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Synthesis of various 5-alkoxymethyluracil analogues and structure–cytotoxic activity relationship study

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ABSTRACT

A number of 5-alkoxymethyluracil analogues were synthesized to evaluate their cytotoxic activity. 5-Alkoxymethyluracil derivatives **1** were prepared via known nucleophilic substitution of 5-chloromethyluracil **5** and subsequently transformed to their corresponding nucleosides **2**. All prepared compounds were submitted to cytotoxic activity testing against drug sensitive and drug resistant leukaemia cells and solid tumour derived cell lines. In addition, the cytotoxic activity of 5-alkoxymethyluracil analogues **1** and **2** was compared with the previously published 5-[alkoxy(4-nitrophenyl)methyl]uracil analogues **3** and **4**. Extensive structure–cytotoxic activity relationship studies are reported.

1. Introduction

Various 5-alkoxymethyluracil analogues have been studied over the last 60 years in connection with either their synthesis or nucleic acid metabolism. The oldest work describes the synthesis of 5-alkoxymethyluracil analogues via formaldehyde addition,[1] from 5-bromomethyl and 5-chloromethyluracil or 5-hydroxymethyluracil.[2–4] However, intensive efforts to find new successful drugs of antimetabolite type have led, among others, to studies focused on the potential antiviral and cytotoxic activity of 5-alkoxymethyluracil analogues.

To illustrate the antiviral activity of 5-alkoxymethyl derivatives derived from 2′,3′-dideoxyuridine and 2′,3′-dideoxycytidine analogues,[5] 5-alkoxymethyl-3′-azido-2′,3′-dideoxyuridines,[6] 3′-amino-2′,3′-dideoxyuridine[7] or agents with an ethoxymethyl side chain at C-5 and an ethyl group at the N-1 position of the uracil ring[8] or 5-alkoxymethylazidothymidine analogues and their corresponding α-anomers[9] were reported. On the other hand, research on new anticancer agents in the field of 5-alkoxymethyluracil analogues has attracted much less attention. One of the few examples is the 5-alkoxymethyl-3′-amino-2′,3′-dideoxynucleosides tested against human epidermoid cervical cancer cells.[7]

A considerable part of this work is based on study of the chemical reactivity of the hydroxymethyl group of 5-hydroxymethyluracil and its conversion to the corresponding 5-alkoxymethyluracil. Despite the fact that many published studies describe synthesis and biological activity of various 5-alkoxymethyluracils (**1a–o**, Fig. 1) with alkyl chain length C_1–C_{12} (except C_9 and C_{11}),[1–3,5,10,11] 5-alkoxymethyluridines with alkyl chains longer than C_2 were not studied to date.[1,12,13] Herein, we report a relatively facile and efficient method for the synthesis of various 5-alkoxymethyluridines with a C_3–C_{12} chain length (**2c–2o**, Fig. 1). Because little is known about anticancer studies of the 5-alkoxymethyluracil analogues **1** and **2**, this work also demonstrates the cytotoxic potential of 5-alkoxymethyluracil analogues **1** and **2** in vitro against cancer cells of different histogenetic origin, genetic background and drug resistance profile.

In earlier studies we have also reported on the cytotoxic activity and structure–activity relationship of 5-[alkoxy(4-nitrophenyl)methyl]uracils **3**[14] and 5-[alkoxy(4-nitrophenyl)methyl] uridines **4f–i**[15] (Fig. 2). In the context of the current paper, the relationship between structure and cytotoxic activity is derived from 5-alkoxymethyluracils **1**, 5-alkoxymethyluridines **2**, 5-[alkoxy(4-nitrophenyl)methyl]uracils **3** and 5-[alkoxy(4-nitrophenyl)methyl] uridines **4** to evaluate the effect of the 4-nitrophenylmethyl group in position 5 and the ribose moiety in position 1.

2. Results and discussion

2.1. Synthesis

In the work reported here, a series of 5-alkoxymethyluracil analogues **1** and **2** were prepared via nucleophilic substitution of 5-

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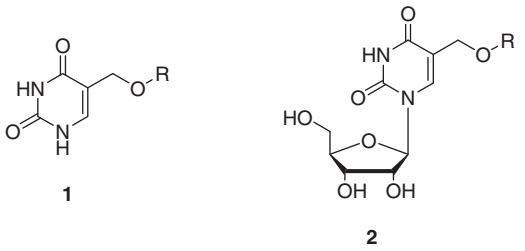
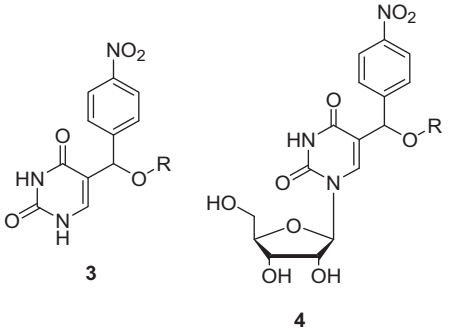


a) R = -CH_3
b) R = -CH_2CH_3
c) R = -$(CH_2)_2CH_3$
d) R = -$(CH_2)_3CH_3$
e) R = -$(CH_2)_4CH_3$
f) R = -$(CH_2)_5CH_3$
g) R = -$(CH_2)_6CH_3$
h) R = -$(CH_2)_7CH_3$
i) R = -$(CH_2)_8CH_3$
j) R = -$(CH_2)_9CH_3$
k) R = -$(CH_2)_{10}CH_3$
l) R = -$(CH_2)_{11}CH_3$
m) R = -i-Pr
n) R = -s-But
o) R = -t-But

Figure 1. 5-Alkoxymethyluracils **1** and 5-alkoxymethyluridines **2**.



a) R = -CH_3
b) R = -CH_2CH_3
c) R = -$(CH_2)_2CH_3$
d) R = -$(CH_2)_3CH_3$
e) R = -$(CH_2)_4CH_3$
f) R = -$(CH_2)_5CH_3$
g) R = -$(CH_2)_6CH_3$
h) R = -$(CH_2)_7CH_3$
i) R = -$(CH_2)_8CH_3$
j) R = -$(CH_2)_9CH_3$
k) R = -$(CH_2)_{10}CH_3$
l) R = -$(CH_2)_{11}CH_3$
m) R = -*i*-Pr
n) R = -*s*-But
o) R = -*t*-But

Figure 2. 5-[Alkoxy(4-nitrophenyl)methyl]uracils **3** and 5-[alkoxy(4-nitrophenyl)methyl]-uridines **4**.

chloromethyluracil **5**. This starting material was synthesized by a well-known and described reaction[2] from 5-hydroxymethyluracil. Subsequently, this reactive intermediate was heated at 100 °C in various aliphatic linear alcohols C_1–C_{12} as well as in selected branched alcohols such as isopropanol, *sec*-butanol and *tert*-butanol. However, only two of this series, 5-nonyloxymethyluracil (**1i**) and 5-undecyloxymethyluracil (**1k**) have not yet been described and their preparation is included in Section 4.

All prepared alkoxymethyluracils **1** were silylated in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) at reflux with addition of $(NH_4)_2SO_4$ as the catalyst (Scheme 1). Silylated derivatives **6** were coupled with 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose **7** using trimethylsilyl trifluoromethanesulfonate as the Lewis acid. This so-called Vorbrügen method[16] led to the synthesis of protected nucleosides **8**, which were successfully purified using silica gel column chromatography to afford the parent nucleosides in 34–69% yields. Treatment of benzoylated nucleosides **8** with an excess of methanolic ammonia solution gave a series of fifteen alkoxynucleosides **2**, where derivatives (**2c–o**) are newly synthesized compounds (Scheme 1).

2.2. Cytotoxic activity and structure–activity relationship

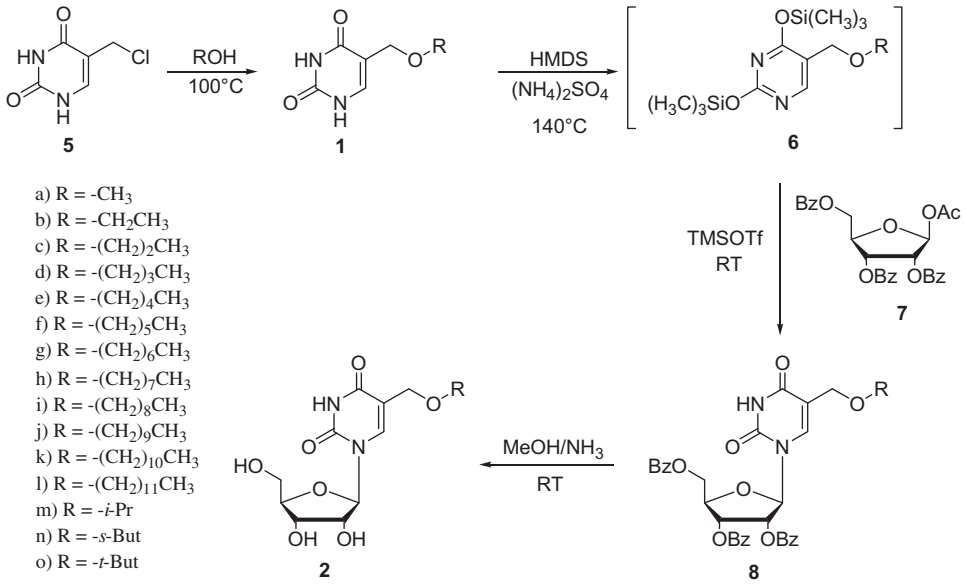
All compounds prepared within this paper were tested under in vitro conditions for their cytotoxic activity against cancer cell lines CEM, K562, their drug resistant counterparts CEM-DNR-bulk and K562-tax, and A549, HCT116p53 and HCT116p53−/− cell lines. In previous work we have also demonstrated the cytotoxic activity of various 5-[alkoxy(4-nitrophenyl)methyl]uracils **3**[14] and 5-[alkoxy(4-nitrophenyl)methyl]uridines **4**.[15] Within the structure–cytotoxic activity relationship studied in this paper, we extended the cytotoxic studies of derivatives **3** and **4** and tested their activity for two more cancer cell lines (HCT116p53 and HCT116p53−/−). The presence of the nitrophenyl moiety offers an interesting opportunity to study the relationships between the structure of 5-alkoxymethyluracils **1**, 5-alkoxymethyluridines **2**, 5-[alkoxy(4-nitrophenyl)methyl]uracils **3** and 5-[alkoxy(4-nitrophenyl)methyl]uridines **4**, the various lengths of the alkoxy side chain versus cytotoxic activity.

First, the cytotoxic activity of modified nucleobases **1** was investigated against a diverse range of cancer cells. All results are reported in Table 1. While derivatives with a short linear as well as branched side chain exhibit no significant activity against any of the tested cell lines, interesting dependences on the length of the alkyl chain is observed in comparison of derivatives **1a–l**. All those activities were affected by varying the alkyl chain and they are illustrated in Figure 3.

It is evident that the maximum cytotoxicity is observed for derivatives with an alkyl chain length of between 6 and 9 methylene groups excepting drug resistant lines K562-tax and CEM-DNR-bulk. However, another carbon addition leads to marked decrease in cytotoxic activity. Although none of derivatives **1a–l** exhibit interesting activity against CEM, K562, A562, HCT116p53 or HCT116p53−/− cancer cell lines, more interesting results were obtained in case of drug resistant leukaemia cell lines (CEM-DNR-bulk and K562-tax), where derivatives **1** exhibit activity in low-micromolar concentrations (CEM-DNR-bulk, derivative **1k**: relative IC_{50} = 2.4 μM). Figure 3 shows the selectivity of tested compounds **1** against CEM-DNR-bulk cell line, where the cytotoxic effect is directly proportional to the increasing length of the alkyl chain. On the other hand, the trend of increasing cytotoxicity against the K562-tax cell line with growing number of carbons in alkyl chain ends with 11 methylene groups. The evidence of increasing cytotoxic activity specifically in drug resistant cell lines but not in drug sensitive counterparts with growing length of alkyl chain might indicate interaction of long lipophilic groups with multidrug resistance transporters such as P-glycoprotein or the multidrug resistance-associated protein-1 (MRP).

On the other hand, one might suppose that derivatives **1**, as well as the majority of antimetabolites, might inhibit DNA and/or RNA synthesis, for instance, via incorporation into the nucleic acids, arrest cell division and induce apoptosis. Therefore, the modified nucleobases **1** were transformed to the corresponding nucleosides **2**. Moreover, introduction of the ribose moiety positively affects the solubility of compounds in water. The activities of nucleosides **2** are summarized in Table 2 and illustrated in Figure 4.

In contrast to bases **1** it is apparent that the most active nucleosides **2** are those with a longer alkyl chain containing 9–11 meth-



Scheme 1. General synthetic route of the lead compounds **2**.

Table 1
Summary of cytotoxic activity of derivatives **1**[a]

Compound code	R	K562	K562-tax	CEM	CEM-DNR-bulk	HCT116p53	HCT116p53−/−	A549
1a	CH_3	192.6	134.3	85.2	53.1	200.0	191.5	244.6
1b	CH_2CH_3	188.1	133.7	75.3	60.7	200.3	193.8	241.7
1c	$(CH_2)_2CH_3$	189.2	115.9	77.1	58.4	196.6	187.2	228.4
1d	$(CH_2)_3CH_3$	174.9	74.0	77.1	28.3	214.4	207.6	231.4
1e	$(CH_2)_4CH_3$	199.7	148.8	104.7	65.1	223.4	198.2	248.1
1f	$(CH_2)_5CH_3$	149.4	129.7	74.3	39.0	168.7	148.6	217.1
1g	$(CH_2)_6CH_3$	74.1	50.8	51.8	26.2	83.3	91.7	167.2
1h	$(CH_2)_7CH_3$	48.8	46.2	53.5	18.0	136.0	107.8	151.4
1i	$(CH_2)_8CH_3$	109.1	22.8	55.0	6.1	211.1	148.5	245.5
1j	$(CH_2)_9CH_3$	151.0	9.3	77.6	4.9	227.4	173.1	249.1
1k	$(CH_2)_{10}CH_3$	163.8	6.8	73.0	2.4	226.7	176.5	248.0
1l	$(CH_2)_{11}CH_3$	169.5	30.5	92.4	2.4	225.5	185.1	243.3
1m	*i*-Pr	176.5	131.9	85.2	55.3	190.5	192.8	228.8
1n	*s*-But	188.8	131.3	85.9	42.1	191.8	175.6	243.2
1o	*t*-But	162.6	163.7	102.9	132.1	185.9	215.5	160.6

[a] Average values of IC_{50} from 3 to 4 independent experiments with SD ranging from 10% to 25% of the average values.

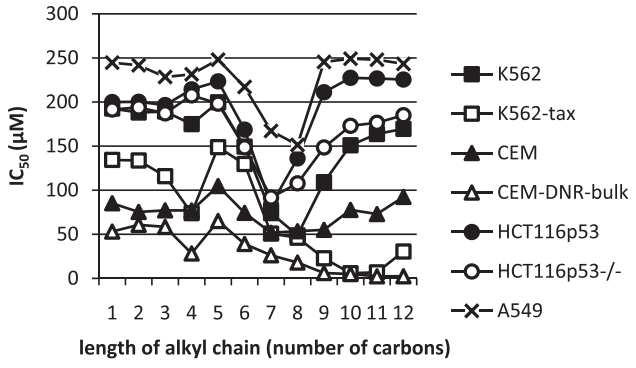


Figure 3. Cytotoxic activity of compounds **1** as a function of chain length in different cell lines.

ylene groups. While the activity of nucleosides **2a–h** against CEM, A549, K562 and both colorectal carcinoma cell lines is approaching the activity of bases **1a–h**, nucleosides **2i–l** exhibit much better activity than bases **1i–l**. Most interestingly, a comparison of cytotoxic activity of nucleosides **2** and bases **1** against drug resistant leukaemia cancer cell lines (CEM-DNR-bulk and K562-tax) indicates significantly decreased activity of nucleosides **2**. Cytotoxic activities of compounds **1** and **2** in drug sensitive versus MDR positive cell lines collectively suggest the importance of lipophilic groups for interaction of the compounds with ATP-dependent MDR transporters.

The next aim of our study was to investigate the role of substitution of nucleobases **1** in position C-5 with the bulky nitrophenyl group. This group causes a rise of chirality of the substituent in position 5. Because of the impossibility of separating the enantiomers, the compounds **3** were tested in their racemic mixture.[14] Indeed, comparison of cytotoxic activity of bases **1** and **3** (Tables 1 and 3) indicates that substitution of the methylene group by the nitrophenyl moiety positively influences the cytotoxic activity against CEM, A549, K562 and both colorectal carcinoma cell lines. On the other hand, the activity of bases **3j–3k** against P-gp positive K562-tax cell line is diminished in comparison to active analogues **1j–1k**. Also the activity against the MRP-1 positive CEM-DNR-bulk line is diminished namely in case of derivatives **1i–1l**, suggesting variable activity in those two MDR transporters.

As mentioned above, a detailed study of the structure–activity relationship was complicated due to the chirality of the carbon in position C-5 of uracil derivatives **3**. Because the corresponding enantiomers **3** are impossible to separate, they were converted to

Table 2
Summary of cytotoxic activity of derivatives **2**[a]

Compound code	R	K562	K562-tax	CEM	CEM-DNR-bulk	HCT116p53	HCT116p53−/−	A549
2a	CH_3	181.5	194.6	92.2	180.6	183.8	210.1	160.7
2b	CH_2CH_3	180.1	183.0	98.0	170.1	187.4	220.5	165.4
2c	$(CH_2)_2CH_3$	180.3	180.4	100.7	178.6	177.5	229.2	147.5
2d	$(CH_2)_3CH_3$	203.8	196.8	93.3	155.4	193.5	210.7	181.2
2e	$(CH_2)_4CH_3$	192.2	180.1	100.2	174.6	184.5	199.5	180.6
2f	$(CH_2)_5CH_3$	138.3	173.0	109.6	173.5	174.8	204.1	166.5
2g	$(CH_2)_6CH_3$	134.5	167.3	81.3	176.2	142.6	195.8	166.1
2h	$(CH_2)_7CH_3$	70.2	153.3	82.4	137.9	117.0	165.1	138.2
2i	$(CH_2)_8CH_3$	38.8	109.6	52.5	62.7	118.4	144.6	104.3
2j	$(CH_2)_9CH_3$	13.6	94.5	35.3	54.0	64.9	97.5	41.8
2k	$(CH_2)_{10}CH_3$	13.6	74.0	28.0	82.2	90.4	121.5	17.8
2l	$(CH_2)_{11}CH_3$	35.1	72.1	31.2	88.6	84.9	117.5	41.4
2m	*i*-Pr	179.6	183.0	103.2	173.7	196.8	205.6	168.8
2n	*s*-But	207.9	192.2	94.8	172.7	199.3	215.8	180.4
2o	*t*-But	192.4	186.1	83.1	208.3	192.5	205.7	177.2

[a] Average values of IC_{50} from 3 to 4 independent experiments with SD ranging from 10% to 25% of the average values.

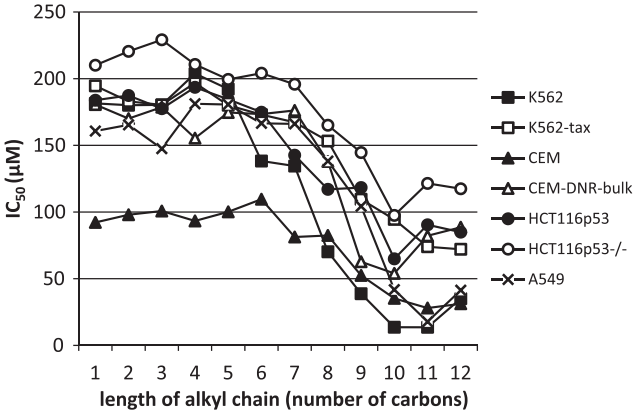


Figure 4. Cytotoxic activity of compounds **2** as a function of chain length in different cell lines.

corresponding diastereoisomeric nucleosides **4(+)** and **4(−)**. Activities of model diastereoisomers **4(+)** and **4(−)** (Table 4) were compared in order to identify any possible effect of chirality for compounds bearing appropriate chiral centres. However, the trend of activity was similar for both diastereoisomers **4(+)** as well as for **4(−)** and the cytotoxic potencies of (+) and (−) diastereoisomers were similar regardless of their chain length. Therefore, we conclude that the chirality of carbon in position C-5 of uracil does not influence the cytotoxic activity of the tested compounds.

When bases **3** and ribosides **4** are compared, a slight increase of activities can be defined in case of some nucleosides, especially for derivative **4i**, when a micromolar value of IC_{50} against CEM and HCT116p53 was reached.

3. Conclusion

In summary, 5-alkoxymethyluracil analogues were synthesized employing Vorbrügen ribosylation. The cytotoxic activity of both 5-alkoxymethyluracils **1** and 5-alkoxymethyluridines **2** was evaluated and extensive SAR studies are reported. The present SAR studies illustrate that modified nucleobases **1** are more active against multidrug drug resistant K562-tax and CEM-DNR-bulk cell lines in direct comparison with corresponding nucleosides **2**, whereas nucleosides **2** exhibit higher activity against drug sensitive cell lines, especially longer alkyl chain derivatives **2i–l** with cytotoxic activity in low micromolar concentrations. Compounds **1i–l** and **3j–l** exhibited substantial selectivity against chemoresistant line K562-tax (P-glycoprotein positive), while in CEM-DNR-bulk cells (MRP-1 positive), selective activity was seen only in compounds **1i–l**. This interesting phenomenon will be a subject of mechanistic study in the future. Introduction of the nitrophenyl moiety enhanced cytotoxicity of the bases **3** in comparison to **1** with the exception of the multidrug resistant CEM-DNR-bulk cell line suggesting that nitrophenyl moiety is involved in MRP-1 mediated drug efflux from the cell. While the presence of a ribose moiety in the structure of derivatives **4** modulates in vitro anticancer po-

Table 3
Summary of cytotoxic activity of derivatives **3**[a]

Compound code	R	K562	K562-tax	CEM	CEM-DNR-bulk	HCT116p53	HCT116p53−/−	A549
3a	CH_3	187.4	177.3	134.1	169.9	166.1	163.3	158.2
3b	CH_2CH_3	168.0	172.9	128.6	171.8	158.2	149.8	151.7
3c	$(CH_2)_2CH_3$	139.0	135.8	49.9	151.8	110.2	112.7	126.0
3d	$(CH_2)_3CH_3$	116.5	111.6	57.3	144.5	87.4	109.3	115.2
3e	$(CH_2)_4CH_3$	64.9	81.7	49.1	116.7	54.5	88.0	78.8
3f	$(CH_2)_5CH_3$	118.5	91.3	113.7	137.7	70.4	26.3	83.0
3g	$(CH_2)_6CH_3$	34.4	37.7	28.8	44.1	33.0	41.0	39.7
3h	$(CH_2)_7CH_3$	38.7	44.2	24.3	46.9	33.7	40.5	39.3
3i	$(CH_2)_8CH_3$	36.1	31.3	25.2	48.9	27.7	41.3	42.2
3j	$(CH_2)_9CH_3$	78.7	23.5	22.3	63.9	26.7	40.3	67.7
3k	$(CH_2)_{10}CH_3$	118.0	26.2	20.5	96.0	68.5	50.4	95.8
3l	$(CH_2)_{11}CH_3$	47.7	14.1	14.2	114.3	166.0	23.5	120.1
3m	*i*-Pr	172.4	172.7	124.7	169.6	155.1	143.4	148.5
3n	*s*-But	148.4	161.1	103.0	165.3	136.7	141.5	137.8
3o	*t*-But	175.0	175.5	131.1	162.8	178.5	158.5	161.5

[a] Average values of IC_{50} from 3 to 4 independent experiments with SD ranging from 10% to 25% of the average values. Compounds **3** were tested in their racemic mixture.

Table 4
Summary of cytotoxic activity of derivatives **4**[a]

Compound code	R	K562	K562-tax	CEM	CEM-DNR-bulk	HCT116p53	HCT116p53−/−	A549
4f (+)	$(CH_2)_5CH_3$	58.4	141.4	39.8	131.0	53.0	104.4	121.3
4f (−)	$(CH_2)_5CH_3$	64.5	136.9	45.5	145.8	51.9	105.0	156.0
4g (+)	$(CH_2)_6CH_3$	33.6	42.8	12.8	103.7	24.8	38.5	39.8
4g (−)	$(CH_2)_6CH_3$	36.7	52.3	29.0	95.6	30.0	52.8	69.9
4h (+)	$(CH_2)_7CH_3$	15.1	33.1	11.4	34.6	15.0	28.1	38.7
4h (−)	$(CH_2)_7CH_3$	24.7	34.4	16.9	36.6	15.5	30.7	39.7
4i (+)	$(CH_2)_8CH_3$	10.9	14.6	7.9	32.3	9.0	15.8	23.1
4i (−)	$(CH_2)_8CH_3$	13.0	23.9	10.0	33.8	9.8	17.3	29.1

[a] Average values of IC_{50} from 3 to 4 independent experiments with SD ranging from 10% to 25% of the average values.

tency of the compounds, their chirality had no impact. We expect that our SAR studies will be extended in future. Particularly, we would like to examine the cytotoxicity of derivatives **1** and **2** with alkyl chains longer than 12 carbons in drug resistant cancers, which currently represent the major problem in successful anticancer therapy.

4. Experimental section

4.1. Chemistry

Melting points were determined on a Boetius stage and are uncorrected. NMR spectra were recorded at ambient temperature (21 °C) in DMSO-d_6 solutions at 300 K on a Bruker Avance 300 spectrometer and referenced to the resonance signal of DMSO (with TMS as an internal standard; chemical shifts are reported in ppm, and coupling constants in Hz). The LC/MS analyses were carried out on UHPLC-MS system consisting of UHPLC chromatograph Accela with photodiode array detector and triple quadrupole mass spectrometer TSQ Quantum Access (both Thermo Scientific, CA, USA), using Nucleodur Gravity C_{18} column at 30 °C and flow rate of 800 μL/min (Macherey–Nagel, 1.8 μm, 2.1 × 50 mm, Germany). The mobile phase was (A) 0.01 M ammonium acetate in water, and (B) acetonitrile, linearly programmed from 10% to 80% B over 2.5 min, kept for 1.5 min. The column was pre-equilibrated with 10% of solution B for 1 min. The purity of all compounds was ⩾95%. The APCI source operated at discharge current of 5 μA, vaporizer temperature of 400 °C and capillary temperature of 200 °C. Elemental analyses were performed using an EA 1108 Elemental Analyzer (Fison Instruments). Purification by column chromatography was carried out using silica gel.

4.1.1. 5-[(Nonyloxy)methyl]pyrimidine-2,4(1*H*,3*H*)-dione 1i

Compound **5** (500.0 mg, 3.11 mmol) was heated in 1-nonanol (25 mL) at 100 °C for 4 h. After cooling to rt, the precipitated solid was collected by filtration, washed with 1-nonanol and dried. Yield 625.2 mg (75%), mp 210–214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.79–0.89 (m, 3H) 1.23 (s, 12H) 1.46 (t, J = 6.0 Hz, 2H) 3.35 (t, J = 6.5 Hz, 2H) 4.03 (s, 2H) 7.37 (d, J = 6.0 Hz, 1H) 10.83 (d, J = 5.0 Hz, 1H) 11.11 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.49, 22.62, 26.20, 29.20, 29.39, 29.53, 29.70, 31.81, 64.79, 70.01, 109.80, 140.86, 151.84, 164.32. MS *m/z* calcd for $C_{14}H_{24}N_2O_3$: 268.35, found 267.10 $[M-H]^-$.

4.1.2. 5-[(Undecyloxy)methyl]pyrimidine-2,4(1*H*,3*H*)-dione 1k

Compound **5** (496.0 mg, 3.09 mmol) was heated in 1-undecanol (25 mL) at 100 °C for 4 h. After cooling to rt, the precipitated solid was collected by filtration, washed with the 1-undecanol and dried. Yield 612.4 mg (67%), mp 204–206 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 6.0 Hz, 3H) 1.24 (s, 16H) 1.41–1.53 (m, 2H) 3.35 (t, J = 6.0 Hz, 2H) 4.04 (s, 2H) 7.35 (br s, 1H) 10.77 (br s, 1H) 11.06 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.49, 22.62, 26.20, 29.23, 29.39, 29.53, 29.56, 29.70, 31.83, 64.79, 70.02, 109.80, 140.85, 151.84, 164.32. MS *m/z* calcd for $C_{16}H_{28}N_2O_3$: 296.41, found 295.13 $[M-H]^-$.

4.1.3. General procedure for preparation of 5-alkoxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-diones 8

Uracils **1** were heated at reflux in hexamethyldisilazane with $(NH_4)_2SO_4$ (approximately 5 mg) for 8 h. The solution was the concentrated and the residue was dissolved in anhydrous 1,2-dichloroethane (20 mL). To this solution, 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose and trimethylsilyl trifluoromethanesulfonate were added. This mixture was stirred at room temperature for 24 h, washed with water (20 mL) and EtOAc (3 × 60 mL), dried over sodium sulfate, filtered and evaporated to dryness. The crude product was purified by preparative chromatography using $CHCl_3$–CH_3CN (5:1) to get the nucleosides **8**.

4.1.3.1. 5-Methoxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8a. Nucleoside **8a** was prepared from **1a** (238.5 mg, 1.53 mmol), HMDS (10 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (847.7 mg, 1.68 mmol) and trimethylsilyl trifluoromethanesulfonate (415 μl, 2.29 mmol) according to the general procedure. Yield 557.4 mg (61%), mp 78–80 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.15 (s, 3H) 3.90–4.04 (m, 2H) 4.58–4.80 (m, 3H) 5.94 (d, J = 4.0 Hz, 2H) 6.23 (d, J = 3.5 Hz, 1H) 7.39–7.56 (m, 6H) 7.60–7.72 (m, 3H) 7.82 (s, 1H) 7.91 (d, J = 7.0 Hz, 2H) 7.87 (d, J = 7.0 Hz, 2H) 8.03 (d, J = 7.0 Hz, 2H) 11.61 (s, 1H). MS *m/z* calcd for $C_{32}H_{28}N_2O_{10}$: 600.57, found 599.10 $[M-H]^-$. Anal. Calcd for $C_{32}H_{28}N_2O_{10}$ (600.57): C, 64.00; H, 4.70; N, 4.66. Found: C, 63.7 8; H, 4.62; N, 4.43.

4.1.3.2. 5-Ethoxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8b. Nucleoside **8b** was prepared from **1b** (351.4 mg, 2.07 mmol), HMDS (15 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (1041.8 mg, 2.07 mmol) and trimethylsilyl trifluoromethanesulfonate (415 μl, 2.29 mmol) according to the general procedure. Yield 644.6 mg (69%), mp 72–75 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (t, J = 7.0 Hz, 3H) 3.30–3.38 (m, 2H) 3.94–4.09 (m, 2H) 4.58–4.81 (m, 3H) 5.95 (d, J = 3.0 Hz, 2H) 6.22 (d, J = 3.0 Hz, 1H) 7.40–7.56 (m, 6H) 7.60–7.72 (m, 3H) 7.81 (s, 1H) 7.91 (d, J = 8.0 Hz, 2H) 7.87 (d, J = 8.0 Hz, 2H) 8.03 (d, J = 7.5 Hz, 2H) 11.60 (s, 1H). MS *m/z* calcd for $C_{33}H_{30}N_2O_{10}$: 614.60, found 613.18 $[M-H]^-$. Anal. Calcd for $C_{33}H_{30}N_2O_{10}$ (614.60): C, 64.49; H, 4.92; N, 4.56. Found: C, 64.64; H, 4.91; N, 4.50.

4.1.3.3. 5-Propoxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8c. Nucleoside **8c** was prepared from **1c** (293.8 mg, 1.60 mmol), HMDS (15 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (804.7 mg, 1.60 mmol) and trimethylsilyl trifluoromethanesulfonate (320 μl, 1.77 mmol) according to the general procedure. Yield 437.4 mg (44%), mp 70–72 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.79 (t, J = 7.0 Hz, 3H)

1.35–1.49 (m, 2H) 3.25 (td, *J* = 7.0, 2.0 Hz, 2H) 4.01 (q, *J* = 12.0 Hz, 2H) 4.58–4.81 (m, 3H) 5.95 (d, *J* = 3.5 Hz, 2H) 6.23 (d, *J* = 3.0 Hz, 1H) 7.40–7.56 (m, 6H) 7.61–7.71 (m, 3H) 7.81 (s, 1H) 7.83–7.95 (m, 4H) 8.03 (d, *J* = 7.0 Hz, 2H) 11.60 (s, 1H). MS *m/z* calcd for $C_{34}H_{32}N_2O_{10}$: 628.63, found 627.14 $[M-H]^-$. Anal. Calcd for $C_{34}H_{32}N_2O_{10}$ (628.63): C, 64.96; H, 5.13; N, 4.46. Found: C, 64.88; H, 5.06; N, 4.30.

4.1.3.4. 5-Isopropoxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8m. Nucleoside **8m** was prepared from **1m** (191.6 mg, 1.04 mmol), HMDS (15 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (524.8 mg, 1.04 mmol) and trimethylsilyl trifluoromethanesulfonate (210 μl, 1.16 mmol) according to the general procedure. Yield 307.7 mg (47%), mp 46–47 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98–1.07 (m, 6H) 3.48–3.60 (m, 1H) 4.02 (q, *J* = 12.0 Hz, 2H) 4.58–4.81 (m, 3H) 5.95 (d, *J* = 4.0 Hz, 2H) 6.22 (d, *J* = 3.0 Hz, 1H) 7.40–7.56 (m, 6H) 7.61–7.72 (m, 3H) 7.78 (s, 1H) 7.84–7.95 (m, 4H) 8.02 (d, *J* = 7.0 Hz, 2H) 11.59 (s, 1H). MS *m/z* calcd for $C_{34}H_{32}N_2O_{10}$: 628.63, found 627.11 $[M-H]^-$. Anal. Calcd for $C_{34}H_{32}N_2O_{10}$ (628.63): C, 64.96; H, 5.13; N, 4.46. Found: C, 64.78; H, 5.02; N, 4.34.

4.1.3.5. 5-Butoxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8d. Nucleoside **8d** was prepared from **1d** (166.8 mg, 0.84 mmol), HMDS (15 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (424.5 mg, 0.84 mmol) and trimethylsilyl trifluoromethanesulfonate (170 μl, 0.94 mmol) according to the general procedure. Yield 185.1 mg (34%), mp 63–66 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77–0.86 (m, 3H) 1.24 (sxt, *J* = 7.0 Hz, 2H) 1.33–1.46 (m, 2H) 3.25–3.32 (m, 2H) 4.01 (q, *J* = 12.0 Hz, 2H) 4.58–4.72 (m, 2H) 4.72–4.80 (m, 1H) 5.94 (d, *J* = 3.5 Hz, 2H) 6.23 (d, *J* = 3.0 Hz, 1H) 7.40–7.56 (m, 6H) 7.60–7.72 (m, 3H) 7.81 (s, 1H) 7.91 (d, *J* = 7.5 Hz, 2H) 7.87 (d, *J* = 7.0 Hz, 2H) 8.03 (d, *J* = 7.0 Hz, 2H) 11.59 (br s, 1H). MS *m/z* calcd for $C_{35}H_{34}N_2O_{10}$: 642.65, found 641.14 $[M-H]^-$. Anal. Calcd for $C_{35}H_{34}N_2O_{10}$ (642.65): C, 65.41; H, 5.33; N, 4.26. Found: C, 65.39; H, 5.30; N, 4.39.

4.1.3.6. 5-*sec*-Butoxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8n. Nucleoside **8n** was prepared from **1n** (303.7 mg, 1.53 mmol), HMDS (12 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (772.9 mg, 1.53 mmol) and trimethylsilyl trifluoromethanesulfonate (420 μl, 2.32 mmol) according to the general procedure. Yield 457.2 mg (46%), mp 67–70 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 (td, *J* = 7.0, 2.0 Hz, 3H) 0.95–1.04 (m, 3H) 1.21–1.45 (m, 2H) 3.25–3.31 (m, 1H) 3.89–4.15 (m, 2H) 4.58–4.81 (m, 3H) 5.91–5.98 (m, 2H) 6.23 (d, *J* = 2.0 Hz, 1H) 7.39–7.56 (m, 6H) 7.60–7.71 (m, 3H) 7.78 (s, 1H) 7.91 (d, *J* = 8.0 Hz, 2H) 7.87 (d, *J* = 8.0 Hz, 2H) 8.02 (d, *J* = 7.0 Hz, 2H) 11.59 (br s, 1H). MS *m/z* calcd for $C_{35}H_{34}N_2O_{10}$: 642.65, found 641.14 $[M-H]^-$. Anal. Calcd for $C_{35}H_{34}N_2O_{10}$ (642.65): C, 65.41; H, 5.33; N, 4.36. Found: C, 65.27; H, 5.26; N, 4.42.

4.1.3.7. 5-*tert*-Butoxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8o. Nucleoside **8o** was prepared from **1o** (186.0 mg, 0.94 mmol), HMDS (15 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (473.4 mg, 0.94 mmol) and trimethylsilyl trifluoromethanesulfonate (190 μl, 1.05 mmol) according to the general procedure. Yield 248.0 mg (41%), mp 88–90 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10 (s, 9H) 3.99 (d, *J* = 12.0 Hz, 2H) 4.56–4.81 (m, 3H) 5.96 (br s, 2H) 6.22 (br s, 1H) 7.38–7.57 (m, 6H) 7.59–7.71 (m, 3H) 7.73 (s, 1H) 7.89 (t, *J* = 8.0 Hz, 4H) 8.02 (d, *J* = 7.0 Hz, 2H) 11.57 (s, 1H). MS *m/z* calcd for $C_{35}H_{34}N_2O_{10}$: 642.65, found 641.04 $[M-H]^-$. Anal. Calcd for $C_{35}H_{34}N_2O_{10}$ (642.65): C, 65.41; H, 5.33; N, 4.36. Found: C, 65.55; H, 5.41; N, 4.33.

4.1.3.8. 5-Pentyloxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8e. Nucleoside **8e** was prepared from **1e** (145.6 mg, 0.69 mmol), HMDS (10 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (346.1 mg, 0.69 mmol) and trimethylsilyl trifluoromethanesulfonate (137 μl, 0.76 mmol) according to the general procedure. Yield 165.1 mg (37%), mp 62–64 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82 (t, *J* = 7.0 Hz, 3H) 1.12–1.29 (m, 4H) 1.30–1.47 (m, 2H) 3.23–3.31 (m, 2H) 4.00 (q, *J* = 12.0 Hz, 2H) 4.57–4.82 (m, 3H) 5.94 (d, *J* = 3.5 Hz, 2H) 6.23 (d, *J* = 3.0 Hz, 1H) 7.37–7.57 (m, 6H) 7.59–7.72 (m, 3H) 7.81 (s, 1H) 7.89 (dd, *J* = 12.0, 7.32 Hz, 4H) 8.03 (d, *J* = 7.0 Hz, 2H) 11.14 (br s, 1H). MS *m/z* calcd for $C_{36}H_{36}N_2O_{10}$: 656.68, found 655.14 $[M-H]^-$. Anal. Calcd for $C_{36}H_{36}N_2O_{10}$ (656.68): C, 65.84; H, 5.53; N, 4.27. Found: C, 65.98; H, 5.45; N, 4.07.

4.1.3.9. 5-Hexyloxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8f. Nucleoside **8f** was prepared from **1f** (341.8 mg, 1.51 mmol), HMDS (10 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (838.3 mg, 1.66 mmol) and trimethylsilyl trifluoromethanesulfonate (410 μl, 2.27 mmol) according to the general procedure. Yield 405.2 mg (40%), mp 50–51 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75–0.90 (m, 3H) 1.10–1.31 (m, 6H) 1.32–1.48 (m, 2H) 3.22–3.32 (m, 2H) 4.01 (q, *J* = 12.0 Hz, 2H) 4.58–4.82 (m, 3H) 5.89–6.00 (m, 2H) 6.23 (d, *J* = 3.0 Hz, 1H) 7.38–7.57 (m, 6H) 7.59–7.72 (m, 3H) 7.81 (s, 1H) 7.89 (dd, *J* = 12.0, 7.0 Hz, 4H) 8.03 (d, *J* = 7.0 Hz, 2H) 11.60 (s, 1H). MS *m/z* calcd for $C_{37}H_{38}N_2O_{10}$: 670.71, found 669.16 $[M-H]^-$. Anal. Calcd for $C_{37}H_{38}N_2O_{10}$ (670.71): C, 66.26; H, 5.71; N, 4.18. Found: C, 66.12; H, 5.58; N, 4.29.

4.1.3.10. 5-Heptyloxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8g. Nucleoside **8g** was prepared from **1g** (374.9 mg, 1.56 mmol), HMDS (12 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (787.1 mg, 1.56 mmol) and trimethylsilyl trifluoromethanesulfonate (420 μl, 2.32 mmol) according to the general procedure. Yield 526.3 mg (49%), mp 48–50 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82 (t, *J* = 7.0 Hz, 3H) 1.11–1.31 (m, 8H) 1.32–1.46 (m, 2H) 3.28 (td, *J* = 6.5, 3.0 Hz, 2H) 4.01 (q, *J* = 12.0 Hz, 2H) 4.57–4.81 (m, 3H) 5.94 (d, *J* = 4.0 Hz, 2H) 6.23 (d, *J* = 3.0 Hz, 1H) 7.39–7.57 (m, 6H) 7.60–7.72 (m, 3H) 7.81 (s, 1H) 7.89 (dd, *J* = 12.0, 7.0 Hz, 4H) 8.02 (d, *J* = 7.0 Hz, 2H) 11.60 (s, 1H). MS *m/z* calcd for $C_{38}H_{40}N_2O_{10}$: 684.73, found 683.14 $[M-H]^-$. Anal. Calcd for $C_{38}H_{40}N_2O_{10}$ (684.73): C, 66.65; H, 5.89; N, 4.09. Found: C, 66.48; H, 5.90; N, 4.17.

4.1.3.11. 5-Oktyloxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8h. Nucleoside **8h** was prepared from **1h** (300.3 mg, 1.18 mmol), HMDS (12 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (655.2 mg, 1.30 mmol) and trimethylsilyl trifluoromethanesulfonate (320 μl, 1.77 mmol) according to the general procedure. Yield 379.9 mg (46%), mp 56–57 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82 (t, *J* = 7.0 Hz, 3H) 1.11–1.30 (m, 10H) 1.32–1.47 (m, 2H) 3.23–3.32 (m, 2H) 3.92–4.10 (m, 2H) 4.59–4.81 (m, 3H) 5.94 (d, *J* = 3.5 Hz, 2H) 6.23 (d, *J* = 3.0 Hz, 1H) 7.39–7.55 (m, 6H) 7.60–7.72 (m, 3H) 7.81 (s, 1H) 7.89 (dd, *J* = 12.0, 7.0 Hz, 4H) 8.02 (d, *J* = 7.0 Hz, 2H) 11.60 (s, 1H). MS *m/z* calcd for $C_{39}H_{42}N_2O_{10}$: 698.76, found 697.22 $[M-H]^-$. Anal. Calcd for $C_{39}H_{42}N_2O_{10}$ (698.76): C, 67.04; H, 6.06; N, 4.01. Found: C, 67.17; H, 6.18; N, 4.21.

4.1.3.12. 5-Nonyloxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8i. Nucleoside **8i** was prepared from **1i** (505.9 mg, 1.89 mmol), HMDS (12 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (1046.2 mg, 2.07 mmol) and trimethylsilyl trifluoromethanesulfonate (515 μl, 2.85 mmol) according to the general procedure. Yield 623.4 mg (46%), mp

58–60 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78–0.89 (m, 3H) 1.13–1.29 (m, 12H) 1.33–1.46 (m, 2H) 3.23–3.32 (m, 2H) 4.01 (d, J = 11.0 Hz, 2H) 4.58–4.81 (m, 3H) 5.94 (d, J = 3.0 Hz, 2H) 6.23 (d, J = 3.0 Hz, 1H) 7.39–7.56 (m, 6H) 7.60–7.71 (m, 3H) 7.81 (s, 1H) 7.89 (dd, J = 12.0, 7.5 Hz, 4H) 8.02 (d, J = 7.5 Hz, 2H) 11.60 (s, 1H). MS *m/z* calcd for $C_{40}H_{44}N_2O_{10}$: 712.78, found 711.20 [M−H]$^-$. Anal. Calcd for $C_{40}H_{44}N_2O_{10}$ (712.78): C, 67.40; H, 6.22; N, 3.93. Found: C, 67.59; H, 6.32; N, 4.05.

4.1.3.13. 5-Decyloxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8j. Nucleoside **8j** was prepared from **1j** (338.1 mg, 1.20 mmol), HMDS (12 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (604.0 mg, 1.20 mmol) and trimethylsilyl trifluoromethanesulfonate (325 μl, 1.80 mmol) according to the general procedure. Yield 425.9 mg (49%), mp 67–68 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.76–0.89 (m, 3H) 1.11–1.31 (m, 14H) 1.39 (t, J = 6.0 Hz, 2H) 3.23–3.32 (m, 2H) 3.93–4.08 (m, 2H) 4.59–4.81 (m, 3H) 5.94 (d, J = 3.5 Hz, 2H) 6.23 (d, J = 3.0 Hz, 1H) 7.38–7.57 (m, 6H) 7.60–7.72 (m, 3H) 7.81 (s, 1H) 7.89 (dd, J = 12.5, 7.0 Hz, 4H) 8.02 (d, J = 7.0 Hz, 2H) 11.60 (s, 1H). MS *m/z* calcd for $C_{41}H_{46}N_2O_{10}$: 726.81, found 725.21 [M−H]$^-$. Anal. Calcd for $C_{41}H_{46}N_2O_{10}$ (726.81): C, 67.75; H, 6.38; N, 3.85. Found: C, 67.86; H, 6.53; N, 3.81.

4.1.3.14. 5-Undecyloxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8k. Nucleoside **8k** was prepared from **1k** (215.9 mg, 0.73 mmol), HMDS (12 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (367.5 mg, 0.73 mmol) and trimethylsilyl trifluoromethanesulfonate (198 μl, 1.09 mmol) according to the general procedure. Yield 181.5 mg (34%), mp 69–72 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77–0.90 (m, 3H) 1.11–1.31 (m, 16H) 1.33–1.46 (m, 2H) 3.22–3.31 (m, 2H) 3.92–4.08 (m, 2H) 4.56–4.81 (m, 3H) 5.94 (d, J = 3.5 Hz, 2H) 6.23 (d, J = 3.0 Hz, 1H) 7.39–7.55 (m, 6H) 7.59–7.72 (m, 3H) 7.80 (s, 1H) 7.89 (dd, J = 12.5, 7.0 Hz, 4H) 8.02 (d, J = 7.0 Hz, 2H) 11.60 (s, 1H). MS *m/z* calcd for $C_{42}H_{48}N_2O_{10}$: 740.84, found 739.27 [M−H]$^-$. Anal. Calcd for $C_{42}H_{48}N_2O_{10}$ (740.84): C, 68.09; H, 6.53; N, 3.78. Found: C, 68.23; H, 6.65; N, 3.98.

4.1.3.15. 5-Dodecyloxymethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 8l. Nucleoside **8l** was prepared from **1l** (359.3 mg, 1.16 mmol), HMDS (12 mL), 1-*O*-acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose (583.9 mg, 1.16 mmol) and trimethylsilyl trifluoromethanesulfonate (315 μl, 1.74 mmol) according to the general procedure. Yield 535.4 mg (61%), mp 77–78 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (t, J = 6.5 Hz, 3H) 1.12–1.30 (m, 18H) 1.32–1.46 (m, 2H) 3.21–3.31 (m, 2H) 3.92–4.09 (m, 2H) 4.58–4.81 (m, 3H) 5.94 (d, J = 4.0 Hz, 2H) 6.23 (d, J = 3.0 Hz, 1H) 7.39–7.55 (m, 6H) 7.60–7.72 (m, 3H) 7.80 (s, 1H) 7.89 (dd, J = 12.5, 7.0 Hz, 4H) 8.02 (d, J = 7.0 Hz, 2H) 11.60 (s, 1H). MS *m/z* calcd for $C_{43}H_{50}N_2O_{10}$: 754.86, found 753.56 [M−H]$^-$. Anal. Calcd for $C_{43}H_{50}N_2O_{10}$ (754.86): C, 68.32; H, 6.78; N, 3.81. Found: C, 68.46; H, 6.69; N, 3.69.

4.1.4. General procedure for preparation of 5-alkoxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-diones 2

Nucleosides **8** were dissolved in MeOH–NH_3 solution and stirred at room temperature for 6 days. Then the mixture was evaporated, co-evaporated with MeOH and purified by preparative chromatography using $CHCl_3$–MeOH (9:0.5) to afford the nucleosides **2**.

4.1.4.1. 5-Propoxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2c. Nucleoside **2c** was prepared from **8c** (390.2 mg, 0.62 mmol) and MeOH–NH_3 solution (15 mL) according to the general procedure. Yield 178.2 mg (91%), mp 134–136 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 7.0 Hz, 3H) 1.43–1.57 (m, 2H) 3.29–3.38 (m, 2H) 3.49–3.68 (m, 2H) 3.84 (q, J = 3.0 Hz, 1H) 3.92–4.12 (m, 4H) 5.05–5.13 (m, 2H) 5.39 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.93 (s, 1H) 11.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.46, 22.28, 60.77, 64.35, 69.81, 71.17, 73.43, 84.74, 87.54, 110.61, 138.94, 150.53, 162.57. MS *m/z* calcd for $C_{13}H_{20}N_2O_7$: 316.31, found 315.05 [M−H]$^-$.

4.1.4.2. 5-Isopropoxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2m. Nucleoside **2m** was prepared from **8m** (195.1 mg, 0.27 mmol) and MeOH–NH_3 solution (10 mL) according to the general procedure. Yield 91.8 mg (94%), mp 113–115 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09 (d, J = 6.0 Hz, 6H) 3.49–3.68 (m, 3H) 3.80–3.88 (m, 1H) 3.92–4.14 (m, 4H) 5.04–5.13 (m, 2H) 5.39 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.90 (s, 1H) 11.37 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.54, 22.57, 61.45, 62.43, 70.51, 71.03, 74.05, 85.39, 88.16, 111.85, 139.09, 151.18, 163.13. MS *m/z* calcd for $C_{13}H_{20}N_2O_7$: 316.31, found 315.07 [M−H]$^-$.

4.1.4.3. 5-Butoxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2d. Nucleoside **2d** was prepared from **8d** (157.7 mg, 0.25 mmol) and MeOH–NH_3 solution (10 mL) according to the general procedure. Yield 73.4 mg (91%), mp 125–127 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 7.0 Hz, 3H) 1.21–1.37 (m, 2H) 1.40–1.54 (m, 2H) 3.35–3.42 (m, 2H) 3.49–3.68 (m, 2H) 3.84 (d, J = 3.5 Hz, 1H) 3.92–4.13 (m, 4H) 5.09 (br s, 2H) 5.39 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.93 (s, 1H) 11.39 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.32, 19.37, 31.72, 61.41, 65.01, 69.83, 70.43, 74.05, 85.38, 88.18, 111.24, 139.60, 151.16, 163.21. MS *m/z* calcd for $C_{14}H_{22}N_2O_7$: 330.33, found 329.06 [M−H]$^-$.

4.1.4.4. 5-*sec*-Butoxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2n. Nucleoside **2n** was prepared from **8n** (300.2 mg, 0.47 mmol) and MeOH–NH_3 solution (15 mL) according to the general procedure. Yield 147.7 mg (96%), mp 120–121 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82 (t, J = 7.0 Hz, 3H) 1.07 (d, J = 6.0 Hz, 3H) 1.31–1.53 (m, 2H) 3.34–3.44 (m, 1H) 3.58 (q, J = 12.0 Hz, 2H) 3.84 (d, J = 3.0 Hz, 1H) 3.92–4.18 (m, 4H) 5.10 (d, J = 5.0 Hz, 2H) 5.38 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.89 (s, 1H) 11.37 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.08, 19.59, 29.14, 61.47, 62.70, 70.54, 74.05, 76.01, 85.39, 88.10, 111.93, 139.13, 151.19, 163.15. MS *m/z* calcd for $C_{14}H_{22}N_2O_7$: 330.33, found 329.08 [M−H]$^-$.

4.1.4.5. 5-*tert*-Butoxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2o. Nucleoside **2o** was prepared from **8o** (277.3 mg, 0.43 mmol) and MeOH–NH_3 solution (15 mL) according to the general procedure. Yield 114.6 mg (80%), mp 79–81 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.17 (s, 9H) 3.47–3.67 (m, 2H) 3.85 (d, J = 3.0 Hz, 1H) 3.91–4.09 (m, 4H) 5.01–5.14 (m, 2H) 5.38 (d, J = 5.5 Hz, 1H) 5.81 (d, J = 5.5 Hz, 1H) 7.84 (s, 1H) 11.34 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.84, 56.79, 61.58, 70.65, 73.51, 74.05, 85.45, 88.10, 112.56, 138.49, 151.18, 163.03. MS *m/z* calcd for $C_{14}H_{22}N_2O_7$: 330.33, found 329.11 [M−H]$^-$.

4.1.4.6. 5-Pentyloxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2e. Nucleoside **2e** was prepared from **8e** (152.6 mg, 0.23 mmol) and MeOH–NH_3 solution (20 mL) according to the general procedure. Yield 52.6 mg (66%), mp 122–125 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80–0.90 (m, 3H) 1.19–1.34 (m, 4H) 1.48 (quin, J = 6.5 Hz, 2H) 3.32–3.41 (m, 2H) 3.49–3.68 (m, 2H) 3.84 (d, J = 3.5 Hz, 1H) 3.92–4.12 (m, 4H) 5.06–5.13 (m, 2H) 5.39 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.93 (s, 1H) 11.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.48, 22.48, 28.40, 29.34, 61.44, 65.01, 70.15, 70.43, 74.05, 85.39, 88.20, 111.25, 139.60, 151.16, 163.21. MS *m/z* calcd for $C_{15}H_{24}N_2O_7$: 344.36, found 343.19 [M−H]$^-$.

4.1.4.7. 5-Hexyloxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2f. Nucleoside **2f** was prepared from **8f** (315.7 mg, 0.47 mmol) and MeOH–NH_3 solution (15 mL) according to the general procedure. Yield 143.4 mg (85%), mp 119–121 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 6.0 Hz, 3H) 1.17–1.34 (m, 6H) 1.41–1.55 (m, 2H) 3.35–3.41 (m, 2H) 3.48–3.70 (m, 2H) 3.84 (d, J = 3.0 Hz, 1H) 3.92–4.13 (m, 4H) 5.05–5.14 (m, 2H) 5.39 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.93 (s, 1H) 11.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.46, 22.61, 25.85, 29.63, 31.65, 61.42, 65.01, 70.15, 70.43, 74.07, 85.39, 88.22, 111.24, 139.63, 151.16, 163.21. MS *m/z* calcd for $C_{16}H_{26}N_2O_7$: 358.39, found 357.13 $[M-H]^-$.

4.1.4.8. 5-Heptyloxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2g. Nucleoside **2g** was prepared from **8g** (504.0 mg, 0.74 mmol) and MeOH–NH_3 solution (20 mL) according to the general procedure. Yield 236.7 mg (86%), mp 120–122 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78–0.91 (m, 3H) 1.24 (br s, 8H) 1.41–1.54 (m, 2H) 3.35–3.41 (m, 2H) 3.49–3.69 (m, 2H) 3.84 (d, J = 3.5 Hz, 1H) 3.90–4.13 (m, 4H) 5.04–5.14 (m, 2H) 5.39 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.93 (s, 1H) 11.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.86, 21.96, 25.50, 28.43, 29.04, 31.16, 60.79, 64.39, 69.50, 69.80, 73.43, 84.75, 87.57, 110.59, 139.01, 150.53, 162.57. MS *m/z* calcd for $C_{17}H_{28}N_2O_7$: 372.41, found 371.13 $[M-H]^-$.

4.1.4.9. 5-Octyloxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2h. Nucleoside **2h** was prepared from **8h** (343.1 mg, 0.49 mmol) and MeOH–NH_3 solution (15 mL) according to the general procedure. Yield 188.6 mg (99%), mp 124–125 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78–0.91 (m, 3H) 1.24 (s, 10H) 1.47 (br s, 2H) 3.35–3.41 (m, 2H) 3.48–3.68 (m, 2H) 3.84 (d, J = 3.0 Hz, 1H) 3.91–4.13 (m, 4H) 5.09 (d, J = 3.0 Hz, 2H) 5.39 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.93 (s, 1H) 11.38 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.48, 22.62, 26.20, 29.22, 29.38, 29.67, 31.80, 61.42, 65.01, 70.15, 70.43, 74.07, 85.39, 88.22, 111.24, 139.63, 151.16, 163.21. MS *m/z* calcd for $C_{18}H_{30}N_2O_7$: 386.44, found 385.16 $[M-H]^-$.

4.1.4.10. 5-Nonyloxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2i. Nucleoside **2i** was prepared from **8i** (578.6 mg, 0.81 mmol) and MeOH–NH_3 solution (20 mL) according to the general procedure. Yield 251.5 mg (77%), mp 125–127 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.79–0.91 (m, 3H) 1.24 (s, 12H) 1.47 (t, J = 6.0 Hz, 2H) 3.36–3.42 (m, 2H) 3.49–3.69 (m, 2H) 3.84 (d, J = 3.5 Hz, 1H) 3.91–4.12 (m, 4H) 5.09 (br s, 2H) 5.39 (d, J = 5.0 Hz, 1H) 5.79 (d, J = 5.0 Hz, 1H) 7.93 (s, 1H) 11.38 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.51, 22.64, 26.20, 29.23, 29.44, 29.54, 29.67, 31.83, 61.42, 65.01, 70.15, 70.43, 74.07, 85.39, 88.20, 111.22, 139.65, 151.16, 163.22. MS *m/z* calcd for $C_{19}H_{32}N_2O_7$: 400.47, found 399.19 $[M-H]^-$.

4.1.4.11. 5-Decyloxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2j. Nucleoside **2j** was prepared from **8j** (347.3 mg, 0.48 mmol) and MeOH–NH_3 solution (15 mL) according to the general procedure. Yield 175.3 mg (89%), mp 129–131 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80–0.90 (m, 3H) 1.24 (s, 14H) 1.41–1.54 (m, 2H) 3.34–3.39 (m, 2H) 3.48–3.69 (m, 2H) 3.84 (d, J = 3.5 Hz, 1H) 3.91–4.12 (m, 4H) 5.04–5.13 (m, 2H) 5.38 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.93 (s, 1H) 11.38 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.49, 22.64, 26.20, 29.25, 29.44, 29.53, 29.58, 29.67, 31.84, 61.42, 65.03, 70.17, 70.43, 74.07, 85.39, 88.23, 111.24, 139.63, 151.16, 163.21. MS *m/z* calcd for $C_{20}H_{34}N_2O_7$: 414.49, found 413.18 $[M-H]^-$.

4.1.4.12. 5-Undecyloxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2k. Nucleoside **2k** was prepared from **8k** (161.4 mg, 0.22 mmol) and MeOH–NH_3 solution (10 mL) according to the general procedure. Yield 84.5 mg (91%), mp 131–133 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75–0.90 (m, 3H) 1.24 (s, 16H) 1.38–1.55 (m, 2H) 3.34–3.40 (m, 2H) 3.50–3.69 (m, 2H) 3.84 (d, J = 3.5 Hz, 1H) 3.91–4.12 (m, 4H) 5.03–5.14 (m, 2H) 5.39 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.93 (s, 1H) 11.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.86, 22.00, 25.56, 28.63, 28.80, 28.92, 28.95, 28.95, 29.04, 31.20, 60.79, 64.39, 69.53, 69.80, 73.43, 84.75, 87.57, 110.59, 138.99, 150.53, 162.57. MS *m/z* calcd for $C_{21}H_{36}N_2O_7$: 428.52, found 427.25 $[M-H]^-$.

4.1.4.13. 5-Dodecyloxymethyl-1-(β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione 2l. Nucleoside **2l** was prepared from **8l** (530.1 mg, 0.70 mmol) and MeOH–NH_3 solution (20 mL) according to the general procedure. Yield 250.1 mg (81%), mp 132–133 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.79–0.90 (m, 3H) 1.23 (s, 18H) 1.40–1.53 (m, 2H) 3.34–3.40 (m, 2H) 3.49–3.69 (m, 2H) 3.81–3.88 (m, 1H) 3.92–4.12 (m, 4H) 5.05–5.13 (m, 2H) 5.39 (d, J = 5.5 Hz, 1H) 5.79 (d, J = 5.5 Hz, 1H) 7.93 (s, 1H) 11.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.48, 22.64, 26.20, 29.25, 29.26, 29.44, 29.56, 29.57, 29.60, 29.67, 31.84, 61.42, 65.03, 70.17, 70.43, 74.07, 85.39, 88.23, 111.24, 139.63, 151.16, 163.21. MS *m/z* calcd for $C_{22}H_{38}N_2O_7$: 442.55, found 441.25 $[M-H]^-$.

4.2. Biological activity

4.2.1. Cell lines

All cells were purchased from the American Tissue Culture Collection (ATCC), unless otherwise indicated: the CEM line are highly chemosensitive T-lymphoblastic leukaemia cells, K562 cells were derived from patient with acute myeloid leukaemia with bcr-abl translocation, A549 line is lung adenocarcinoma, HCT116 is colorectal tumour cell line and its p53 gene knock-down counterpart (HCT116p53-, Horizon Discovery, UK) is a model of human cancers with p53 mutation frequently associated with poor prognosis. The daunorubicin-resistant subline of CEM cells (CEM-DNR bulk) and paclitaxel resistant subline K562-tax were selected in our laboratory by the cultivation of maternal cell lines in increasing concentrations of daunorubicine or paclitaxel, respectively.[17] The CEM-DNR bulk cells overexpress MRP-1 protein, while K562-tax cells overexpress P-glycoprotein, both proteins belong to family of ABC transporters and are involved in primary and/or acquired multidrug resistance phenomenon.[17] The cells were maintained in Nunc/Corning 80 cm^2 plastic tissue culture flasks and cultured in cell culture medium (DMEM/RPMI 1640 with 5 g/L glucose, 2 mM glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, 10% foetal calf serum, and $NaHCO_3$).

4.2.2. Cytotoxic MTT assay[18]

Cell suspensions were prepared and diluted according to the particular cell type and the expected target cell density (2500–30,000 cells/well based on cell growth characteristics). Cells were added by pipette (80 μL) into 96-well microtiter plates. Inoculates were allowed a pre-incubation period of 24 h at 37 °C and 5% CO_2 for stabilization. Four-fold dilutions, in 20 μL aliquots, of the intended test concentration were added to the microtiter plate wells at time zero. All test compound concentrations were examined in duplicate. Incubation of the cells with the test compounds lasted for 72 h at 37 °C, in a 5% CO_2 atmosphere at 100% humidity. At the end of the incubation period, the cells were assayed using MTT. Aliquots (10 μL) of the MTT stock solution were pipetted into each well and incubated for a further 1–4 h. After this incubation period the formazan produced was dissolved by the addition of 100 μL/well of 10% aq SDS (pH 5.5), followed by a further incuba-

tion at 37 °C overnight. The optical density (OD) was measured at 540 nm with a Labsystem iEMS Reader MF. Tumour cell survival (TCS) was calculated using the following equation: TCS = ($OD_{drug\text{-}exposed\ well}$/mean $OD_{control\ wells}$) × 100%. The TCS_{50} value, the drug concentration lethal to 50% of the tumour cells, was calculated from appropriate dose–response curves.

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