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Pyridazine Derivatives. Part 21:[1] Synthesis and Structural Study of Novel 4-Aryl-2,5-dioxo-8-phenylpyrido[2,3-*d*]pyridazines

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Abstract—New substituted 4-aryl-2,5-dioxo-8-phenylpyrido[2,3-*d*]pyridazines **4a**–**f** have been prepared in one step from the corresponding arylidene substituted Meldrum's acid (**1**) and 5-amino-6-phenyl-3(2*H*)-pyridazinone (**2**) in good yields. Semiempirical theoretical calculations (AM1) reveal two favoured conformations (**A** and **B**) for compounds **4a**–**f**, with a screw boat conformation in the pyridone system and a planar pyridazinone ring. X-Ray crystallographic analysis shows that in the solid state, conformation **A** bearing the phenyl ring in a pseudoaxial position is the most stable. Compounds **4a**–**f** fulfil, from the structural point of view, all the requirements needed for exhibiting cardiotonic effects.

Introduction

It is well known that pyridazines and related compounds possess important pharmacological activity, most of them related to the cardiovascular system.[2,3] Also, a wide variety of compounds containing the 2(*1H*)-pyridone ring are found in nature and in some cases useful biological properties have been detected.[4] 2(*1H*)-Pyridones are very close in structure to 1,4-dihydropyridines, which possess interesting pharmacological activity and have been used as effective drugs for the treatment of cardiovascular diseases.[5–8]

Our recent publications have provided an efficient method for the synthesis of various fused heterocyclic compounds containing the dihydropyridone moiety. In general, these dihydropyridones can be easily prepared from Meldrum's acid by heterocyclization reaction with a β-ketoester and an aromatic aldehyde in the presence of ammonium acetate in acetic acid as solvent.[9]

Also bicyclic compounds containing the 2(*1H*)-pyridone moiety such as pyrido[2,3-*d*]pyrimidines, can be obtained by reaction of equimolar amounts of an enamine compound in acetic acid with the appropriate 5-arylidene substituted Meldrums's acid.[10,11]

Very recently, we have described the synthesis and conformational study of 5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones[12] and other bicyclic pyridone derivatives related to other structures showing cardiotonic properties.[13]

Synthesis of the five and six-member hetero-condensed pyridazinones have aroused great interest in recent years because of the range of their biological and pharmacological properties.[14–17] Thus, systems of thieno[2,3-*d*]pyridazines, pyrrolo[2,3-*d*]pyridazines and pyrido[2,3-*d*]pyridazines type were designed and synthesised as selective phosphodiesterase (PDE) IV inhibitors and their biological evaluations have shown a good selectivity profile toward the PDE IV family.[17]

As a part of our studies aimed at synthesising pyridazinones with substitution patterns required for a biological chemical programme, and continuing our interest in the chemistry and pharmacology of bicyclic derivatives of 2(*1H*)-pyridones, in this paper we apply our approach to the synthesis of novel 4-aryl-2,5-dioxo-8-phenylpyrido[2,3-*d*]pyridazines (**4**) as a novel dihydropyridone derivative condensed with a pyridazinone moiety. Since the determination of the favoured conformation has been used to account for the pharmacological effect of different compounds with similar

Keywords: pyrido[2,3-*d*]pyridazines; 3,4-dihydropyridones; theoretical calculations; conformational analysis.

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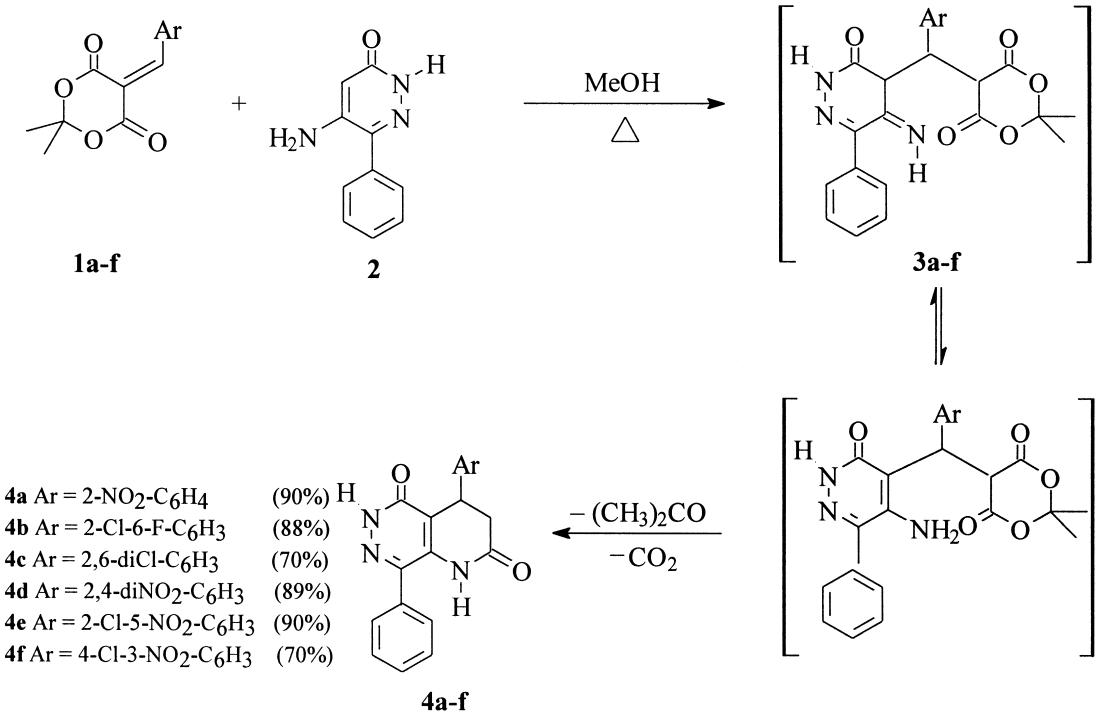

Scheme 1.

structures[18,19] and in order to predict the biological activity of compounds **4**, we also present a structural study of these compounds by X-ray analysis and quantum chemical calculations using the AM1 method.

Results and Discussion

The preparation of compounds **4** has been carried out by refluxing equimolecular amounts of the appropriate 5-arylidene substituted Meldrum's acid (**1**) with 5-amino-6-phenyl-3(2*H*)-pyridazinone (**2**) in methanol or a mixture of methanol/acetic acid by following a Hantzsch-like approach. (See Scheme 1).

Formation of **4** takes place through a conjugated addition of 5-amino-6-phenyl-3(2*H*)-pyridazinone **(2)**, obtained as we have previously reported,[20] to the Knoevenagel product **1**, synthesised from Meldrum's acid and the corresponding aromatic aldehyde in the presence of triethylamine by following a reported procedure,[21] followed by imino–enamine tautomerism and subsequent 6-*exo-trig* cyclization.[22] The subsequent loss of acetone and carbon dioxide yields the novel compounds **4** as stable crystalline solids in 70–90% yields (see Scheme 1).

Although the method appears to be quite general, the reaction times depend on the nature of the substituent in the aromatic ring of the Knovenagel compound. Thus, two strong electron acceptor groups substituted at the phenyl group decrease the reaction time. For instance, the compound **4d** was obtained in just 8 h while the formation of compound **4a** required 20 h (see Experimental).

It is worth mentioning that the use of catalytic glacial acetic acid results in shorter reaction times and increased yields. Thus, the pyridopyridazine derivatives **4a** and **4c** could be obtained in higher yields than without catalyst.

Pyrido[2,3-*d*]pyridazines **4a**–**f** now prepared were fully characterised by their analytical and spectroscopical data. Thus compounds **4a**–**f** showed the presence of NH and carbonyl groups at 3380–3280 cm^{-1} and 1715–1640 cm^{-1}, respectively. In the ^1H NMR the NH corresponding to pyridazinone and pyridone rings appears at $\delta\backsim$13.10 and δ 9.75–9.45, respectively, as a broad singlet and it is deuterium oxide exchangeable. Also, ^1H NMR spectra of compounds **4** show the two protons on C3 at δ 3.43–3.33 and δ 2.63–2.55 as part of an ABX system which was confirmed by a doublet of doublets at δ 4.9–4.7 corresponding to the proton on C-4 due to splitting by coupling with the protons on C3 ($J_{4,3}$=1.6 and $J_{4,3'}$=7.2 Hz). The ^{13}C NMR spectra show the signals for the olefinic carbons C4a ($\delta\backsim$116) and C8a ($\delta\backsim$147) as unusually low and high δ values, respectively, thus indicating a strong *push–pull* effect due to the electronic behaviour of the substituent. This finding has been previously observed in other related molecules.[11–13,23,24] The ^{13}C NMR assignment was supported by DEPT 135°, DEPT 90°, HMBC and HMQC experiments.

X-Ray crystallography and quantum chemical calculations have been widely used for the structural and conformational analysis of related compounds[25] and determination of the favoured conformation has allowed the pharmacological effect of the compound[26] to be accounted for. Here we report the conformational study of 4-aryl-2,5-dioxo-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazines. The results of semiempirical molecular orbital calculations (AM1) are

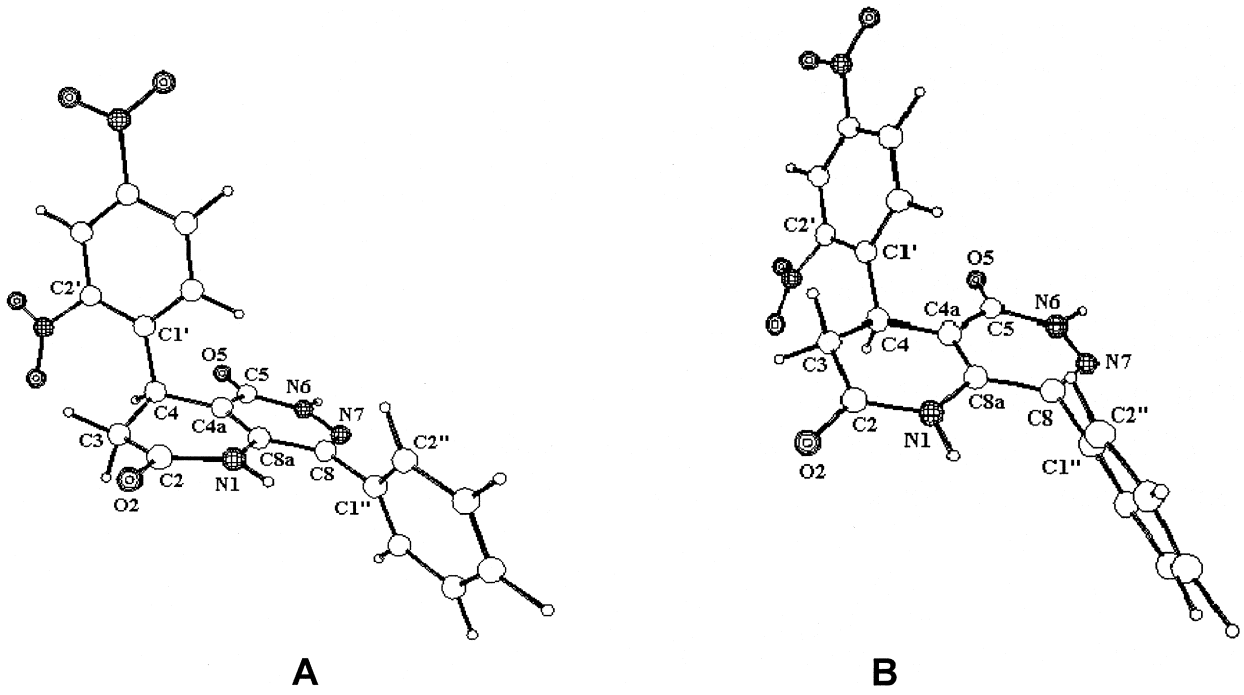

Figure 1. Semiempirical (AM1) optimised geometries for lowest energy conformers (**A** and **B**) of compound **4d**.

compared with the data obtained by X-ray crystallographic study for **4b** and **4e**.

Initially, we have carried out the determination of the favoured geometry for all novel compounds **4a**–**f** with the quantum chemical AM1 method and two favoured conformations (**A** and **B**) were found for these compounds (Fig. 1). In both cases the pyridone ring showed a twisted conformation,

Table 1. Most relevant bond distances, valence angles and dihedral angles for minimum energy conformation found. All geometrical data is referring to conformation **A**. (The numbering scheme is shown in Fig. 1)

Compound	**4a** (AM1)	**4b** (AM1)	**4b** (X-Ray)	**4c** (AM1)	**4d** (AM1)	**4e** (AM1)	**4e** (X-ray)	**4f** (AM1)
Bond distances								
N1–C8a	1.383	1.383	1.394(4)	1.383	1.382	1.383	1.395(4)	1.383
C8a–C4a	1.383	1.385	1.369(4)	1.383	1.385	1.385	1.364(5)	1.384
C4a–C4	1.490	1.492	1.508(4)	1.490	1.491	1.490	1.504(8)	1.492
C4–C3	1.526	1.527	1.546(4)	1.526	1.527	1.527	1.534(5)	1.523
C3–C2	1.508	1.508	1.504(4)	1.508	1.509	1.511	1.504(6)	1.511
C2–N1	1.399	1.403	1.363(4)	1.398	1.404	1.402	1.364(7)	1.401
C4–C1′	1.504	1.504	1.517(5)	1.505	1.505	1.503	1.525(5)	1.503
C8–C1″	1.473	1.472	1.499(5)	1.473	1.472	1.472	1.486(5)	1.472
Valence angles								
C2–N1–C8a	121.9	121.3	123.2(3)	121.9	121.3	121.3	123.2(3)	121.4
C4a–C4–C3	113.4	111.1	109.6(2)	113.5	111.3	110.9	109.2(3)	111.1
O5–C5–C4a	126.9	126.7	124.3(4)	127.0	126.4	126.6	124.0(4)	126.4
O2–C2–N1	118.2	118.2	120.7(4)	118.2	118.3	118.6	121.5(3)	118.7
Dihedral angles								
N1–C8a–C4a–C4	0.8	0.6	−6.7(4)	0.3	−0.3	2.2	−6.5(4)	3.5
C8a–C4a–C4–C3	−14.1	−24.8	−17.2(4)	−13.4	−23.8	−27.3	−19.9(5)	−27.1
C4a–C4–C3–C2	22.7	37.3	38.1(3)	22.0	36.6	39.0	40.1(4)	28.0
C4–C3–C2–N1	−19.8	−28.7	−37.6(4)	−19.5	−28.5	−29.0	−36.0(4)	−28.5
C3–C2–N1–C8a	6.2	3.7	12.8(4)	6.1	3.7	3.0	8.1(5)	3.9
C2–N1–C8a–C4a	3.8	11.3	10.1(4)	3.9	11.6	11.4	13.1(4)	9.4
$\sum\|\rho\|$[a]	**67.4**	**106.4**	**122.5**	**65.2**	**104.5**	**111.9**	**123.7**	**110.4**
O5–C5–C4a–C8a	177.1	177.8	176.5(3)	176.9	178.3	176.5	−176.2(3)	178.0
O2–C2–N1–C8a	−176.6	−178.8	−171.0(3)	−176.6	−178.7	−178.1	−174.5(3)	−178.3
H3a–C3–C4–H4	−99.4	−83.8	−85.59(3)	−100.4	−84.1	−98.8	−82.8(3)	−82.3
H3b–C3–C4–H4	18.0	33.3	30.92(3)	16.9	32.9	18.5	33.4(3)	35.7
C8a–C4a–C4–C1′	113.9	100.1	111.2(3)	114.5	101.1	113.0	107.1(3)	99.2
C2′–C1′–C4–C4a	−59.0	151.6	118.1(3)	−56.3	71.1	151.6	158.5(4)	−94.4
C2″–C1″–C8–C8a	−63.6	−62.9	−124.4(3)	−63.7	−63.2	−62.8	−59.9(5)	−62.0

[a] $\sum|\rho|$ Sum of the modular values of internal dihedral angles of dihydropyridone ring.

with C4 and C3 placed out of the molecular pseudoplane. In conformation **A**, the aryl substituent at carbon C4 lies in a pseudoaxial position, while in **B** the aryl substituent is in a pseudoequatorial position. Although the theoretical calculations showed two minimum energy conformations, the calculated heats of formation for these compounds indicated that the conformation **A** is approximately 2 kcal/mol more stable than conformation **B**. In both cases the magnitude of the C2′–C1′–C4–C4a torsion angle shows that the aryl ring is orthogonal to the mean plane of the pyridone ring. This orientation is preferred in the *ortho* phenyl substituted derivatives (**4a**–**e**) because it minimises the steric strain imposed by the *ortho* phenyl substituent. The pyridazinone ring, in all cases, is essentially planar and the phenyl group is orthogonal to this plane as shown in Fig. 1.

The geometrical features predicted by AM1 calculations for the two conformations (**A** and **B**) of **4a**–**f** and determined by X-ray analysis (for **4b** and **4e**) are listed in Table 1, showing the most relevant bond distances, valence angles and dihedral angles.

The X-ray structure of compound **4b** (Fig. 2) shows that the pyridone ring has a screw-boat conformation (starting on N1, C2···8a closewise) with bowsprit at C3 pointing down and puckering parameters[27] Q=0.355(3) Å, θ=116.4(5)° and ϑ=307.1(5)°. Mirror symmetry is dominant with a local pseudo-mirror plane running along C3···C8a. The C1 substituent on the phenyl ring is *syn*periplanar to the H atom at C4 in the pyridone ring, while the F is *anti*periplanar oriented. The dihedral angle between the least-squares planes of the substituted phenyl and the pyridone rings is 79.78(2)° and between the pyridazinone ring and the unsubstitued phenyl ring is 57.37(2)°. The mean Csp^2–Csp^2 bond length within the phenyl rings at C4 and C8 is 1.383(2) and 1.377(2) Å, respectively. The pyridazinone ring is essentially planar. The crystal structure is stabilised by means of hydrogen bonds and van der Waals interactions. There are two intermolecular hydrogen bonds [N6···O5 (2−x, −y, −z)=2.795(3) Å and N1···O2 (1−x, 1−y, −z)= 2.888(3) Å].

Compound **4e** crystallised with two independent molecules in the asymmetric unit. As in **4b**, the pyridone ring (in each independent molecule) has a boat conformation with bowsprit at C3a (C3b, in molecule B) pointing down and puckering parameters[25] [molecule A: Q=0.367(4) Å, θ=114.2(6)° and ϑ=313.7(7)°; molecule B: Q= 0.398(5) Å, θ=116.6(6)° and ϑ=317.6(7)°]. Mirror symmetry is dominant with a local pseudo-mirror plane running along C3a···C8aa [C3b···C8ab, in molecule B].

The C1 substituent on the phenyl ring is *syn*periplanar to the H atom at C4 in the pyridone ring, while the nitro group is *anti*periplanar oriented, for each molecule in the asymmetric unit. The dihedral angle between the least-squares planes of the substituted phenyl ring and the pyridone moiety is 81.8(2)° (82.0(2)°, in molecule B), and between the pyridazinone ring and the unsubstituted phenyl ring is 57.4(2)° (49.2(2)°, in molecule B). The mean Csp^2–Csp^2 bond length within the phenyl rings at C4 and C8 is 1.378(5) and 1.382(4) Å, in molecule A, and 1.377(5) and 1.379(5) Å in molecule B, respectively.

The pyridazinone ring in each independent molecule is essentially planar. In this case, the crystal structure is also stabilised by means of hydrogen bonds and van der Waals interactions. There is an intramolecular hydrogen bond [N1a···O2b=3.24(2) Å, and N1b···O2a=2.83(2) Å]

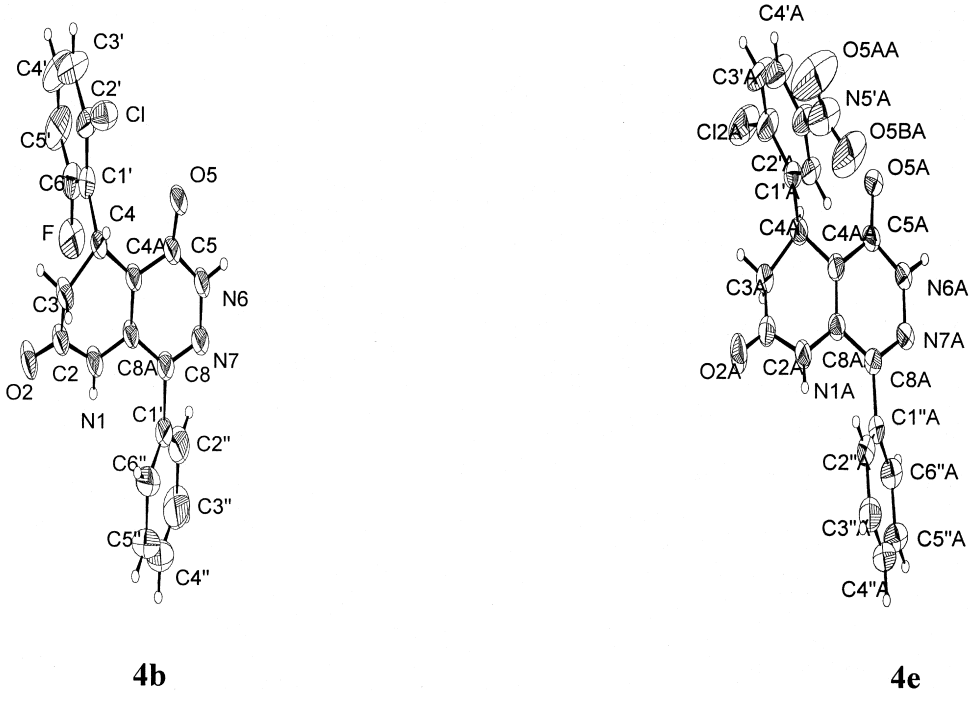

Figure 2. X-Ray structure of compounds **4b** and **4e** showing the numbering scheme.

and an intermolecular hydrogen bond [N6a···O5a (−x+1, −y+2, −z+1)=2.77(2) Å, and N6b···O5b (−x+2, −y, −z)=2.75(2) Å], for each molecule in the asymmetric unit, respectively.

Although predicted values compare in general quite well with the experimental data, it is important to note some interesting deviations from the predictions of the theoretical model. Thus AM1 calculations overestimate the C2–N1 distance and underestimate the C4a–C4 distance, both bonds belonging to the dihydropyridone ring (see Table 1).

The pseudo-boat conformation for the 3,4-dihydropyridone ring with a pseudoaxial orientation of the aryl group is evident in all cases, although an enforced planarity of this region of the dihydropyridone ring by the carbamoyl group is observed. X-Ray analysis shows a more distorted boat-type conformation of the dihydropyridone ring than that predicted from theoretical calculations (see in Table 1 the internal dihedral angles of the dihydropyridone ring ($\sum|\rho|^{28}$)). In particular, the C4 and N1 atoms are placed further above the plane of the pyridone ring than predicted by AM1 calculations. (See dihedral angles containing C4: C4a–C4–C3–C2, C8a–C4a–C4–C3 and N1: C2–N1–C8a–C4a, C3–C2–N1–C8a.) This fact has also been observed for other dihydropyridone rings.[12,13]

The torsion angle values O2–C2–N1–C8a close to 180° show that the dihydropyridone ring is extremely flattened around N1 due to the amide-type character of the N1–C2 bond.

The *exo*cyclic carbonyl oxygen at position 2 is placed between eclipsed and bisected conformation with respect to the methylene hydrogens of C-3, and is strongly conjugated with *endo*cyclic C4a–C8a double bond, leading to a slight distortion of the pyridone ring in a twist conformation. The value of C2–N1–C8a close to 120°, calculated by semiempirical method and determined by X-ray, shows sp^2 hybridisation for the nitrogen atom.

The calculations and experimental data show that the pyridazinone ring fused to the pyridone is essentially planar and the phenyl group in C8 is orthogonal to the former ring indicating no conjugation between the aromatic ring in C4 and C8. It is important to note that the geometrical parameters calculated for the more stable conformation **A** are in good agreement with those found by X-ray analysis. These findings suggest that semiempirical methods (AM1) are useful for predicting conformational features on this class of compound.

In summary, we describe a novel synthesis of pyrido[2,3-*d*]-pyridazines from the corresponding arylidene substituted Meldrum's acid **1** and the enamine compound **2** by a Hantzsch-like mechanism. Theoretical calculations reveal favoured geometry with a twisted boat conformation in the dihydropyridone system and a planar pyridazinone moiety. The biological data for these compounds will be reported elsewhere and it should be pointed out that compounds **4** fulfil most geometrical features found for other related compounds exhibiting remarkable pharmacological activity.

Experimental

Melting points were determined in a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured with a Perkin–Elmer 1640 FTIR spectrophotometer as potassium bromide pellets. The NMR spectra were obtained on Bruker AM300 and XM500 spectrophotometers. Chemical shifts are given as δ values against tetramethylsilane as internal standard and *J* values are given in Hz. Mass spectra were determined on a Varian MAT-711 instrument. Elemental analyses were performed on a Perkin–Elmer 240B apparatus at the Microanalysis Service of the University of Santiago de Compostela. The reactions were monitored by TLC chromatography with 2.5 mm Merck silica gel GF 254 strips, and the purified compounds each showed a single spot; unless otherwise stated iodine vapour and/or UV light were used for detection. Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification.

Semiempirical AM1 calculations[29] were carried out by using the MOPAC[30] program. Previously, the molecular geometry was optimised by using Allinger's Molecular Mechanics[31] with PCMODEL program.[32] Calculations were performed on a PC 486/33 computer.

The X-ray determination was performed in a Siemens P4 four-circle diffractometer with graphite monochromated and Cu–Kα radiation (**4b**) and in a Stoe STADI-4 four-circle diffractometer with graphite monochromated and Mo–Kα radiation (**4e**).

5-Arylidene-2,2-dimethyl-1,3-dioxan-4,6-diones (1a–f) were obtained by following the method previously reported in the literature.[21]

5-Amino-6-phenyl-3(2*H*)-pyridazinone (2) was obtained by the standard procedure previously reported by us in the literature.[20]

4-Aryl-2,5-dioxo-8-phenyl-1,2,3,4,5,6-hexahydropyrido-[2,3-*d*]pyridazines (4)

General procedure. A mixture of the appropriate arylidene-2,2-dimethyl-1,3-dioxane-4,6-dione **1** (40 mmol) and 5-amino-6-phenyl-3(2*H*)-pyridazinone (**2**) (40 mmol) in methanol (50 mL) were refluxed for a variable length of time (8–28 h, monitored by TLC) and then the solution was poured into ice water. The solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from ethanol. Glacial acetic acid (10 mL) was used as catalyst for the synthesis of **4a** and **4c**.

2,5-Dioxo-4-(2-nitrophenyl)-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazine (4a). This compound was obtained by following the above general procedure, by refluxing **1a** and **2** for 20 h in 90% yield as a white solid, mp 264°C (dec) (from ethanol) [Found: C, 62.80; H, 3.77; N, 15.35; $C_{19}H_{14}N_4O_4$ requires C, 62.98; H, 3.89; N, 15.46%]; ν_{max} cm^{-1} 3384 (NH), 3111 (CH), 1715, 1645 (C═O), 1576, 1518 (C═C), 1530 (NO_2) and 1341 (NO_2); δ_H (300 MHz, DMSO-d_6) 13.09 (1H, br s, NH, deuterium

oxide exchangeable), 9.53 (1H, br s, NH, deuterium oxide exchangeable), 8.01 (1H, dd, J=7.7, 0.9 Hz, Ph), 7.61–7.49 (2H, m, Ph), 7.47 (5H, s, Ph), 7.18 (1H, dd, J=7.7, 0.9 Hz, Ph), 4.78 (1H, dd, J=7.2, 1.6 Hz, H-4), 3.34 (1H, dd, J=7.2, 9.6 Hz, H-3), 2.60 (1H, dd, J=9.6, 1.6 Hz, H-3′); δ_C (DMSO-d_6) 168.9, 159.9, 149.0, 140.1, 139.9, 135.2, 133.4, 134.3, 129.5, 129.1, 129.0, 128.4, 127.9, 125.5, 117.6, 37.0, 31.2; m/z 362 (M^+, 2%), 332 (80), 314 (100), 290 (62) and 256 (28).

4-(2-Chloro-6-fluorophenyl)-2,5-dioxo-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazine (4b). This compound was obtained by following the above general procedure, by refluxing **1b** and **2** for 8 h in 88% yield as a white solid, mp 292–293°C (from ethanol) [Found: C, 61.69; H, 3.36; N, 11.47; requires $C_{19}H_{13}ClFN_3O_2$ C, 61.72; H, 3.54; N, 11.36%]; ν_{max} cm^{-1} 3300 (NH), 3150 (CH), 1708, 1640 (C═O), 1573, 1500 (C═C); δ_H (300 MHz, DMSO-d_6) 13.20 (1H, br s, NH, deuterium oxide exchangeable), 9.45 (1H, br s, NH, deuterium oxide exchangeable), 7.49 (5H, s, Ph), 7.35 (2H, m, Ph), 7.15 (1H, m, Ph), 4.89 (1H, dd, J=6.5, 0.7 Hz, H-4), 3.34 (1H, dd, J=8.3, 6.5 Hz, H-3), 2.60 (1H, dd, J=8.3, 0.7 Hz, H-3′); δ_C (DMSO-d_6) 168.7, 160.0, 145.0, 140.0, 139.9, 134.7, 134.5, 132.5, 133.5, 133.2, 131.5, 131.0, 128.5, 126.5, 115.8, 39.0, 30.4; m/z 369 (M^+, 7%), 335 (22), 334 (100) and 292 (22).

X-Ray structure analysis. Crystals of **4b** were grown by slow evaporation from an ethanol solution.

Crystal data

$C_{19}H_{13}ClFN_3O_2$, M=369.78, Monoclinic, a=12.471(3), b=7.926(2), c=18.217(6) Å, β=103.37(3)°, V=1751.9(9) $Å^3$ (by least-squares refinement on diffractometer angles for 53 automatically centred reflections with $4.96<\theta<39.40°$, λ=1.54178 Å, T=293(2) K), space group $P2_1/c$, Z=4, D_c=1.4020(7) g cm^{-3}, μ=2.19 mm^{-1}. A prismatic colourless crystal (0.50×0.34×0.10 mm) was used for the analysis. Detailed crystallographic data for compound **4b** have been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC 134225) and are available on request.

4-(2,6-Dichlorophenyl)-2,5-dioxo-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazine (4c). This compound was obtained by following the above general procedure, by refluxing **1c** and **2** for 28 h in 70% yield as a white solid, mp 285–287°C (from ethanol) [Found: C, 58.97; H, 3.25; N, 10.81; requires $C_{19}H_{13}Cl_2N_3O_2$ C 59.08; H 3.39; N 10.88%]; ν_{max} cm^{-1} 3380 (NH), 3130 (CH), 1710, 1640 (C═O) and 1576, 1518 (C═C); δ_H (300 MHz, DMSO-d_6) 13.09 (1H, br s, NH, deuterium oxide exchangeable), 9.45 (1H, br s, NH, deuterium oxide exchangeable), 7.50 (5H, s, Ph), 7.35 (2H, m, Ph), 7.20 (1H, m, Ph), 4.89 (1H, dd, J=6.5, 0.7 Hz, H-4), 3.34 (1H, dd, J=8.3, 6.5 Hz, H-3), 2.60 (1H, dd, J=8.3, 0.7 Hz, H-3′); δ_C (DMSO-d_6) 170.0, 164.3, 150.3, 150.6, 143.4, 141.8, 139.0, 135.0, 134.0, 133.8, 132.4, 129.0, 128.5, 124.9, 117.2, 37.5, 32.7; m/z 385 (M^+, 9%), 351 (79) and 314 (100).

2,5-Dioxo-4-(2,4-dinitrophenyl)-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazine (4d). This compound was obtained by following the above general procedure, by refluxing **1d** and **2** for 8 h in 89% yield as a white solid, mp 287°C (dec) (from ethanol), [Found: C, 55.81; H, 3.31; N, 17.25; requires $C_{19}H_{13}N_5O_6$ C, 56.02; H, 3.21; N, 17.19%]; ν_{max} cm^{-1} 3284 (NH), 3100 (CH), 1710, 1645 (C═O), 1576, 1518 (C═C); 1530 (NO_2) and 1341 (NO_2); δ_H (300 MHz, DMSO-d_6) 13.12 (1H, br s, NH, deuterium oxide exchangeable), 9.64 (1H, br s, NH, deuterium oxide exchangeable), 8.77 (1H, d, J=2.1 Hz, Ph), 8.42 (1H, dd, J=8.6, 2.1 Hz, Ph), 7.60 (1H, m, Ph), 7.50 (5H, s, Ph), 4.85 (1H, dd, J=7.2, 1.6 Hz, H-4), 3.43 (1H, dd, J=7.2, 9.6 Hz, H-3), 2.63 (1H, dd, J=9.6, 1.6 Hz, H-3′); δ_C (DMSO-d_6) 171.9, 163.3, 152.5, 150.6, 145.7, 143.8, 143.4, 136.9, 133.9, 133.0, 132.5, 129.3, 128.7, 124.4, 119.9, 39.9, 35.3; m/z 407 (M^+, 9%), 377 (79), 358 (60), 313 (100) and 289 (42).

4-(2-Chloro-5-nitrophenyl)-2,5-dioxo-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazine (4e). This compound was obtained by following the above general procedure, by refluxing **1e** and **2** for 10 h in 90% yield as a white solid, mp 325°C (dec) (from ethanol) [Found: C, 57.45; H, 3.39; N, 14.21; requires $C_{19}H_{13}ClN_4O_4$ C, 57.51; H, 3.30; N, 14.12%]; ν_{max} cm^{-1} 3300 (NH), 3160 (CH), 1709, 1648 (C═O), 1523, 1487 (C═C); 1551 (NO_2) and 1347 (NO_2); δ_H (300 MHz, DMSO-d_6) 13.15 (1H, br s, NH, deuterium oxide exchangeable), 9.75 (1H, br s, NH, deuterium oxide exchangeable), 8.12 (1H, dd, J=6.3, 1.0 Hz, Ph) 7.80 (1H, d, J=6.3 Hz, Ph), 7.60 (1H, m, Ph) 7.50 (5H, s, Ph), 4.85 (1H, dd, J=7.2, 1.6 Hz, H-4), 3.33 (1H, dd, J=9.6, 7.2 Hz, H-3), 2.55 (1H, dd, J=9.6, 1.6 Hz, H-3′); δ_C (DMSO-d_6) 168.6, 159.8, 147.0, 140.6, 140.1, 139.8, 139.6, 133.5, 132.0, 131.3, 129.9, 129.0, 127.8, 122.1, 116.7, 35.8, 33.0; m/z 396 (M^+,10%), 361 (100), 315 (16) and 273 (5).

X-Ray structure analysis. Crystals of **4e** were grown by slow evaporation from an ethanol solution.

Crystal data

$C_{19}H_{13}N_4O_4Cl$, M=396.78, Triclinic, a=7.59(4), b=15.149(10), c=17.909(10) Å, α=115.03(4), β=98.41(4), γ=92.54(4)°, V=1833(10) $Å^3$ (by least-squares refinement on diffractometer angles for 24 automatically centred reflections in the range $\bar{1}9<\theta<25°$, λ=0.71069 Å, T=293(2) K), space group $P\bar{1}$, Z=4, D_c=1.438(8) g cm^{-3}, μ=0.24 mm^{-1}. A prismatic colourless crystal (0.5×0.25×0.25 mm) was used for the analysis. Detailed crystallographic data for compound **4e** have been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC 134226) and are available on request.

4-(4-Chloro-3-nitrophenyl)-2,5-dioxo-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazine (4f). This compound was obtained by following the general procedure, by refluxing **1f** and **2** for 12 h in 70% yield as a white solid, mp 310°C (from ethanol) [Found: C, 57.39; H, 3.41; N, 14.27; requires $C_{19}H_{13}ClN_4O_4$ C 57.51; H 3.30; N 14.12%]; ν_{max} cm^{-1} 3380 (NH), 3100 (CH), 1720, 1645 (C═O), 1570, 1520 (C═C); 1530 (NO_2) and 1341 (NO_2); δ_H (300 MHz, DMSO-d_6) 13.15 (1H, br s, NH, deuterium oxide exchangeable), 9.60

(1H, br s, NH, deuterium oxide exchangeable), 8.15 (1H, d, J=1.8 Hz, Ph), 7.87 (1H, d, J=7.0 Hz, Ph), 7.60 (1H, d, J=7.0 Hz, Ph), 7.50 (5H, s, Ph), 4.85 (1H, dd, J=7.2, 1.6 Hz, H-4), 3.33 (1H, dd, J=9.6, 7.2 Hz, H-3), 2.55 (1H, dd, J=9.6, 1.6 Hz, H-3′); δ_C (DMSO-d_6) 168.9, 160.3, 150.5, 147.6, 145.0, 142.1, 139.4, 136.9, 135.9, 134.1, 130.8, 128.9, 127.2, 123.4, 115.9, 38.5, 32.3; m/z 396 (M^+, 8%), 361 (100), 315 (10) and 273 (3).

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