Bioorganic & Medicinal Chemistry Letters 19 (2009) 6775–6779

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Preliminary SAR analysis of novel antiproliferative N^6,5′-bis-ureidoadenosine derivatives

Matt A. Peterson *, Marcelio Oliveira, Michael A. Christiansen, Christopher E. Cutler

Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602, United States

ARTICLE INFO

Article history:
Received 3 September 2009
Accepted 22 September 2009
Available online 2 October 2009

Keywords:
Purine nucleosides
Bio-active adenosine derivatives
Antiproliferative/growth inhibitory nucleosides

ABSTRACT

A preliminary library of novel N^6,5′-bis-ureidoadenosine analogs and related derivatives was prepared and tested for activity against the NCI 60 panel of human cancers. A 2′-*O*-TBS group was found to be necessary, but not sufficient, for optimal antiproliferative activity. Neither the N^6- nor 5′-ureido substituents were sufficient to achieve significant antiproliferative effects when present in the absence of the other. The 2′-*O*-TBS, and N^6,5′-bis-ureido substitution patterns were found to be necessary for optimal antiproliferative activity.

Derivatives of naturally occurring nucleosides have attracted considerable interest over the years as their potential for providing potent and selective treatments for viral infections and/or cancer has been elucidated.[1] Of the approximately 60 small molecule drugs approved by the U.S. FDA for treating cancer, 10 are nucleoside or nucleobase derivatives, while nucleosides continue to comprise the single largest class of clinically useful antiviral agents.[1a] In the area of HIV, 8 of the 12 currently approved reverse transcriptase inhibitors are nucleoside derivatives.[2] Numerous derivatives of adenosine have been reported. Modifications of both the sugar and the nucleobase have been examined. Many of these derivatives have been prepared in efforts to develop potent and selective adenosine receptor agonists and/or antagonists.[3] Adenosine receptors play important roles in such diverse physiological processes as cell growth and differentiation,[4a] platelet aggregation,[4b] immunosuppression,[4c] regulation of myocardial oxygen and coronary blood flow,[4d] and apoptosis.[4a]

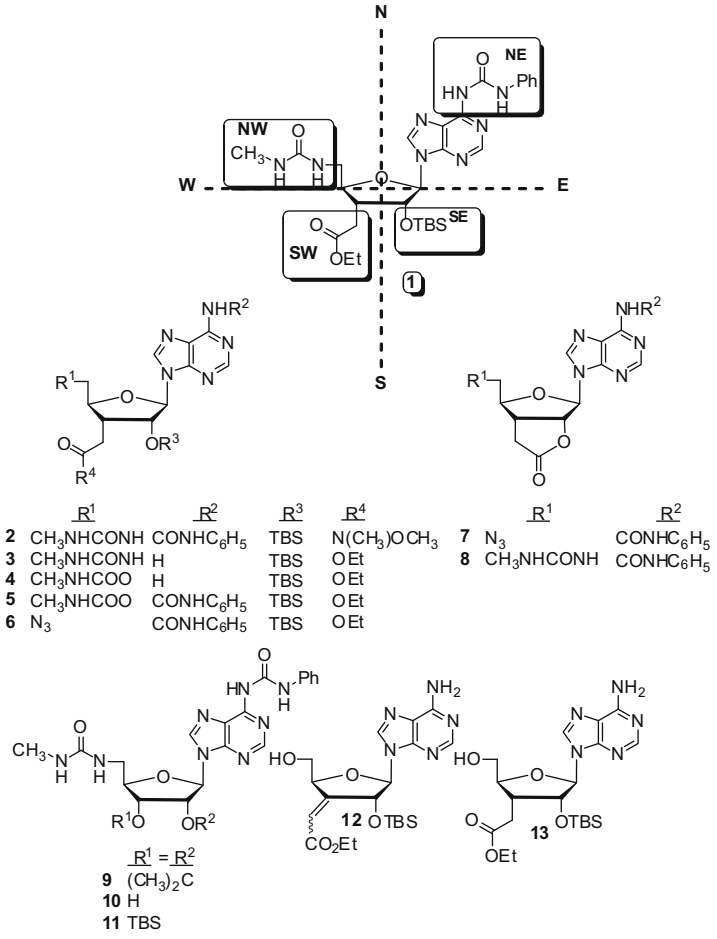
Of the possible ureidoadenosine derivatives studied so far, the N^6-ureido analogs have been most extensively examined.[5] 3′-Ureido derivatives have also been studied,[6] while 5′-ureido derivatives have been the subject of more limited investigation.[7] Until only recently, N^6,5′-bis-ureidoadenosines appear never to have been investigated.[8] Here, we report the biological evaluation of a preliminary array of N^6,5′-bis-ureidoadenosines or N^6- or 5′-ureidoadenosine derivatives and related analogs (Fig. 1). The analogs tested were designed to probe the minimal structural requirements for antiproliferative activity in the NCI 60 panel of human cancers, and variations in all four canonical quadrants of lead compound **1** were investigated (Fig. 1).

Compounds **1** and **2** had been examined previously and showed comparable low micromolar antiproliferative activities (GI_{50} = 1–6 μM) against all six leukemia cell lines and similar activities were exhibited against numerous other cell lines in the NCI 60 panel.[8b] Interestingly, in the same study, compounds **7**–**10** were almost completely devoid of significant antiproliferative activities at 10 μM compound concentration.[8b] This prompted us to conclude that a minimal structural requirement for antiproliferative activity is a lipophilic TBS group in the SE quadrant. Left in doubt from these initial studies was the relative impact of substituents in the NE, NW, and SW quadrants. Accordingly, compounds **3**–**6** and **11**–**13** were prepared and tested. Compounds **3**, **6**, **12**, and **13** were prepared as previously reported[8a] while compounds **4**, **5**, and **11** were prepared via the routes depicted (Scheme 1). Briefly, treatment of **13**[9] with 4-nitrophenyl-*N*-methylcarbamate gave **4** with only trace amounts (2–3%) of N^6-ureido byproduct. Treatment of **4** with phenylisocyanate gave **5**.[10] Compound **14**[11] could be converted to intermediate **15** via a two-pot, three step method, and compound **15** was converted cleanly to compound **11**.[10]

The results from the NCI 60 single dose growth inhibition assay are given in Table 1. Importantly, only compounds **5** and **11** gave significant growth inhibition (GI percent ⩽ 50). Compound **11** inhibited 45 of the 57 cell lines at this level, while compound **5** inhibited 22. Of the remaining compounds, only **12** inhibited proliferation with GI percent ⩽ 50, and this was observed for a single cell line (ovarian cancer; IGROV1). As points of comparison, compound **1** inhibited proliferation with GI percent ⩽ 50 in 20 of the NCI 60 cell lines in a 10 μM single dose growth inhibition assay, and compounds **7**–**10** were essentially devoid of significant

* Corresponding author.
E-mail address: matt_peterson@byu.edu (M.A. Peterson).

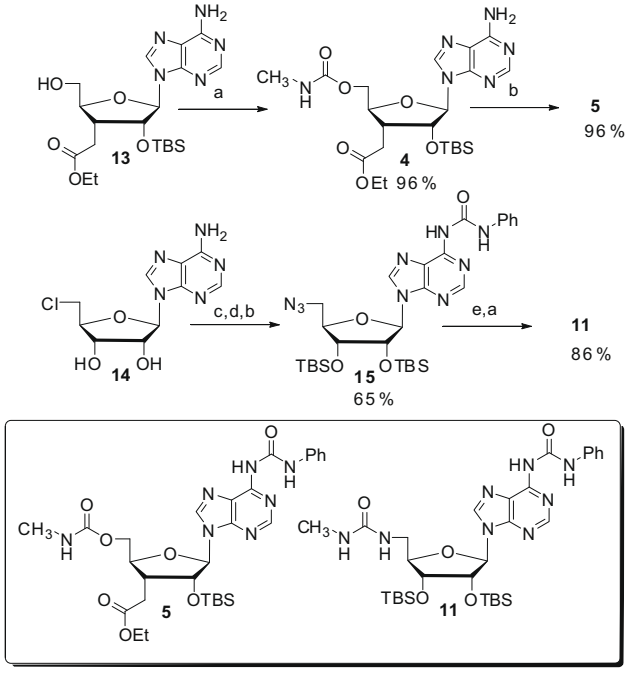
0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.09.083



	R^1	R^2	R^3	R^4
2	$CH_3NHCONH$	$CONHC_6H_5$	TBS	$N(CH_3)OCH_3$
3	$CH_3NHCONH$	H	TBS	OEt
4	CH_3NHCOO	H	TBS	OEt
5	CH_3NHCOO	$CONHC_6H_5$	TBS	OEt
6	N_3	$CONHC_6H_5$	TBS	OEt

	R^1	R^2
7	N_3	$CONHC_6H_5$
8	$CH_3NHCONH$	$CONHC_6H_5$

Figure 1.



Scheme 1. Reagents and conditions: (a) *p*-NO_2–$C_6H_4OCONHCH_3$/base/EtOAc, rt; (b) PhN=C=O/CH_2Cl_2, rt, 5d; (c) NaN_3/DMF, 150 °C, 1 h; (d) TBSCl/DMF, rt, 16 h; (e) H_2/Pd-C/EtOAc.

antiproliferative activities at this concentration. The lack of significant antiproliferative activities for compounds **3** and **4** points to the critical nature of the substituent in the NE quadrant.

Although **3** and **4** each possess the 2′-*O*-TBS, 3′-ethoxycarbonylmethyl and 5′-*N*-methylurea or 5′-*N*-methylcarbamate in the SE, SW, and NW quadrants, respectively, absence of the N^6-phenylurea in the NE quadrant essentially abrogates their antiproliferative activities. Lack of significant activity for compound **6** on the other hand points to the critical nature of the substituent in the NW quadrant since activity is lost in spite of the fact that **6** possesses the NE, SE, and SW substitution patterns required by the active analogs. The lack of activity exhibited by compounds **7**–**10** had indicated that a lipophilic 2′-*O*-TBS was an essential requirement for optimal growth inhibition. However, the importance of this substitution relative to substituents in the other quadrants was more fully clarified by the activities exhibited by compounds **12** and **13**, each of which lacks substituents in the NE and NW quadrants. Clearly, 2′-*O*-TBS substitution in the SE quadrant is necessary, but not sufficient, for maximal antiproliferative activity as illustrated by the lack of activity exhibited by compounds **12** and **13**. We were delighted to learn that introduction of a TBS group at the 3′-position in compound **11** seemed to be well tolerated and compound **11** exhibited promising activities in the single dose growth inhibition assay. These activities suggest that the more synthetically challenging 3′-ethoxycarbonylmethyl substituents in the SW quadrants of **1**, **2**, and **5** are not necessary for optimal activity. The synthesis of compound **11** is from 4 to 6 steps shorter than corresponding methods for preparing compounds **1** and **2**, respectively. The relatively easy

Table 1
Results of Single Dose Growth Inhibition Assay (GI Percent at 10 μM)[a]

Cell line	3	4	5	6	11	12	13
Leukemia							
CCRF-CEM	98	98	57	63	43	119	83
HL-60(TB)	107	80	23	51	24	76	89
K-562	106	86	23	72	34	84	84
MOLT-4	108	55	34	79	24	75	74
RPMI-8226	98	79	39	75	20	81	99
Non-small cell lung cancer							
A549/ATCC	84	92	51	103	23	100	100
EKVX	92	83	68	89	23	86	75
HOP-62	84	74	77	98	62	99	91
HOP-92	94	95	62	100	−3	90	81
NCI-H226	99	79	56	62	49	90	90
NCI-H23	97	105	88	97	36	99	107
NCI-H322M	94	99	91	99	87	81	91
NCI-H460	111	106	13	104	−7	110	101
NCI-H522	79	75	45	90	46	74	92
Colon cancer							
COLO 205	117	104	67	114	−100	76	109
HCC-2998	84	55	−9	121	−1	71	104
HCT-116	100	81	17	82	0	52	94
HCT-15	97	87	52	84	21	90	91
HT29	111	100	9	104	−68	65	98
KM12	103	102	31	101	−4	60	109
SW620	96	104	72	101	36	88	103
Melanoma							
LOX IMVI	92	88	49	96	13	74	92
MALME-3M	95	96	54	97	49	105	93
M14	106	100	57	101	33	87	99
SK-MEL-2	91	111	60	91	57	94	106
SK-MEL-28	107	106	72	116	60	111	112
SK-MEL-5	94	68	24	104	48	75	81
UACC-257	86	94	60	88	43	95	105
UACC-62	80	77	65	83	42	79	73
CNS cancer							
SF-268	97	97	60	95	36	98	98
SF-295	101	92	66	94	45	88	97
SF-539	97	89	33	89	33	92	91
SNB-19	99	92	99	92	76	88	103
SNB-75	86	83	45	73	46	98	75
U251	98	86	52	95	17	53	99
Ovarian cancer							
IGROV1	97	118	49	93	53	46	90
OVCAR-3	98	98	51	111	−29	65	98
OVCAR-4	99	78	42	66	30	71	97
OVCAR-5	87	115	94	107	69	88	101
OVCAR-8	100	98	74	98	33	104	103
SK-OV-3	110	94	95	101	78	102	103
Renal cancer							
786-0	93	87	73	89	17	77	97
A498	109	98	77	121	–	78	98
ACHN	90	89	26	92	21	70	102
CAKI-1	96	79	61	87	60	85	92
RXF393	138	78	35	111	−37	105	112
SN12C	88	96	35	81	−79	90	85
TK-10	101	110	88	103	34	85	94
UO-31	87	95	42	83	48	76	72
Breast cancer							
BT-549	85	74	65	100	40	80	79
HS578T	98	93	57	92	61	107	102
MCF7	87	98	12	85	0	94	89
MDA-MB-231/ATCC	96	85	72	95	38	81	90
MDA-MB-468	92	77	62	95	36	71	94
T-47D	95	84	29	73	14	79	82
Prostate cancer							
DU-145	98	100	59	105	52	71	93
PC-3	98	84	32	64	8	93	85

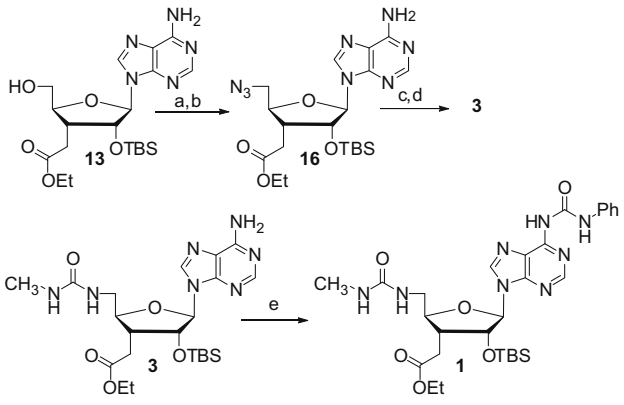
[a] Growth inhibition percent calculated as: $[(T_i - T_z)/C - T_z)] \times 100$ for $T_i \geqslant T_z$; $[(T_i - T_z)/T_z)] \times 100$ for $T_i < T_z$; where T_z = absorbance at $t = 0$; T_i = absorbance at $t = 48$ h (10 μM test compound); C = absorbance of control at $t = 48$ h.

accessibility of compound **11** opens the door for more extensive SAR studies designed to test the effect of various substituents in the NE and NW quadrants.

Our original interest in exploring the activities of 5′-carbamoyl compounds **4** and **5** had been to potentially avoid the problems inherent with preparing the 5′-azido-5′-deoxyadenosine intermediates needed to prepare 5′-ureas. The classical approach for preparing 5′-ureidoadenosine derivatives involves activation of the 5′-position with a good leaving group followed by nucleophilic substitution with azide to give the requisite 5′-azido-5′-deoxyadenosine products. Unfortunately, such syntheses are notoriously inefficient, since intramolecular cyclonucleoside formation and attendant decomposition compete with the desired *intermolecular* nucleophilic substitution.[12] The most challenging step in the conversion of **13** to **1**, for example, involves conversion of **13** to compound **16** (Scheme 2). Coming relatively late in the synthesis from adenosine as this step does, a high yield, synthetically straightforward alternative method for introducing an effective substituent in the NW quadrant would be advantageous. We were thus delighted to learn that the 5′-*N*-methylcarbamoyl moiety of compound **4** could be introduced in one easy step from **13** (Scheme 1), in contrast to the more synthetically demanding four-step approach needed to convert **13** to compound **3** (Scheme 2).[8b]

The 5′-*N*-methylcarbamoyl moiety is an acceptable alternative for the 5′-*N*-methylurea in the NW quadrant, as illustrated by a comparison of the antiproliferative activities of compounds **1**, **2**, and **5** in the multi-dose growth inhibition assay (Table 2). It is interesting to note that the antiproliferative activities exhibited by these compounds followed the order of **1** > **5** > **2** (determined by comparison of the total number of cell lines with GI_{50} values $\leqslant 6.0$ μM: 35, 25, and 12, respectively). The NH to O substitution involved in going from **1** to **5** is apparently well tolerated in this class of molecules, in contrast to the well known effect of NH to O substitution observed in the naturally occurring substitution of D-alanine by D-lactate in Vancomycin resistant bacteria.[13] Tolerance of a 5′-*N*-methylcarbamoyl group opens the possibility of using **5** (or a 5′-*N*-methylcarbamoyl substituted analog of compound **11**) as templates for more in-depth SAR studies designed to probe the effect of substitution in the NE, SE, and SW quadrants.

In summary, we have prepared and tested a preliminary library of compounds that demonstrate the impact of substitution in all four canonical quadrants of lead antiproliferative agent, compound **1**. From this preliminary study it can be concluded that a 2′-*O*-TBS group is necessary (but not sufficient) for growth inhibition, as is also true for the 5′- and N^6-ureido substitutions. When occurring individually in the absence of the other, neither 5′- nor N^6-ureido



Scheme 2. Reagents and conditions: (a) $TsCl/CH_2Cl_2$, −23 °C, 15 h; (b) $(CH_3)_2NC{=}NH_2N(CH_3)_2N_3$/DMF, 100 °C, 7 h; (c) H_2/Pd-C/EtOAc (d) *p*-NO_2–$C_6H_4OCONHCH_3/Na_2CO_3$/EtOAc, rt, 4 h; (e) $PhN{=}C{=}O/CH_2Cl_2$, rt, 5d.

Table 2
Results of multi-dose growth inhibition assay (GI_{50}, μM)[a]

Cell line	1	2	5
Leukemia			
CCRF-CEM	6.69	6.37	3.23
HL-60(TB)	3.01	1.81	1.39
K-562	3.59	3.12	3.09
MOLT-4	2.39	2.23	1.99
RPMI-8226	1.09	1.58	2.16
SR	2.23	1.27	—
Non-small cell lung cancer			
A549/ATCC	4.18	9.35	6.93
EKVX	17.7	26.4	3.39
HOP-62	8.96	24.9	14.7
HOP-92	<0.01	2.71	6.52
NCI-H226	>100	41.9	11.8
NCI-H23	33.3	57.2	12.9
NCI-H322M	>100	>100	31.7
NCI-H460	5.54	7.49	4.45
NCI-H522	4.36	11.1	9.58
Colon cancer			
COLO 205	3.84	12.3	7.70
HCC-2998	>100	30.6	8.76
HCT-116	3.20	4.20	2.33
HCT-15	8.50	6.47	11.7
HT29	4.20	5.37	3.97
KM12	3.95	23.9	3.21
SW620	4.80	>100	4.59
Melanoma			
LOX IMVI	5.46	7.30	7.78
MALME-3M	10.3	11.4	3.34
M14	2.51	15.2	6.37
SK-MEL-2	5.42	14.9	13.2
SK-MEL-28	6.85	7.77	7.77
SK-MEL-5	4.34	5.81	5.70
UACC-257	5.68	22.6	20.8
UACC-62	>100	41.9	15.8
CNS cancer			
SF-268	6.53	8.29	5.06
SF-295	5.73	9.09	2.83
SF-539	5.19	22.3	11.5
SNB-19	29.0	>100	49.2
SNB-75	4.56	12.7	10.3
U251	4.69	5.66	7.57
Ovarian cancer			
IGROV1	3.85	3.72	13.7
OVCAR-3	4.59	7.11	2.42
OVCAR-4	12.3	53.0	10.7
OVCAR-5	31.1	38.2	12.8
OVCAR-8	4.92	9.02	10.3
SK-OV-3	21.0	52.7	40.4
Renal cancer			
786-0	2.00	9.01	7.94
A498	3.34	3.87	4.65
ACHN	8.55	14.4	5.92
CAKI-1	29.7	53.8	3.72
RXF393	2.01	9.74	2.94
SN12C	9.10	85.3	2.17
TK-10	12.4	20.5	10.7
UO-31	12.1	7.79	5.70
Breast cancer			
BT-549	>100	29.0	2.07
HS578T	3.60	5.79	3.39
MCF7	3.42	5.59	3.37
MDA-MB-231/ATCC	3.96	12.3	17.5
MDA-MB-435	6.21	10.9	3.26
T-47D	2.55	13.9	4.95
Prostate cancer			
DU-145	4.97	16.6	5.21
PC-3	2.25	—	2.87

[a] GI_{50} = concentration at which cell growth is inhibited by 50%; $[(T_i - T_z)/(C - T_z)] \times 100 = 50$; where T_z = absorbance at $t = 0$; T_i = absorbance at $t = 48$ h; C = absorbance of control at $t = 48$ h.

substitution gave rise to potent growth inhibition, even in the presence of the essential 2′-*O*-TBS moiety. Substitution at the 3′-position (SW quadrant) did not seem to be as critical as substitution in the other three quadrants. Thus, bis-*O*-TBS analog **11** exhibited comparable activity to the synthetically more challenging lead compound **1**. Substitution of a carbamoyl group for the urea in the NW quadrant gave compound **5** which also exhibited comparable activities to compound **1**. Compounds **11** and **5** offer synthetically viable alternatives for preparing more extensive compound libraries based on bis-*O*-TBS and/or 5′-*N*-methylcarbamoyl-substituted adenosine templates. We are currently pursuing this line of research.

Acknowledgments

Generous support from the BYU Cancer Research Center is gratefully acknowledged. The NCI is also thanked for performance of cytotoxicity evaluations.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.09.083.

References and notes

1. (a) Secrist, J. A., III *Nuc. Acids Symp. Ser.* **2005**, *49*, 15–16; (b) Kong, W.; Engel, K.; Wang, J. *Curr. Drug Met.* **2004**, *5*, 63–84; (c) Galmarini, C. M.; Mackey, J. R.; Dumontet, C. *Lancet Oncol.* **2002**, *3*, 415–424.
2. Djuricich, P.; Vázquez, E. In *The Journal of the Test Positive Aware Network*; Berry, J. Ed.; Chicago, IL, 2009; pp 24–55. Available from: <http://www.tpan.com/> and <www.fda.gov>.
3. (a) Jacobson, K. A.; Gao, Z.-G. *Nat. Rev. Drug Disc.* **2006**, *5*, 247–264; (b) Yan, L.; Burbiel, J. C.; Maass, A.; Müller, C. E. *Expert Opin. Emerging Drugs* **2003**, *8*, 537–576.
4. (a) Abbrachio, M. P. *Drug Dev. Res.* **1996**, *39*, 393–406; (b) Hourani, S. M. O.; Cusack, N. J. *Pharmacol. Rev.* **1991**, *43*, 243–298; (c) Haskó, G.; Cronstein, B. N. *Trends Immunol.* **2004**, *25*, 33–39; (d) Cristalli, G.; Lambertucci, C.; Taffi, S.; Vittori, S.; Volpini, R. *Curr. Top. Med. Chem.* **2003**, *3*, 387–401.
5. (a) Douglass, J. G.; Patel, R. I.; Yerxa, B. R.; Shaver, S. R.; Watson, P. S.; Bednarski, K.; Plourde, R.; Redick, C. C.; Brubaker, K.; Jones, A. C.; Boyer, J. L. *J. Med. Chem.* **2008**, *51*, 1007–1025; (b) Douglass, J. G.; deCamp, J. B.; Fulcher, E. H.; Jones, W.; Mahanty, S.; Morgan, A.; Smirnov, D.; Boyer, J. L.; Watson, P. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2167–2171; (c) Baraldi, P. G.; Fruttarolo, F.; Tabrizi, M. A.; Romagnoli, R.; Preti, D.; Bovero, A.; Infantas, M. J. P.; Moorman, A.; Varani, K.; Borea, P. A. *J. Med. Chem.* **2004**, *47*, 5535–5540; (d) Sigmund, H.; Pfleiderer, W. *Helv. Chim. Acta* **1994**, *77*, 1267–1280; (e) Hong, C. I.; Chheda, G. B.; Dutta, S. P.; O'Grady-Curtis, A.; Tritsch, G. L. *J. Med. Chem.* **1973**, *16*, 139–147.
6. (a) Gao, Z.-G.; Duong, H. T.; Sonina, T.; Kim, S.-K.; Van Rompaey, P.; Calenbergh, S. V.; Mamedova, L.; Kim, H. O.; Kim, M. J.; Kim, A. Y.; Liang, B. T.; Jeong, L. S.; Jacobson, K. A. *J. Med. Chem.* **2006**, *49*, 2689–2702; (b) Jeong, L. S.; Choe, S. A.; Kim, A. Y.; Kim, H. O.; Gao, Z.-G.; Jacobson, K. A.; Chun, M. W.; Moon, H. R. *Nucleos. Nucleotid. Nucl.* **2007**, *26*, 717–719; (c) Chun, M. W.; Lee, H. W.; Kim, A. Y.; Kim, M. J.; Kim, H. O.; Gao, Z.-G.; Jacobson, K. A.; Jeong, L. S. *Nucleos. Nucleotid. Nucl.* **2005**, *24*, 1119–1121; (d) Jeong, L. S.; Kim, M. J.; Kim, H. O.; Gao, Z.-G.; Kim, S.-K.; Jacobson, K. A.; Chun, M. W. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4851–4854; (e) Calenbergh, S. V.; Link, A.; Fujikawa, S.; de Ligt, R. A. F.; Vanheusden, V.; Golisade, A.; Blaton, N. M.; Rozenski, J.; IJzerman, A. P.; Herdewijn, P. *J. Med. Chem.* **2002**, *45*, 1845–1852.
7. (a) Wang, T.; Lee, H. J.; Tosh, D. K.; Kim, H. O.; Pal, S.; Choi, S.; Lee, Y.; Moon, H. R.; Zhao, L. X.; Lee, K. M.; Jeong, L. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4456–4459; (b) Montgomery, J. A.; Thomas, H. J. *J. Med. Chem.* **1979**, *22*, 1109–1113.
8. (a) Peterson, M. A.; Ke, P.; Shi, H.; Jones, C.; McDougall, B. R.; Robinson, W. E. *Nucleos. Nucleotid. Nucl.* **2007**, *26*, 499–519; (b) Peterson, M. A.; Oliveira, M.; Christiansen, M. A. *Nucleos. Nucleotid. Nucl.* **2009**, *28*, 394–407.
9. (a) Robins, M. J.; Sarker, S.; Xie, M.; Zhang, W.; Peterson, M. A. *Tetrahedron Lett.* **1996**, *37*, 3921–3924; (b) Peterson, M. A.; Nilsson, B. L.; Sarker, S.; Doboszewski, B.; Zhang, W.; Robins, M. J. *J. Org. Chem.* **1999**, *64*, 8183–8192.
10. Full experimental details for all new compounds can be found in the Supplementary data. ^{1}H and ^{13}C NMR and HRMS data for new compounds follows: **4**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32 (s, 1H), 8.13 (s, 1H), 5.95 (s, 1H), 5.85 (br s, 2H), 5.01 (d, J = 4.5 Hz, 1H), 4.90 (d, J = 3.5 Hz, 1H), 4.45 (dd, J = 2.0, 12.5 Hz, 1H), 4.35 (dd, J = 4.0, 12.5 Hz, 1H), 4.26–4.24 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 2.79 (d, J = 5.0 Hz, 3H), 2.67–2.63 (m, 2H), 2.43 (d, J = 13.0 Hz, 1H), 1.22 (t, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.25 (s, 3H), 0.083 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 156.5, 155.3, 152.9, 149.3, 138.6, 120.2, 91.5, 82.3, 77.1, 63.2, 60.7, 38.6, 29.3, 27.6, 25.7, 18.0, 14.1, −4.4, −5.6; MS (FAB) *m/z*

509.2565 (MH^+ [$C_{22}H_{37}N_6O_6Si$]) = 509.2538; **5**: ^1H NMR ($CDCl_3$, 500 MHz) δ 11.98 (s, 1H), 9.50 (s, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 8.0 Hz, 2H), 7.14–7.11 (m, 1H), 6.04 (s, 1H), 5.75 (q, J = 5.0 Hz, 1H), 4.86 (d, J = 3.5 Hz, 1H), 4.51 (dd, J = 2.8, 12.8 Hz, 1H), 4.40 (dd, J = 1.5, 12.5 Hz, 1H), 4.26 (d, J = 8.5 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 2.66–2.60 (m, 5H), 2.53–2.50 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H), 0.92 (s, 9H), 0.24 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 156.8, 152.1, 150.6, 150.04, 149.98, 141.9, 137.9, 129.0, 124.1, 121.0, 120.7, 91.4, 82.8, 77.5, 62.4, 60.7, 38.3, 29.2, 27.4, 25.8, 18.0, 14.1, −4.4, −5.6; MS (FAB) m/z 628.2906 (MH^+ [$C_{29}H_{42}N_7O_7Si$]) = 628.2909; **15**: ^1H NMR ($CDCl_3$, 500 MHz) δ 11.78 (s, 1H), 8.61 (s, 1H), 8.46 (br s, 1H), 8.33 (br s, 1H), 7.63 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.11 (t, J = 7.3 Hz, 1H), 5.97 (d, J = 4.0 Hz, 1 H), 4.84 (t, J = 4.5 Hz, 1H), 4.30 (t, J = 4.3 Hz, 1H), 4.22 (t, J = 4.5 Hz, 1H), 3.70 (dd, J = 6.3, 4.8 Hz, 2H), 0.92 (s, 9H), 0.82 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.00 (s, 3H), −0.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.3, 150.8, 150.1, 142.5, 138.0, 129.0, 123.9, 121.2, 120.4, 89.7, 82.9, 74.7, 72.3, 51.6, 25.8, 25.7, 18.0, 17.9, −4.38, −4.68, −4.84, −4.88; MS (FAB) m/z 640.3204 (MH^+ [$C_{29}H_{45}N_9O_4Si_2$]) = 640.3206; **11**: ^1H NMR ($CDCl_3$, 500 MHz) δ 11.92 (br s, 1H), 9.03 (br s, 1H), 8.67 (s, 1H), 8.61 (s, 1H), 7.57 (d, J = 7.5 Hz), 7.39 (t, J = 8.3 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 6.51 (d, J = 6.0 Hz, 1 H), 6.01 (d, J = 8.0 Hz, 1H), 4.74–4.73 (m, 1H), 4.64 (dd, J = 7.5, 4.5 Hz, 1 H), 4.36 (d, J = 4.5 Hz, 1H), 4.18 (t, J = 2.5 Hz, 1H), 3.99 (ddd, J = 14.5, 9.0, 2.5 Hz, 1H), 3.19 (dt, J = 14.5, 3.1 Hz, 1H), 2.72 (d, J = 4.5 Hz, 3H), 0.95 (s, 9H), 0.70 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), −0.13 (s, 3H), −0.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 152.9, 151.0, 150.4, 150.3, 144.1, 137.1, 129.2, 125.0, 121.8, 121.2, 88.0, 87.8, 75.9, 73.5, 41.6, 26.8, 25.9, 25.6, 18.0, 17.7, −4.53, −4.79, −5.65; MS (FAB) m/z 671.3525 (MH^+ [$C_{31}H_{51}N_8O_5Si_2$]) = 671.3516.

11. Robins, M. J.; Hansske, F.; Wnuk, S. F.; Kanai, T. *Can. J. Chem.* **1991**, *69*, 1468–1474.
12. (a) Clark, V. M.; Todd, A. R.; Zussman, J. *J. Chem. Soc.* **1951**, 2952–2958; (b) Anzai, K. *Agric. Biol. Chem.* **1976**, *40*, 373–376; (c) Liu, F.; Austin, D. J. *Tetrahedron Lett.* **2001**, *42*, 3153–3154; (d) Liu, F.; Austin, D. J. *J. Org. Chem.* **2001**, *66*, 8643–8645.
13. Dancer, R. J.; Try, A. C.; Sharman, G. J.; Williams, D. H. *J. Chem. Soc., Chem. Commun.* **1996**, 1445.