin (5) and 8-methyl-1,4-bis(pyrrolidincarbonyl)pyridazino[4,5-*j*]angelicin (6).

These compounds were prepared from **4** (108 mg) with pyrrolidine (125 μL).

Compound **5**. Yield 91 mg (75%); mp 265–266°C. IR (KBr) 1731, 1651, 1631, 1452, 1384, 1234, 1062 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.98 (d, 1H, J=8.8 Hz, H-7), 7.74 (d, 1H, J=8.8 Hz, H-6), 6.40 (d, 1H, J=1.1 Hz, H-9), 4.36 (s, 3H, OCH_3), 3.85 (m, 4H, CH_2NCH_2), 2.55 (d, J=1.1 Hz, 3H, CH_3), 2.02 (m, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$) δ 165.06, 160.83, 158.41, 158.18, 152.50, 152.30, 149.72, 144.54, 128.38, 119.16, 116.79, 114.43, 109.19, 107.81, 54.42, 48.88, 46.82, 26.33, 24.11, 19.41. EI-MS *m/z* (%) 407 (M^+, 4), 376, 320, 252, 251, 221, 195, 185, 140, 71, 70 (100), 56. HRMS-EI calcd for $C_{21}H_{17}N_3O_6$: 407.1117. Found: 407.1122.

This compound was also obtained in 92% yield using the same procedure but with 1.5 mmol of pyrrolidine.

Compound **6**. Yield 20 mg (15%); mp 256–259°C. IR (KBr) 1729, 1645, 1614, 1451, 1362, 1068 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.96 (d, 1H, J=8.8 Hz, H-7), 7.72 (d, 1H, J=8.8 Hz, H-6), 6.37 (d, 1H, J=1.2 Hz, H-9), 4.15 (m, 2H), 3.85 (m, 4H), 3.44 (m, 2H), 2.54 (d, 3H, J=1.2 Hz, CH_3), 2.02 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 163.92, 161.64, 158.79, 158.56, 154.51, 152.90, 152.56, 149.87, 144.54, 128.48, 119.12, 117.17, 114.87, 109.47, 108.17, 49.25, 48.62, 47.15, 46.39, 26.72, 26.35, 24.89, 24.54, 19.41. EI-MS *m/z* (%) 448 (3), 446 (M^+, 12), 348, 321, 251, 98, 70 (100), 58 (37). HRMS-EI calcd for $C_{24}H_{22}N_4O_5$: 446.1590. Found: 446.1579.

4.4.2. 6,10-Dimethyl-1-methoxycarbonyl-4-pyrrolidincarbonylpyridazino[4,5-*h*]psoralen (12) and 6,10-dimethyl-1,4-bis(pyrrolidincarbonyl)pyridazino[4,5-*h*]psoralen (13).

These compounds were prepared from **11** (114 mg) with pyrrolidine (125 μL).

Compound **12**. Yield 49 mg (39%); mp 272–275°C. ^1H NMR ($CDCl_3$) δ 9.16 (s, 1H, H-11), 6.40 (s, 1H, H-9), 4.25 (s, 3H, OCH_3), 3.88 (t, 2H, J=6.6 Hz, CH_2–N), 3.75 (t, J=6.6 Hz, 2H, CH_2–N), 2.75 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.05 (m, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$) δ 165.20, 161.22, 160.30, 158.08, 154.58, 153.32, 146.66, 145.44, 131.81, 125.64, 121.90, 118.76, 114.82, 111.63, 54.11, 49.16, 47.14, 26.71, 24.57, 19.75, 9.48. EI-MS *m/z* (%) 421 (M^+, 5), 265, 235, 168, 98, 70 (100), 55. HRMS-EI calcd for $C_{22}H_{19}N_3O_6$: 421.1273. Found: 421.1279.

Compound **13**. Yield 48 mg (35%); mp 288–291°C. ^1H NMR ($CDCl_3$) δ 8.63 (s, 1H, H-11), 6.29 (d, 1H, J=1.1 Hz, H-9), 3.82 (m, 6H), 3.62 (m, 2H), 2.66 (s, 3H, CH_3), 2.54 (d, 3H, J=1.1 Hz, CH_3), 1.95 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 163.52, 161.67, 160.42, 157.76, 153.93, 153.35, 151.80, 145.10, 124.05, 120.54, 118.59, 115.30, 114.66, 111.10, 49.73, 48.97, 47.63, 46.99, 26.94, 26.64, 24.64, 24.48, 19.73, 9.48. EI-MS *m/z* (%) 460 (M^+, 3), 265, 235, 168, 98, 70 (100), 55. HRMS-EI calcd for $C_{25}H_{24}N_4O_5$: 460.1746. Found: 460.1755.

4.5. General procedure for the amidation with *N*,*N*-dimethylethylenediamine of dimethoxycarbonylpyridazinofurocoumarins 4 and 11

To the corresponding dimethoxycarbonylpyridazinofurocoumarin (1 mmol) in dry CH_2Cl_2 (10 mL) was added anhydrous $MgCl_2$ (3 mmol) and the mixture was stirred for 5 min at room temperature. *N*,*N*-Dimethylethylenediamine (5 mmol) was added and the mixture was stirred for 3 h at room temperature. The mixture was acidified with 0.5 M HCl (15 mL) and washed with CH_2Cl_2. The aqueous phase was then basified with $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed, dried over $NaSO_4$, evaporated under reduced pressure, and purified by flash chromatography (SiO_2) using CH_2Cl_2/EtOH/NH_3 (68:30:2) as eluent.

4.5.1. 8-Methyl-4-(dimethylaminoethylcarbamoyl)-1-methoxycarbonyl-pyridazino[4,5-*j*]angelicin (7) and 8-methyl-1,4-bis(dimethylaminoethylcarbamoyl)pyridazino[4,5-*j*]angelicin (8).

These compounds were prepared from **4** (108 mg) with *N*,*N*-dimethylethylenediamine (166 μL).

Compound **7**. Yield 70 mg (57%); mp 225–226°C. IR (KBr) 3432, 1747, 1685, 1619, 1519, 1443, 1382, 1058, 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.63 (bs, 1H, NH), 8.00 (d, 1H, J=8.9 Hz, H-7), 7.81 (d, 1H, J=8.9 Hz, H-6), 6.39 (d, 1H, J=1.2 Hz, H-9), 4.37 (s, 3H, OCH_3), 3.71 (m, 2H, CH_2NHCO), 2.62 (t, 2H, J=6.1 Hz, CH_2NMe_2), 2.56 (d, J=1.2 Hz, CH_3-4), 2.32 (s, 6H, $N(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ 165.32, 161.27, 159.18, 158.78, 153.10, 152.77, 152.06, 150.14, 140.73, 129.04, 120.53, 117.22, 114.78, 109.81, 107.85, 58.11, 54.86, 37.56, 19.80. HRMS-EI calcd for $C_{21}H_{20}N_4O_6$: 424.1382. Found: 424.1373.

Compound **8**. Yield 40 mg (29%); mp 242–244°C. IR (KBr) 3421, 3306, 1736, 1671, 1522, 1459, 1381, 1060 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.63 (bs, 1H, NH), 7.97 (d, 1H, J=8.7 Hz, H-7), 7.78 (d, 1H, J=8.7 Hz, H-6), 7.44 (bs, 1H, NH), 6.36 (s, 1H, H-9), 3.93 (m, 2H, CH_2NCO), 3.69 (m, 2H, CH_2NCO), 2.72 (t, 2H, J=6.0 Hz, CH_2NMe_2), 2.62 (t, 2H, J=6.2 Hz, CH_2NMe_2), 2.54 (s, 3H, CH_3–C8), 2.32 (s, 12H, $2N(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ 164.87, 161.40, 159.32, 158.90, 154.88, 153.67, 152.48, 150.30, 140.59, 128.74, 121.10, 117.21, 114.82, 109.53, 108.37, 58.08, 57.55, 45.66, 45.41, 37.91, 37.50, 19.76. HRMS-EI calcd for $C_{24}H_{28}N_6O_5$: 480.2121. Found: 480.2129.

4.5.2. 6,10-Dimethyl-1-methoxycarbonyl-4-(dimethylaminoethylcarbamoyl)-pyridazino[4,5-*h*]psoralen (14) and 6,10-dimethyl-1,4-bis(dimethylaminoethylcarbamoyl)pyridazino[4,5-*h*]psoralen (15). These compounds were prepared from **11** (114 mg) with *N*,*N*-dimethylethylenediamine (166 μL).

Compound **14**. Yield 14 mg (11%). IR (KBr) 3432, 1747, 1725, 1650, 1449, 1365, 1230, 1180, 1101 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.16 (s, 1H, H-11), 8.79 (bs, 1H, NH), 6.40 (s, 1H, H-9), 4.26 (s, 3H, OCH_3), 3.73 (m, 2H, CH_2NCO), 2.80 (s, 3H, CH_3), 2.65 (m, 5H, CH_3+CH_2NMe_2), 2.38 (s, 6H, $N(CH_3)_2$). HRMS-EI calcd for $C_{22}H_{22}N_4O_6$: 438.1539. Found: 438.1547.

Compound **15**. Yield 110 mg (74%); mp 265–268°C. IR (KBr) 3333, 1729, 1673, 1637, 1597, 1518, 1462, 1366, 1333, 1218, 1180, 1101 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.45 (s, 1H, H-11), 8.82 (s, 1H, NH), 8.57 (s, 1H, NH), 6.36 (s, 1H, H-9), 3.73 (m, 4H, $2CH_2NCO$), 2.77 (s, 3H, CH_3), 2.64 (m, 7H, CH_3 + $2CH_2NMe_2$), 2.35 (s, 6H, $N(CH_3)_2$), 2.34 (s, 6H, $N(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ 162.65, 160.98, 160.00, 158.19, 155.38, 154.04, 153.30, 149.14, 140.25, 125.19, 123.13, 118.22, 114.50, 114.07, 110.86, 57.75, 57.71, 45.29, 45.26, 37.31, 37.05, 19.45, 8.96. HRMS-EI calcd for $C_{25}H_{30}N_6O_5$: 494.2277. Found: 494.2267.

4.6. 8-Methyl-1-(dimethylaminoethylcarbamoyl)-4-pyrrolidincarbonyl-pyridazino[4,5-*j*]angelicin (9)

To compound **5** (28 mg, 0.07 mmol) in dry CH_2Cl_2 (2 mL) was added anhydrous $MgCl_2$ (18 mg, 0.19 mmol) and the mixture was stirred for 5 min at room temperature. *N*,*N*-Dimethylethylenediamine (40 μL, 0.37 mmol) was added and the mixture stirred for 48 h at room temperature. 0.5 M HCl (10 mL) was added and the mixture washed with CH_2Cl_2. The aqueous layer was basified using Na_2CO_3 and extracted with CH_2Cl_2. The organic phase was washed, dried over $NaSO_4$, evaporated under reduced pressure, and the residue purified by flash chromatography using CH_2Cl_2/EtOH/NH_3 (90:10:1) as eluent; yield 23 mg (72%); mp 264–267°C (dec.). IR (KBr) 3300, 1733, 1674, 1652, 1614, 1456, 1376, 1062, 857, 817 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.95 (d, 1H, J=8.9 Hz, H-7), 7.71 (d, 1H, J=8.9 Hz, H-6), 7.38 (bs, 1H, NH), 6.36 (d, 1H, J=1.1 Hz, H-9), 3.80 (m, 6H), 2.71 (t, 2H, J=6.1 Hz, CH_2NMe_2), 2.53 (d, J=1.1 Hz, CH_3), 2.29 (s, 6H, $N(CH_3)_2$), 2.00 (m, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$) δ 164.65, 161.06, 158.59, 158.36, 153.51, 152.95, 152.07, 149.92, 144.52, 128.12, 119.75, 116.82, 114.51, 108.96, 108.38, 57.17, 48.87, 46.80, 45.09, 37.56, 26.36, 24.13, 19.41. HRMS-EI calcd for $C_{24}H_{25}N_5O_5$: 463.1855. Found: 463.1867.

4.7. 6,10-Dimethyl-1-(dimethylaminoethylcarbamoyl)-4-pyrrolidincarbonyl-pyridazino[4,5-*h*]psoralen (16)

This compound was prepared from **12** (42 mg) in an analogous manner to **9** from **5**. The crude product was purified by flash chromatography using CH_2Cl_2/EtOH/NH_3 (90:10:0.5) as eluent; yield 33 mg (69%); mp 275–278°C. IR (KBr) 3330, 1750, 1734, 1671, 1639, 1522, 1448, 1364, 1098 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.50 (s, 1H, H-11), 8.81 (t, 1H, J=5.3 Hz, NH), 6.37 (s, 1H, H-9), 3.89 (t, 2H, J=6.6 Hz), 3.63 (m, 4H), 2.73 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 2.35 (s, 6H, $2CH_3$), 2.06 (m, 4H), 1.91 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 163.46, 161.48, 160.53, 158.09, 154.53, 154.35, 153.81, 148.78, 145.41, 124.61, 123.57, 118.65, 115.47, 114.48, 111.13, 58.21, 48.99, 47.00, 45.71, 37.74, 26.65, 24.63, 19.90, 9.45. MS-CI *m*/*z* (%) 478.2 ($[M+1]^+$, 13), 177.0, 78.9, 40.9 (53), 30.3 (53), 27.0 (52), 17.0 (57), 19.1 (100). HRMS-CI calcd for $C_{25}H_{28}N_5O_5$: 478.2090. Found: 478.2082.

Acknowledgements

We thank the Spanish Ministry of Education, Culture and Sport (PM99-0125) for financial support and the University of Santiago de Compostela for the award of a fellowship to J. C. G. G.

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