Synthesis and Physicochemical Properties of New 1N *o*-(*m*- and *p*-) bromobenzyl Substituted Derivatives of 5-(Aminodialkyl)methylcytosine

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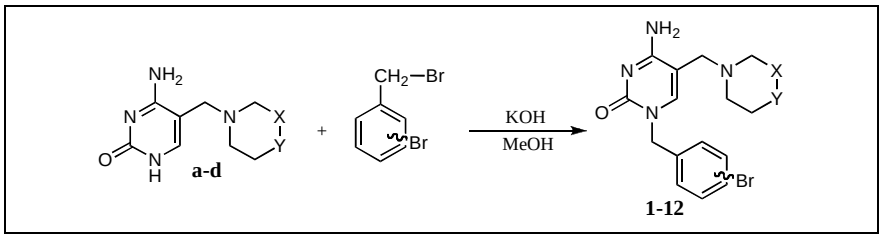

Simple alkylation of 5-(aminodialkyl)methylcytosine **a**-**d** gives twelve new, potentially biologically active 1N *o*-(*m*- or *p*-) bromobenzyl derivatives of 5-substituted cytosine **1**-**12** with high regioselectivity. The structures of all compounds have been confirmed by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectroscopic measurements.

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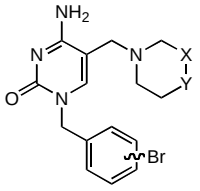
INTRODUCTION

Analogues of pyrimidine nucleosides in which cyclic carbohydrate is replaced by acyclic chains or aryl (arylalkyl) substituent, have long been subjects of interest for their various biological effects, especially their antiviral and/or anticancer activity. The compounds 1N-alkyl, aryl and arylalkyl substituted derivatives of uracil [1], [2], 1N- aryl and arylalkyl substituted derivatives of cytosine, as well as 1N- aryl and arylalkyl derivatives of 5-substituted cytosine have been studied in [3-4]. Also 5-substituted pyrimidines have attracted considerable interest due to their various biological effects [5], including their antiviral and anticancer activity [6]. Such activity has also been confirmed for 5-(4'-morpholinyl)methyluracil [7] and 5-(4'-morpholinyl)methyl-2-thiouracil [8]. In view of above, an attempt has been made at synthesis and determination of physicochemical properties of new compounds, in which cyclic amine is attached *via* methylene bridge to the position 5 of cytosine and with an *ortho*- (*meta*- and *para*-)bromobenzyl substituent at 1N- position.

The structures of 1N *ortho*- (*meta*- and *para*-)bromobenzyl substituted derivatives of 5-(aminodialkyl)-methylcytosine are shown in Figure 1.

RESULTS AND DISCUSSION

A series of twelve 1N *o*-(*m*- or *p*-)bromobenzyl-[5-(4'-morpholinyl)methyl]cytosines (**1**-**3**), 1N *o*-(*m*- or *p*-)bromobenzyl-[5-(1'-piperidinyl)methyl]cytosines (**4**-**6**), 1N *o*-(*m*- or *p*-)bromobenzyl-[5-(4'-methyl-1'-piperidinyl)methyl]cytosines (**7**-**9**) and 1N *o*-(*m*- or *p*-)bromobenzyl-[5-(3'-methyl-1'-piperidinyl)methyl]cytosines (**10**-**12**) have been synthesized in the reaction of the appropriate 5-(4'-morpholinyl)methylcytosine **a** (or 5-(1'-piperidinyl)-methylcytosine **b**, 5-(4'-methyl-1'-piperidinyl)methyl-cytosine **c**, 5-(3'-methyl-1'-piperidinyl)methylcytosine **d** with *o*-(*m*- or *p*-)bromobenzyl bromides in alkaline methanol solutions (Scheme 1).



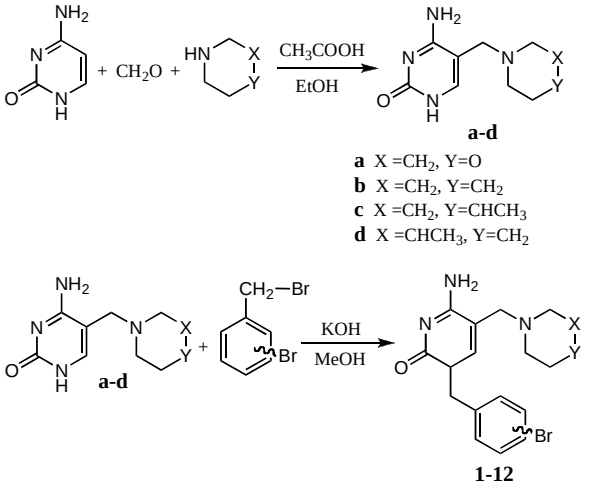
1-12

No	X	Y	Br	No	X	Y	Br
1	CH_2	O	-o	**7**	CH_2	$CHCH_3$	-o
2	CH_2	O	-m	**8**	CH_2	$CHCH_3$	-m
3	CH_2	O	-p	**9**	CH_2	$CHCH_3$	-p
4	CH_2	CH_2	-o	**10**	$CHCH_3$	CH_2	-o
5	CH_2	CH_2	-m	**11**	$CHCH_3$	CH_2	-m
6	CH_2	CH_2	-p	**12**	$CHCH_3$	CH_2	-p

Figure 1. Structures of compounds **1**-**12**.

The synthesis (*via* Mannich reaction) of the substrates for alkylation (**a**-**d**) was described in detail elsewhere [9]. Several methods have been proposed for the preparation of 1-substituted cytosines [10]. A simple alkylation often suffers from the disadvantage that the ambident nature of the amide system leads to both O- and N-alkylation, and the O- and N-substituted derivatives of cytosine are difficult to separate [11]. However, the reaction described here (Scheme 1) is highly regioselective and does not give others products, which has been verified by TLC ($CHCl_3$-CH_3OH 5:1/SiO_2) and then by NMR methods.

Scheme 1



The regioselectivity of alkylation of an ambident nucleophile depends on the substrate and can be rationalised using the HSAB (hard soft acid base) principle [12,13]. In the ambient nucleophiles (**a**-**d**) the oxygen atom represents a "hard" nucleophilic centre, while the 1N-atom is a "soft" one. According to this principle, the "softer" is the carbon atom in the "electrophilic" centre of the second substrate (bromobenzyl halides), the greater extent of 1N-alkylation would be achieved. In view of the above, bromobenzyl bromides were chosen as the second substrates instead of bromobenzyl chlorides in which the carbon in the "electrophilic centre" is "harder" i.e. the electron density at the carbon nucleus is the lowest. The time of the reaction was 24 hours, although the reaction was incomplete even after 72 hours. Due to an excess of KOH during the precipitation procedure of compounds **1**-**12**, all unreacted substrates **a**-**d** remained in the alkaline solution. The excess of bromobenzyl bromides was not very high to avoid the formation of by-products. Yields of the products (**1**-**12**) were between 55-90 % (Table 1).

Table 1

Physical Properties of the Compounds **1**-**12**.

Compound	Formula (mol. weight)	M.p. [^{0}C]	Yield [%]	Elemental analysis [%], Calculated (Found)		
				C	H	N
1	$C_{16}H_{19}N_4O_2Br\times 2H_2O$	218-222	76	46.27	5.58	13.49
	415.28	decomp.		(46.61)	(5.38)	(13.61)
2	$C_{16}H_{19}N_4O_2Br\times 1H_2O$	195-198	71	48.37	5.33	14.10
	397.27	decomp.		(48.35)	(5.25)	(13.95)
3	$C_{16}H_{19}N_4O_2Br\times 2H_2O$	235-238	69	46.27	5.58	13.49
	415.28	decomp.		(46.19)	(5.44)	(13.34)
4	$C_{17}H_{21}N_4OBr\times 2H_2O$	207-210	77	49.40	6.10	13.56
	413.31	decomp.		(49.32)	(6.17)	(13.39)
5	$C_{17}H_{21}N_4OBr\times 1\ H_2O$	212-215	64	51.65	5.86	14.17
	395.29	decomp.		(51.50)	(5.52)	(13.98)
6	$C_{17}H_{21}N_4OBr\times 1\ H_2O$	245-249	69	51.65	5.86	14.17
	395.29	decomp.		(51.73)	(5.52)	(14.28)
7	$C_{18}H_{23}N_4OBr\times 2\ H_2O$	191-194	74	50.59	6.37	13.11
	427.34	decomp.		(50.83)	(6.20)	(13.11)
8	$C_{18}H_{23}N_4OBr\times 1\ H_2O$	165-168	90	52.82	6.16	13.69
	409.32	decomp.		(52.93)	(5.87)	(13.55)
9	$C_{18}H_{23}N_4OBr\times 1\ H_2O$	182-185	95	55.25	5.92	14.32
	409.32	decomp.		(54.95)	(5.77)	(14.31)
10	$C_{18}H_{23}N_4OBr\times 2\ H_2O$	207-210	74	50.59	6.37	13.11
	427.34	decomp.		(50.42)	(6.40)	(13.02)
11	$C_{18}H_{23}N_4OBr\times 1\ H_2O$	165-169	55	52.82	6.16	13.69
	409.32	decomp.		(52.80)	(6.05)	(13.58)
12	$C_{18}H_{23}N_4OBr\times 1\ H_2O$	215-219	56	52.82	6.16	13.69
	409.32	decomp.		(52.65)	(6.21)	(13.55)

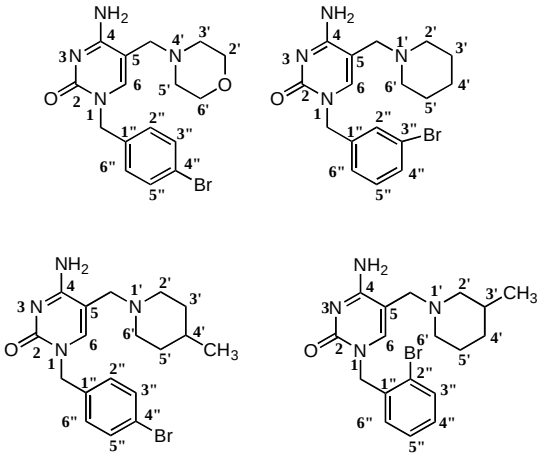


Figure 2. Numbering of the atoms in ^{1}H NMR and ^{13}C NMR data.

All compounds were characterised on the basis of spectral studies (^{1}H NMR, ^{13}C NMR and IR). Their structures were determined by comparison of their spectral data with those of 5-methylcytosine [14,15] and cyclic amines [16-20], and by comparison with the spectra calculated using ACD/ HNMR predictor and ACD/CNMR predictor [21]. The presence of a broad signal in the range of 7.11-7.69 ppm (Table 2) assigned to the 4NH_2 protons and the absence of signals assignable to the 1NH protons up to 10 ppm in the ^{1}H NMR spectra confirmed that the 4N position remained unsubstituted. The signals assigned to the 1NH protons were observed in the spectra of unsubstituted substrates **a**-**d**. The ^{1}H NMR spectra (DMSO-d_6) showed also a characteristic singlet in the 7.57-7.94 ppm range assigned to the proton in position 6 of the cytosine ring, which was downfield-shifted from the H-6 proton signals in substrates **a**-**d** [9]. A characteristic singlet appeared in the 4.81-4.94 ppm range and was assigned to the aliphatic protons in the benzyl moiety attached to the 1N atom. Compounds **1**-**12** were also fully characterised by ^{13}C NMR experiments, which confirmed their structures (Table 3). The ^{13}C NMR spectra of all the possible tautomers of compounds **1**-**12** were calculated and the tautomers shown in Figure 1 are those giving the best fit to the experimental spectra.

The IR spectra of **1**-**12** (KBr disks) reveal strong bands in the 3410-3120 cm^{-1} region, which may be assigned to ν NH_2. These bands are wide and in the spectra of some compounds the bands assigned to the NH_2 vibrations

Table 2

^{1}H NMR Data of Compounds **1-12**

No	(δ, ppm).
1	2.63 (m, 4H, H-2', 6'), 3.73 (m, 4H, H-3', 5'), 7.94 (s, 1H, H-6), 7.15 (br, 2H, 4NH_2), 3.15 (s, 2H, N-CH_2-C^5), 4.94 (s, 2H, 1N-CH_2-Ar), 7.05-7.68 (4H, Ar- H)
2	2.65 (m, 4H, H-2', 6'), 3.65 (m, 4H, H-3', 5'), 7.90(s, 1H, H-6), 7.20 (br, 2H, 4NH_2), 3.50 (s, 2H, N-CH_2-C^5), 4.87 (s, 2H, 1N-CH_2- Ar), 7.29-7.49 (4H, Ar-H)
3	2.32 (m, 4H, H-2', 6'), 3.55 (m, 4H, H-3', 5'), 7.67 (s, 1H, H-6), 6.91 and 7.33(br, 2H, 4NH_2), 3.15 (s, 2H, N-CH_2-C^5), 4.81 (s, 2H, 1N-CH_2-Ar), 7.21-7.54 (4H, Ar-H)
4	1.39 (m, 2H, H-4'), 1.49 (m, 4H, H-3', 5'), 2.30 (m, 4H, H-2', 6'), 7.58 (s, 1H, H-6), 7.18 (br, 2H, 4NH_2), 3.15 (s, 2H, N-CH_2-C^5) , 4.88 (s, 2H, 1N-CH_2-Ar), 6.90-7.66 (4H, Ar-H)
5	1.39 (m, 2H, H-4,), 1.48 (m, 4H, H-3, 5'), 2.29 (m, 4H, H-2', 6'), 7.68 (s, 1H, H-6), 7.12 (br, 2H, 4NH_2), 3.15 (s, 2H, N-CH_2-C^5), 4.83 (s, 2H, 1N-CH_2-Ar), 7.28-7.48 (4H, Ar-H)
6	1.39 (m, 2H, H-4'), 1.49 (m, 4H, H-3', 5'), 2.30 (m, 4H, H-2', 6'), 7.69 (s, 1H, H-6), 7.11 and 7.20 (br, 2H,4NH_2), 3.15 (s, 2H, N-CH_2-C^5), 4.83 (s, 2H, 1N-CH_2-Ar), 7.22-7.55 (4H, Ar-H)
7	0.88 (d, J=6.3 Hz, 3H, CH_3), 1.11 (m, 2H, H-3'a, 5'a), 1.34 (m, 1H, H-4'a), 1.59(m, 2H, H-3'e, 5'e), 1.84 (m, 2H, H-2'a, 6'a), 2.83 (m, 2H, H-2'e, 6'e), 7.59 (s, 1H, H-6),7.20 (br, 2H, 4NH_2), 3.18 (s, 2H, N- CH_2-C^5), 4.88 (s, 2H, 1N-CH_2A r), 6.91-7.66 (4H, Ar-H)
8	0.88 (d, J= 6.3 Hz, 3H, CH_3), 1.11 (m, 2H, H-3'a, 5'a), 1.34 (m, 1H, H-4'a), 1.59(m, 2H, H- 3'e,5'e), 1.84 (m, 2H, H-2a, 6a) 2.81 (m, 2H, H-2e, 6e), 7.71 (s, 1H, H-6), 7.13 (br, 2H, 4NH_2), 3.19 (s, 2H, N-CH_2-C^5), 4.84 (s, 2H, 1N-CH_2-Ar), 7.26-7.49 (4H, Ar-H)
9	0.89 (d, J= 6.3 Hz, 3H, CH_3), 1.11 (m, 2H, H-3'a, 5'a), 1.32 (m, 1H, H-4'a), 1.59(m, 2H, H-3'e, 5'e), 1.82 (m, 2H, H-2'a, 6'a), 2.78 (m, 2H,H-2'e, 6'e), 7.65 (s, 1H, H-6), 7.11 and 7.30 (br, 2H, 4NH_2), 3.15 (s, 2H, N-CH_2- C^5), 4.82 (s, 2H, 1N-CH_2-Ar), 7.22-7.55 (4H, Ar-H)
10	0.83 (d, J= 6.0 Hz, 3H, CH_3), 1.41-1.66 (m, 6H), 1.79 (t, J= 10.5, 1H, H-3'a), 2.74(m, 2H, H-2'e, 6'e), 7.57 (s, 1H, H-6), 7.14 (br, 2H, 4NH_2), 3.15 (s, 2H, N- CH_2-C^5), 4.82 (s, 2H, 1N-CH_2-Ar), 7.22-7.55 (4H, Ar-H)
11	0.83 (d, J= 6.0 Hz, 3H, CH_3), 1.41-1.66 (m, 6H),1.79 (t, J= 10.3 Hz, 1H, H-3'a), 2.72, (m, 2H, H-2'e, 6'e), 7.69 (s, 1H, H-6), 7.11 (br, 2H, 4NH_2), 3.16 (s, 2H, N-CH_2- C^5), 4.85 (s, 2H,1N-CH_2-Ar), 7.24-7.49 (4H, Ar-H)
12	0.81 (d, J= 6.0 Hz, 3H, CH_3), 1.38-1.65 (m, 6H), 1.79 (t, J= 10.2 Hz, 1H, H-3'a) 2.74(m, 2 H, H-2'e, 6'e), 7.64 (s, 1H, H-6), 7.31 and 7.11 (br, 2H, 4-NH_2), 3.13(s, 2H, N- CH_2-C^5), 4.81 (s, 2H, 1N- CH_2-Ar), 7.21-7.54 (4H, Ar-H)

Table 3

^{13}C NMR Data of Compounds **1-12** (δ, ppm).

No	δ (ppm)
1	53.3 (C 2', 6'), 64.3 (C3', 5'), 101.5 (C5), 144.0 (C6), 153.9 (C2), 163.8 (C4), 52.2(N-*C*H_2-C^5), 51.2 (1N-CH_2-Ar), 132.7 (C1"), 122.0 (C2"), 135.6 (C3"), 128.5 (C4"), 127.9 (C5"), 129.5 (C6")
2	54.5 (C2', 6'), 65.1 (C3', 5'), 99.8 (C5), 147.5 (C6), 154.2 (C2), 164.1(C4); 51.8(N-*C*H_2-C^5), 50.9 (1N-CH_2-Ar), 139.9 (C1"),130.6 (C2"), 121.6 (C3"), 126.5(C4"), 130.1 (C5"), 130.2 (C6")
3	55.9 (C2',6'), 66.1 (C3',5'), 100.7 (C5), 144.9 (C6), 155.3 (C2),1 65.2 (C4), 52.5(N-*C*H_2-C^5); 50.7 (1N-CH_2-Ar), 130.2 (C1"),129.6 (C2",6"), 131.2 (C3",5"), 120.3 (C4")
4	23.9 (C4'), 25.6 (C3',5'), 56.6 (C2',6'), 101.5 (C5), 144.7 (C6), 155.3 (C2), 165.5 (C4), 53.3 (N-*C*H_2-C^5); 51.9 (1N-CH_2-Ar),132.4 (C1"), 121.8 (C2"), 136.4 (C3"), 127.9 (C4"), 127.8 (C5"), 128.9 (C6")
5	23.9 (C4'), 25.5 (C3',5'), 56.5 (C2',6'), 101.5 (C5), 144.5 (C6), 155.3 (C2), 165.4 (C4), 53.2 (N-*C*H_2-C^5);50.7 (1N-CH_2-Ar),140.6 (C1"), 130.5 (C2"), 121.5 (C3"), 126.5 (C4"), 130.0 (C5"), 130.1 (C6")
6	23.3 (C4'), 25.6 (C3',5'), 56.6 (C2',6'), 101.5 (C_5), 144.9 (C6), 154.9 (C2), 164.9(C4), 52.4 (N-*C*H_2-C^5); 50.9 (1N-CH_2-Ar),136.9 (C1"), 129.7 (C2",6"), 131.2 (C3",5"), 130.4 (C4")
7	30.2 (C4'), 33.8 (C3',5'), 56.1 (C2',6'), 21,7 (CH_3), 101.5 (C5), 144.8 (C6), 155.2 (C2), 165.4 (C4), 52.5 (N-*C*H_2-C^5), 51.9 (1N-CH_2-Ar), 132.4 (C1"), 121.8 (C2"), 136.3 (C3"), 127.9 (C4"), 127.7 (C5"), 128.9 (C6")
8	30.1 (C4'), 33.7 (C3',5'), 56.1 (C2',6') ,21,7 (CH_3), 101.6 (C5), 144.7 (C6), 155.5 (C2), 165.5 (C4), 52.5 (N-CH_2-C^5) 50.81 (N-CH_2-Ar), 140.7 (C1"), 130.7 (C2"), 121.7 (C3"), 126.6 (C4"), 130.2 (C5"), 130.3 (C6")
9	30.3 (C4'), 33.9 (C3',5'), 56.2 (C2',6'), 21,8 (CH_3), 101.5 (C5), 144.4 (C6), 155.3 (C2), 165.3 (C4), 52.7 (N-CH_2-C^5), 50.72 (1N-CH_2-Ar), 137.3 (C1"), 129.6 (C2",6"), 131.2 (C3",5"), 120.3(C4")
10	24.9 (C5'), 30.6 (C3'), 32.4 (C4'), 52.3 (C6'), 60.5 (C2'), 19.5 (CH_3), 101.5 (C5), 144.7(C6), 155.3 (C2), 165.5 (C4), 52.8 (N-CH_2-C^5), 51.8 (1N-CH_2-Ar), 32.4 (C1"), 128.8 (C2"), 136.3 (C3"), 127.9 (C4"), 127.7 (C5"), 128.9 (C6")
11	24.9 (C5'), 30.7 (C3'), 32.5 (C4'), 52.3 (C6'), 60.4 (C2'), 19.5 (CH_3), 101.1 (C5), 144.5 (C6), 155.4 (C2), 165.4 (C4), 52.8 (N-*C*H_2-C^5), 52.8 (1N-CH_2-Ar), 140.6 (C1"), 130.5(C2"),121.5 (C3"), 126.5 (C4"), 130.0 (C5"), 130.1 (C6")
12	24.9 (C5'), 30.7(C3'), 32.5(C4'), 52.3(C6'), 60.5 (C2), 19.5(CH_3), 101.5(C5), 144.5(C6), 155.4(C2), 165.4(C4), 52.8(N-*C*H_2-C^5); 50.7(1N-CH_2-Ar), 137.3(C1"), 129.6(C2",6"), 131.2 (C3",5"), 120.3 (C4")

overlap the region of the C=C-H stretching vibrations. Very intense bands corresponding to the carbonyl stretching vibrations ν (C=O) are observed in the 1698-1671 cm^{-1} range. Very strong bands are also observed in the 1602-1633 cm^{-1} range, which have been interpreted as originating from amine scissoring vibrations ν (NH_2) and stretching vibrations of the C=C groups (Table 4).

Thus twelve new potentially biological active compounds **1**-**12** were prepared with good yields using a simple alkylation reaction. This reaction appears highly regioselective, and the respective products were isolated by a simple procedure. The compounds synthesised were fully characterised by NMR and IR methods and by elemental analysis.

Table 4

The IR spectra of compounds **1-12** (cm^{-1}).

No	ν NH_2	ν H-C=C	ν C=O mostly	ν NH_2 and ν C=C	ν C=C (Phenyl)
1	3410 s, 3315 s, 3145 s	-*	1698 vs	1602 vs	1518 s
2	3380 s, 3335 s	3088 s	1674 vs	1637 vs	1517 s
3	3386 s	3097 s	1682 vs	1609 vs	1512 s
4	3385 s, 3120 s	-*	1680 vs	1607 vs	1512 s
5	3287 s	3085 s	1674 vs	1629 vs	1516 s
6	3294 s	3095 s	1672 vs	1626 vs	1517 s
7	3390 s, 3155 s	3085 s	1682 vs	1606 vs	1513 s
8	3410 s, 3339 s	3085 s	1682 vs	1626 vs	1512 s
9	3334 s	3098 s	1674 vs	1629 vs	1517 s
10	3366 s, 3123 s	-*	1681 vs	1606 vs	1513 s
11	3317 s	3088 s	1669 vs	1626 vs	1515 s
12	3293 s	3096 s	1671 vs	1627 vs	1516 s

* This band is overlapping with νNH_2, s- strong, vs-very strong.

EXPERIMENTAL

Purity of all compounds studied was checked by m.p.'s, TLC and elemental analysis. Melting points (uncorrected) were determined on a Böetius microscope hot stage. R_f values refer to TLC silica gel F_{254}TLC plates (Merck) developed with $CHCl_3$/CH_3OH 5:1 and observed under UV light (λ = 254 and 366 nm). IR spectra were recorded with a FT-IR Bruker JFS-113 Spectrometer in KBr pallets. ^1H NMR and ^{13}C NMR spectra were determined on a Varian Gemini 300 (300 MHz) Spectrometer in DMSO-d_6 solutions with TMS as internal standard. Chemical shifts are given in the δ scale (ppm) and coupling constants in Hz. ^1H NMR (300.07 MHz) spectra were recorded with 9 kHz spectral width, 2.0 s acquisition time, 6 μs pulse width and double precision acquisition. ^{13}C NMR (75.460 MHz) spectra were recorded with 18.76 kHz spectral width, 1.0 s acquisition time, 1.0 s recycle delay and 15 μs pulse width.

General Procedure for the Preparation of 1N o-(m- or p-) bromobenzyl substituted derivatives of 5-(aminodialkyl) methylcytosine (1-12). A methanol solution (20 ml) consisting of 0.95 mmol of the appropriate 5-methyl-aminoalkyl substituted cytosine (**a**-**d**) and 1.4 mmol of KOH was stirred at room temperature while 1.4 mmol of the appropriate *o*-(*m*- or *p*-)-bromobenzyl bromides were added. The reaction mixture was stirred at room temperature for 24 hours, then half of the solvent volume was evaporated under vacuum and distilled water was added until the solid precipitated. After standing in the refrigerator, the solid was isolated by filtration and washed three times with boiling diethyl ether. The resulting compounds **1**-**12** appear chromatographically pure (TLC $CHCl_3$-CH_3OH 5:1/SiO_2).

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