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Short communication

Synthesis, conformational analysis and antiviral and antitumoral activity of new 1,2-disubstituted carbocyclic nucleosides

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Abstract

New 1′,2′-*cis*-disubstituted 8-azapurine-based carbocyclic analogues of nucleosides with or without a methylene between the carbocycle and the base were synthesised, starting from appropriate amino alcohols, via 6-chloro-8-azapurines; their antiviral and antitumoral activities were evaluated; and their structures were compared with that of 2′,3′-dideoxyadenosine (ddA) on the basis of AM1 calculations. No new compound had antiviral activity. The one with the best overall antitumoral activity against L1210, Molt4/C8 and CEM/0 cells, compound **10**, was that in which the position of the hydroxymethyl group on the carbocycle relative to the heterocyclic base was closest to that found in the best-fitting low-energy conformer of ddA. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: carbonucleosides; azapurine derivatives; AM1 semiempirical method; antiviral agents; antitumor agents

1. Introduction

In recent years a large number of nucleoside analogues with antiviral and/or antitumoral properties have been designed and synthesised [1,2]. Of particular interest are carbocyclic nucleoside analogues (carbonucleosides) [3], in which the endocyclic oxygen of the nucleoside sugar ring is replaced by a methylene group, and 2′,3′-dideoxynucleosides, six of which have been approved for control of HIV infection [4]. In view of the success of these two modifications, in our laboratory we have begun to explore the potential of 1,2-disubstituted carbonucleosides (OTCs), in which the usual 1,3 substitution pattern of the carbocycle is replaced by a 1,2 pattern.

In previous work we studied the structures of pyrimidine-based OTCs in which a hydroxymethyl group at position 2 of the carbocycle is *cis* to the base at position 1 [5], and of purine-based OTCs in which the hydroxymethyl and base are mutually *trans* [6]. In the work described here we synthesised and evaluated the antiviral and antitumoral activities of the 8-azapurine derivatives **7**–**10** (Fig. 1), and performed theoretical calculations on the structures of compounds **9** and **10** and of the previously reported purine derivatives **11** and **12** (Fig. 2) [7]. In compounds **7**, **9** and **11** the carbocycle is directly bound to the purine N9 atom, while in **8**, **10** and **12** the carbocycle and base are linked by a methylene group so that the hydroxymethyl hydroxyl and N9 are separated by the same number of atoms as in natural nucleosides; in all six compounds the substituents on the carbocycle are mutually *cis*, like the substituents on the sugar ring of natural nucleosides. The structural calculations were carried out using the semiempirical method AM1, which has previously been found by ourselves and others [8] to afford results that are consistent with NMR [9] and X-ray diffraction [10] data. Calculations were likewise performed for 2′,3′-dideoxyadenosine (ddA), and the fit between conformers of **9**–**12** and ddA was examined.

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2. Chemistry

2.1. Synthetic procedures

Racemic compounds **7** and **9** were synthesised starting from (±)-*cis*-(2-aminocyclopentyl)methanol (**1**) [11], and compounds **8** and **10** starting from (±)-*cis*-(2-aminomethylcyclopentyl)methanol (**2**) [12] (Fig. 1). Compounds **1** and **2** were condensed with 5-amino-4,6-dichloropyrimidine in refluxing *n*-butanol containing triethylamine [13], affording compounds **3** and **4**, respectively, in both cases in 71% yield. A triazole ring was then formed by intramolecular reaction of the diazonium salt of the primary amino group with sodium nitrite in an acidic medium, affording compounds **5** and **6**. Compounds **5** and **6** were not isolated (because of their great instability), but were subjected directly to nucleophilic substitution reactions in which the chlorine atom at position 6 of the 8-azapurine was replaced by an hydroxyl or an amino group supplied by 1 M hydrochloric acid or ammonium hydroxide, respectively. The 8-azainosine derivatives **7** and **8** were obtained in 76 and 71% yield, respectively, from **3** and **4**, and compounds **9** and **10** in, respectively, 91 and 92% yield from **3** and **4**.

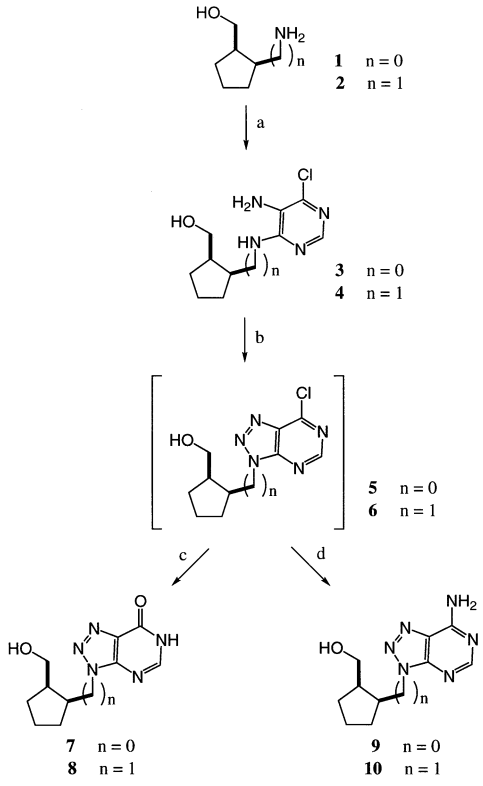

Fig. 1. Reagents and conditions: (a) 5-amino-4,6-dichloropyrimidine–Et_3N–*n*-BuOH, 71%; (b,c) $NaNO_2$–1 M HCl, 76 and 71%; (b,d) $NaNO_2$–1 M HCl then NH_4OH, 91 and 92%.

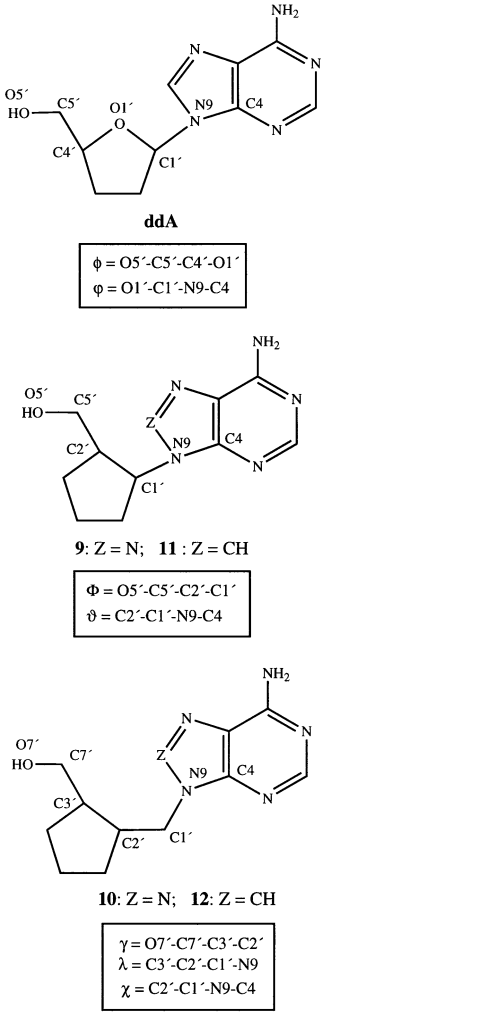

Fig. 2. Atom-numbering and relevant dihedral angles of ddA and compounds **9**–**12**.

2.2. Conformational analyses

Conformational analyses relative to ddA were performed by AM1 calculations considering the parameters with most influence on the position of the base relative to the exocyclic hydroxymethyl group, which is the most important geometric feature for biological activity [14]. Specifically, for ddA we varied the dihedral angles around the exocyclic C4′–C5′ bond (ϕ) and the glycoside bond (φ); for **9** and **11**, the corresponding angles Φ and ϑ; and for **10** and **12** the three exocyclic angles γ, λ and χ (Fig. 2).

The low-energy conformers of compounds **9**–**12** were superimposed on each of the low-energy conformers of ddA by least-squares fits of the N atoms and hydroxymethyl O atom (for **10** and **12**, conformers were examined at 10° intervals in the ranges where the energy surface is flat).

3. Pharmacology

The activities of compounds **9**–**12** against a large series of viruses were evaluated in assays carried out in various cell cultures, as follows: HIV-1 and HIV-2 in human T-lymphocyte (CEM) cells; vesicular stomatitis, Coxsackie B4 and polio-1 viruses in human epithelial (HeLa) cells; HSV-1 (KOS), HSV-2 (G), HSV-1 TK^- (B2006), HSV-2 TK^- (VMW1837) and vaccinia and vesicular stomatitis viruses in human embryonic skin-muscle fibroblast (E6SM) cells; and parainfluenza-3 virus, reovirus-1 and Sindbis, Coxsackie B4 and Semliki Forest virus in African green monkey kidney (Vero) cells.

The antitumoral activities of compounds **7**–**10** were evaluated in parallel with that of Ara A in murine leukaemia cells (L1210), in Molt4/C8 human T lymphocytes and in CEM/0 T cells (the results of identical tests of **11** and **12** against these cell lines have been reported previously [7]).

4. Results and discussion

The main results of the AM1 calculations are listed in Table 1. The energies of ddA conformers ranged from -4.75 to 3.80 kcal mol^{-1}, the three most stable ($\varepsilon = -3.84$, -4.75 and -4.65 kcal mol^{-1}) having ϕ angles of 180°, $+60°$ and $-60°$, respectively, and φ angles of $-90°$, i.e. the *anti* glycoside bond conformation that has been found in stable ddA conformers in previous studies [15] as well as in most active nucleosides [16]. The conformers of compound **11** had energies of 26.00–52.50 kcal mol^{-1}, and those of compound **9** energies of 63.40–87.50 kcal mol^{-1}; in both cases $\Phi = 180°$ or $\pm 60°$ and $\vartheta = -90°$ or $-120°$ in the most stable conformers. Quite similar results were obtained for **12** and **10**: the conformers of **12** had energies of 19.30–64.00 kcal mol^{-1}, those of **10** energies of 57.20–103.50 kcal mol^{-1}, and in the most stable conformers of both $\gamma = \pm(60–100°)$ or 180°, $\lambda = -(60–100°)$ or 180° and $\chi = \pm(60–100°)$ or 180°.

In terms of the root mean square of the $O_{CH_2OH}\cdots N$ distances for N1, N3, N7 and N9, best fit was achieved between the ddA conformer with $\phi = -60°$ and $\varphi = -90°$ and the conformers of **9**–**12** listed in the right-hand panel of Table 1, all of which have energies close to the corresponding minimum-energy conformers ($\Delta\varepsilon = 0.8–2.8$ kcal mol^{-1}). On this basis, compounds **10** and **12**, in which the carbocycle and base are separated by a methylene, fit ddA slightly better than **9** and **11** (Fig. 3), but their carbocycles, unlike those of **9** and **11**, are almost perpendicular to the ddA sugar ring.

Compounds **7**–**10** (this work) and **11** and **12** [7] achieved no significant inhibition of the replication of the studied viruses. Assays comparing their antitumoral activities with that of Ara A showed compounds **8**, **10** and **12** to be the most active, causing a 50% reduction in cell proliferation at concentrations of, respectively, 61.8 ± 20.0, 93.3 ± 12.2 and 102 ± 3 [7] μg mL^{-1} for L1210 murine leukaemia cells (Ara A: 14.2 ± 6.4 μg mL^{-1}), 128 ± 101, 98.8 ± 24.4 and 100 ± 18 [7] μg mL^{-1} for Molt4/C8 human T lymphocytes (Ara A: 11.9 ± 7.3 μg mL^{-1}) and 124 ± 97, 115 ± 14 and 108 ± 11 [7] μg mL^{-1} for CEM/0 T cells (Ara A: 24.8 ± 1.9 μg mL^{-1}).

Table 1

Compound	Most stable conformers [a]			Conformers best fitting ddA					
	ε	Dihedral angles	RMS	$\Delta\varepsilon$ [b]	Dihedral angles	HO···N distances (Å)				RMS
						N1	N3	N7	N9	
ddA	−4.65	$\phi = -60$ $\varphi = -90$				6.81	5.62	3.88	3.53	
11	26.00	$\Phi = 180$ $\vartheta = -120$	0.63	+1.26	$\Phi = -100$ $\vartheta = -120$	6.50	5.46	4.04	3.47	0.15
9	63.40	$\Phi = 180$ $\vartheta = -120$	0.61	+1.61	$\Phi = -100$ $\vartheta = -130$	6.73	5.29	4.17	3.41	0.18
12	19.30	$\gamma = 80$ $\lambda = -70$ $\chi = -80$	0.28	+0.80	$\gamma = 90$ $\lambda = -70$ $\chi = -60$	6.77	5.46	3.81	3.27	0.12
10	57.20	$\gamma = 70$ $\lambda = 180$ $\chi = -100$	1.29	+2.80	$\gamma = 90$ $\lambda = -60$ $\chi = -60$	6.98	5.66	3.89	3.40	0.09

[a] Second most stable in the case of ddA.
[b] Relative to the most stable conformer.

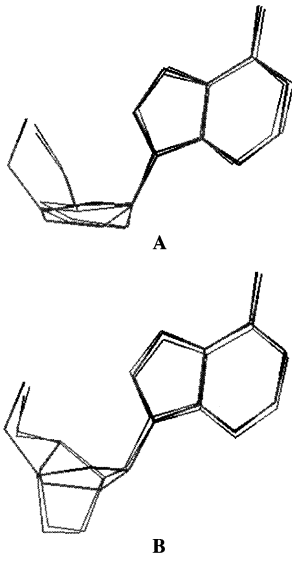

Fig. 3. Superimposition of de ddA and compounds **9**, **11** (A) and **10**, **12** (B).

5. Conclusions

The carbonucleoside purine analogues **7**–**10** were prepared straightforwardly by construction of the heterocyclic base on the primary amino group of the corresponding starting amino alcohol. Comparisons of the structures of **9**–**12** with that of ddA on the basis of AM1 semiempirical calculations showed that all five have stable conformers with the sugar or carbocycle *anti* to the base and with similar r.m.s. distances between the nitrogens of the base and the oxygen of the hydroxymethyl group. However, in spite of these structural similarities with ddA, none of compounds **7**–**12** exhibit antiviral activity, and only **8**, **10** and **12**, in which the base and carbocycle are separated by a methylene group, have significant antitumoral activity (only 0.5–1 orders of magnitude weaker than that of Ara A). It agrees with previous reports [14] that the most active compounds for which structural studies were performed (**10** and **12**) were those in which the position of the hydroxymethyl group relative to the purine system is closest to that found in ddA.

6. Experimental protocols

6.1. Chemistry

Melting points were determined in a Reichert Kofler thermopan or in capillary tubes in a Büchi 510 apparatus, and are uncorrected. IR spectra were recorded in a Perkin–Elmer 1640FT spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in a Bruker AMX spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts in δ values, J in Hz). Mass spectra were obtained using a Hewlett Packard 5988A spectrometer. Elemental analyses (indicated by the symbols of the elements) were performed using a Perkin–Elmer 240B microanalyser and were within $\pm 0.4\%$ of the theoretical values. Silica gel (Merck 60, 230–400 mesh) was used for flash chromatography (FC). Analytical thin layer chromatography (TLC) was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm).

6.1.1. (±)-cis-5-Amino-6-chloro-4-[2-(hydroxymethyl)-cyclopentylamino]pyrimidine (3)

A mixture of the amino alcohol **1** [11] (100 mg; 0.87 mmol), 5-amino-4,6-dichloropyrimidine (150 mg; 0.91 mmol), Et_3N (0.5 mL) and *n*-BuOH (3 mL) was refluxed for 24 h under Ar. The solvent was then evaporated under vacuum and the solid residue was redissolved in ethyl acetate by stirring with IRA-420 (OH) until all turbidity had disappeared. The resin was filtered out of the solution, the solvent was evaporated under vacuum, and the residue was purified by FC using 98:2 CH_2Cl_2–MeOH as eluent, which gave pure **3**. Yield 150 mg (71%). IR cm^{-1}: 3356, 3259, 2878, 1833, 1648, 1585, 1498, 1475, 1459, 1411, 1018, 1007. ^{1}H-NMR (DMSO-d_6) δ: 1.48–1.94 (5 + 1H, 2m, (–CH_2–)$_3$), 2.18 (1H, m, –CH–C–O–), 3.25 (2H, m, –CH_2–O–), 4.44 (1H, m, >CH–N–), 5.10 (2H, bs, –NH_2), 6.36 (1H, d, –NH–, $J = 7.40$), 7.70 (1H, s, H-2). ^{13}C-NMR (DMSO-d_6) δ: 21.8 (4′), 27.0 (3′), 31.7 (5′), 44.6 (2′), 53.8 (1′), 61.1 (6′), 123.8, 137.0, 145.8, 152.1. MS m/z (%): 244 ([M + 2]$^+$, 15), 242 (M$^+$, 46), 221 (39), 169 (18), 146 ([M + 2]$^+$ − $C_6H_{10}O$, 34), 144 (M$^+$ − $C_6H_{10}O$, 100), 117 (10), 67 (9). Anal. $C_{10}H_{15}ClN_4O$ (C, H, N).

6.1.2. (±)-cis-5-Amino-6-chloro-4-[2-(hydroxymethyl)-cyclopentylmethylamino]pyrimidine (4)

This compound was prepared from **2** [12] (300 mg; 2.32 mmol) in an analogous way to **3**. The crude product was purified by FC using 99:1 CH_2Cl_2–MeOH as eluent. Yield 525 mg (88%), m.p.: 148–150 °C. IR (KBr) cm^{-1}: 3356, 3259, 2944, 1659, 1587, 1472, 1424, 1341, 1050. ^{1}H-NMR (DMSO-d_6) δ: 1.31–1.68 (3 + 3H, 2m, (–CH_2–)$_3$), 2.07 and 2.22 (1 + 1H, 2m, >CH–C–O– + >CH–C–N–), 3.26 (2H, m, –CH_2–O–), 3.46 (2H, m, –CH_2–N–), 4.43 (1H, t, –OH, $J = 4.67$), 5.00 (2H, bs, –NH_2), 6.61 (1H, m, –NH–), 7.70 (1H, s, H-2). ^{13}C-NMR (DMSO-d_6) δ: 22.5 (4′), 27.7 (3′), 29.3 (5′), 40.6 (1′), 41.4 (2′), 43.3 (6′), 61.0 (7′), 123.3, 136.5, 145.7, 152.1. MS m/z (%): 258 ([M + 2]$^+$, 5), 256 (M$^+$, 15), 242 ([M + 2]$^+$ − NH_2, 5), 240 (M$^+$ − NH_2, 16), 159 ([M + 2]$^+$ − $C_6H_{11}O$, 34), 157 (M$^+$ − $C_6H_{11}O$, 100), 146 ([M + 2]$^+$ − $C_7H_{12}O$, 33), 144 (M$^+$ − $C_7H_{12}O$, 98), 94 (18), 67 (10). Anal. $C_{11}H_{17}ClN_4O$ (C, H, N).

*6.1.3. (±)-cis-8-Aza-9-[(2-hydroxymethyl)cyclopentyl]-hypoxanthine (**7**)*

$NaNO_2$ (17 mg; 0.25 mmol) was added to a solution of **3** (50 mg; 0.21 mmol) in 1 M HCl (2 mL) at 0 °C, and the mixture was successively stirred for 15 min, refluxed for 30 min, and neutralised with 1 M NaOH. The solvent was evaporated under vacuum (forming an azeotropic mixture with ethanol–toluene) and the solid residue was purified by FC using 98:2 CH_2Cl_2–MeOH as eluent, which gave pure **7**. Yield 37 mg (76%), m.p.: 173–174 °C. IR (KBr) cm^{-1}: 3356, 2953, 1731, 1654, 1589, 1560, 1362, 1273, 866. ^{1}H-NMR (DMSO-d_6) δ: 1.59–2.53 (7H, m, $(–CH_2–)_3$ + >CH–C–O–), 2.95 (2H, m, $–CH_2–O–$), 4.21 (1H, m, –OH), 5.28 (1H, m, >CH–N–), 8.21 (1H, s, H-2), 12.57 (1H, bs, NH). ^{13}C-NMR (DMSO-d_6) δ: 23.3 (4′), 28.0 (3′), 31.8 (5′), 47.0 (2′), 59.4 (1′), 60.6 (6′), 129.5 (5), 149.3 (4), 149.5 (2), 155.9 (6). MS m/z (%): 235 (M^+, 5), 206 ($M^+ -$ CHO, 7), 150 (31), 149 (35), 138 ($M^+ - C_6H_9O$, 100), 111 (32), 83 (22), 67 (30). Anal. $C_{10}H_{13}N_5O_2$ (C, H, N).

*6.1.4. (±)-cis-8-Aza-9-[(2-hydroxymethyl)cyclopentyl-methyl]hypoxanthine (**8**)*

This compound was prepared from **4** (100 mg; 0.39 mmol) in an analogous way to **7**. The crude product was purified by FC using 95:5 CH_2Cl_2–MeOH as eluent. Yield 60 mg (71%), m.p.: 161–162 °C. IR (KBr) cm^{-1}: 3472, 2919, 1700, 1654, 1558, 1508, 1268, 1064. ^{1}H-NMR (DMSO-d_6) δ: 1.22–2.71 (6H, m, $(–CH_2–)_3$), 2.13 (1H, m, >CH–C–O–), 2.62 (1H, m, >CH–C–N), 3.50 (2H, m, $–CH_2–O–$), 4.40 (1H, dd, –*H*CH–N–, $J = 13.76$ and 10.69), 4.66 (1H, dd, –HC*H*–N–, $J =$ 13.76 and 5.51), 8.22 (1H, s, H-2), 12.58 (1H, bs, NH). ^{13}C-NMR (DMSO-d_6) δ: 22.8 (4′), 27.7 (3′), 29.2 (5′), 41.6 (1′), 43.6 (2′), 47.7 (6′), 61.3 (7′), 129.8 (5), 149.0 (4), 149.9 (2), 155.9 (6). MS m/z (%): 249 (M^+, 5), 220 ($M^+ -$ CHO, 24), 219 ($M^+ - CH_2O$, 10), 192 (50), 150 ($M^+ - C_6H_{11}O$, 92), 138 ($M^+ - C_7H_{11}O$, 95), 125 (95), 96 (72), 79 (100), 67 (94). Anal. $C_{11}H_{15}N_5O_2$ (C, H, N).

*6.1.5. (±)-cis-8-Aza-9-[(2-hydroxymethyl)cyclo-pentyl]adenine (**9**)*

$NaNO_2$ (34 mg; 0.51 mmol) was added to a solution of **3** (100 mg; 0.41 mmol) in 1 M HCl (1 mL) at 0 °C and the mixture was stirred for 15 min. Then NH_4OH (2 mL) was added and the mixture was refluxed for 5 min. After cooling, the precipitate was recovered by filtration and purified by FC using 98:2 CH_2Cl_2–MeOH as eluent, which gave pure **9**. Yield 88 mg (91%), m.p.: 208–209 °C. IR (KBr) cm^{-1}: 3227, 3098, 2963, 1697, 1620, 1574, 1337, 1325, 1018, 718. ^{1}H-NMR (DMSO-d_6) δ: 1.63–2.32 (6H, mc, $(–CH_2–)_3$), 2.44 (1H, m, –CH–C–O–), 2.93 (2H, m, $–CH_2–O–$), 4.24 (1H, t, –OH, $J = 5.00$), 5.31 (1H, q, >CH–N–, $J = 6.40$), 8.26 (1H, s, H-2), 8.02 and 8.29 (2H, 2bs, $–NH_2$). ^{13}C-NMR (DMSO-d_6) δ: 23.3 (4′), 28.2 (3′), 31.6 (5′), 47.1 (2′), 59.1 (1′), 60.8 (6′), 123.9 (5), 149.5 (4), 156.6 (2), 156.7 (6). MS m/z (%): 234 (M^+, 12), 203 ($M^+ - CH_3$, 20), 163 (25), 149 (32), 137 ($M^+ - C_6H_9O$, 100), 110 (24), 81 (14), 67 (21). Anal. $C_{10}H_{14}N_6O$ (C, H, N).

*6.1.6. (±)-cis-8-Aza-9-[(2-hydroxymethyl)cyclo-pentylmethyl]adenine (**10**)*

This compound was prepared from **4** (100 mg; 0.39 mmol) in an analogous way to **9**. The crude product was purified by FC using 98:2 CH_2Cl_2–MeOH as eluent. Yield 89 mg (92%), m.p.: 177–178 °C. IR (KBr) cm^{-1}: 3144, 2950, 2870, 1700, 1616, 1576, 1325, 1272, 1017, 725. ^{1}H-NMR (DMSO-d_6) δ: 1.29–1.73 (2 + 4H, 2m, $(–CH_2–)_3$), 2.13 (1H, m, >CH–C–O–), 2.66 (1H, m, >CH–C–N–), 3.49 (2H, m, $–CH_2–O–$), 4.42 (1H, dd, –*H*CH–N–, $J = 13.72$ and 10.60), 4.66 (1H, dd, –HC*H*–N–, $J = 13.72$ and 5.58), 8.04 and 8.30 (1 + 1H, 2bs, $–NH_2$), 8.28 (1H, s, H-2). ^{13}C-NMR (DMSO-d_6) δ: 22.7 (4′), 27.7 (3′), 29.2 (5′), 41.5 (1′), 43.6 (2′), 47.3 (6′), 61.3 (7′), 124.1 (5), 149.2 (4), 156.6 (2), 157.0 (6). MS m/z (%): 248 (M^+, 14), 217 ($M^+ - CH_3O$, 29), 137 ($M^+ - C_7H_{11}O$, 100), 110 (30), 95 (51), 94 (33), 67 (36). Anal. $C_{11}H_{16}N_6O$ (C, H, N).

6.2. Computational methods

Optimization of theoretical molecular geometries was carried out using the AM1 semiempirical method [17] as implemented in AMPAC [18], which was run on an SGI work station. The geometry was optimised by varying the relevant torsion angles simultaneously between 0 and 360° in steps of 20°. The torsion angles varied are defined in Fig. 1.

6.3. Biological activity assays

Assays of antiviral and antitumoral activities were carried out following established procedures [19].

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