Med Chem Res (2016) 25:932–940
DOI 10.1007/s00044-016-1539-5

MEDICINAL CHEMISTRY RESEARCH

CrossMark

ORIGINAL RESEARCH

Synthesis of novel *N*-acyl-*β*-D-glucopyranosylamines and ureas as potential lead cytostatic agents

Vanessa Parmenopoulou[1] · Stella Manta[1] · Athina Dimopoulou[1] · Nikolaos Kollatos[1] · Dominique Schols[2] · Dimitri Komiotis[1]

Received: 12 January 2015 / Accepted: 16 February 2016 / Published online: 29 February 2016
© Springer Science+Business Media New York 2016

Abstract Novel classes of acetylated and fully deprotected *N*-acyl-*β*-D-glucopyranosylamines and ureas have been synthesized and biologically evaluated. Acylation of the per-*O*-acetylated *β*-D-glucopyranosylurea (**5**), easily prepared via its corresponding phosphinimine derivative, by zinc chloride catalyzed reaction of the corresponding acyl chlorides RCOCl (**a–f**) gave the protected *N*-acyl-*β*-D-glucopyranosylureas (**6a–f**), in acceptable-to-moderate yields. Subsequent deacetylation of analogues **6a–f** under Zemplén conditions afforded the fully deprotected derivatives **7a,b,d,e,f**, while the desired urea **7c** was formed after treatment of **6c** with dibutyltin oxide. All protected and unprotected compounds were examined for their cytotoxic activity in different L1210, CEM and HeLa tumor cell lines and were also evaluated against a broad panel of DNA and RNA viruses. Derivative **7c** exhibited cytostatic activity against the three evaluated tumor cell lines (IC_{50} 9–24 μM) and might be the basis for the synthesis of structure-related derivatives with improved cytostatic potential. Only analogue **6f** weakly but significantly inhibited the replication of parainfluenza-3 virus, Sindbis virus and Coxsackie virus B4 in cell cultures at concentrations of 45–58 μM.

Keywords *N*-acyl-*β*-D-glucopyranosylamines · *N*-acyl-*β*-D-glucopyranosylureas · Antitumor agents · Cytotoxic activity · Antiviral activity

✉ Dimitri Komiotis
dkom@bio.uth.gr

[1] Laboratory of Bioorganic Chemistry, Department of Biochemistry and Biotechnology, University of Thessaly, 26 Ploutonos Str., 41 221 Larissa, Greece

[2] Department of Microbiology and Immunology, Rega Institute for Medical Research, KU Leuven, Louvain, Belgium

Introduction

Cancer figures among the major concerns of modern healthcare due to its rapidly increasing rates and associated mortality. In light of the growing prevalence of malignant carcinomas and their implications, equal impetus is being paid by the scientific community to research on the disease (Ferlay *et al.*, 2015). Although significant effort has been made to improve the current preventive and/or therapeutic strategies against carcinogenesis, the development of new selective agents capable of suppressing tumor growth and metastasis would contribute greatly to a better prognosis and current therapy (Sethi and Kang, 2011).

In the beginning of 1990s (Lu *et al.*, 2013), small molecule kinase inhibitors have shown great potential as novel therapeutics for the treatment of cancer (Sausville, 2000) because of their intimate involvement in oncogenic signal transduction pathways that present multiple physiological responses, tumor cell proliferation and cell survival (Blanc *et al.*, 2013). Among them, sorafenib (Nevaxar), a diaryl urea analogue, is a small molecular inhibitor of several tyrosine protein kinases for the treatment of advanced renal cell carcinoma (RCC) and advanced hepatocellular carcinoma (HCC) (Wilhelm *et al.*, 2006; Montagut and Settleman, 2009). In the same manner, PAC-1 bearing the *N*-acylhydrazone pharmacophore is promising as a new antitumor drug that can directly influence the apoptotic machinery or suicide of cells and has shown good results in mouse models (Zhang *et al.*, 2012; Peterson *et al.*, 2009; Putt *et al.*, 2006). Finally, carboxamide analogue sunitinib (Sutent) has proven to be successful in the treatment of renal cancer and pancreatic neuroendocrine tumors, while thiazole carboxamide analogue dasatinib is used for the treatment of several types of leukemia (Jänne *et al.*, 2009). Probably, the use of amide,

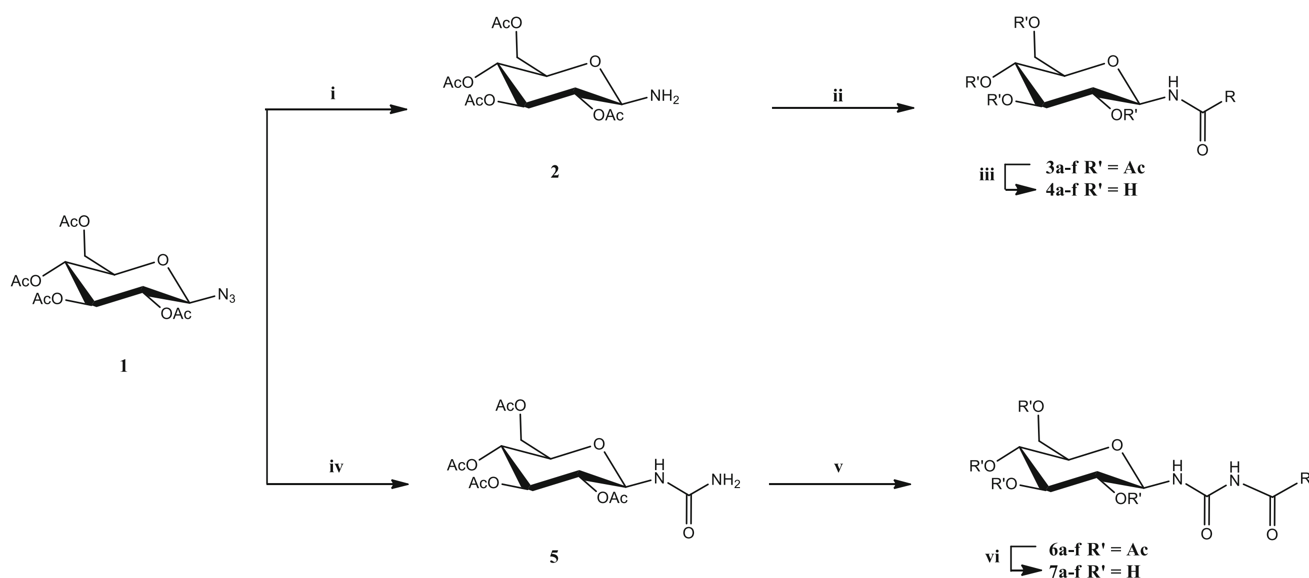
urea or heteroatom linkers such as nitrogen or oxygen in the structure of the aforementioned inhibitors are important features for their selectivity that allow the formation of one or two hydrogen bonds with residues of the specific kinase (Davis *et al.*, 2011).

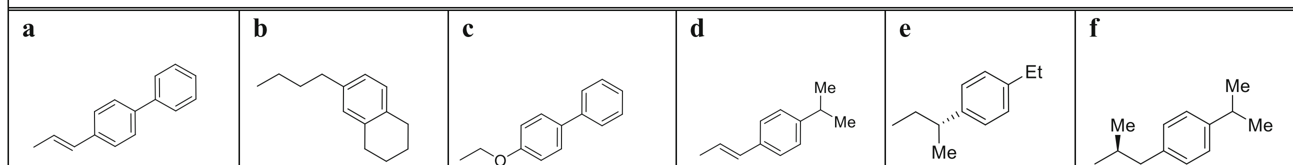
In view of the above observations and as a continuation of our long-term interest in glucopyranosyl analogues as antitumor/antiviral agents and potent enzyme inhibitors (Parmenopoulou *et al.*, 2014; Dimopoulou *et al.*, 2013; Manta *et al.*, 2012; Kantsadi *et al.*, 2012), it was envisaged that compounds bearing a glucopyranosyl moiety linked with various aralkyl and aralkenyl groups (Somsák *et al.*, 2008a, b) via the pharmacophore linkers NHCO and NHCONHCO would be endowed with pronounced antitumor activity. We hereby report the facile synthesis and biological properties of novel acetylated as well as fully deprotected *N*-acyl-*β*-D-glucopyranosylamines (**3a–f**, **4a–f**) and ureas (**6a–f**, **7a–f**), respectively.

Results and discussion

Chemistry

For the synthesis of the target *N*-acyl-*N′*-2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylureas (**6a–f**), the per-*O*-acetylated *β*-D-glucopyranosylurea (**5**), easily prepared via its corresponding phosphinimine derivative (Pinter *et al.*, 1995), seemed a suitable precursor. Therefore, acylation of compound **5** (Pinter *et al.*, 1995) by zinc chloride ($ZnCl_2$) catalyzed reaction of the corresponding acyl chlorides RCOCl (**a–f**) gave derivatives **6a–f**, in acceptable-to-moderate yields (35–67 %). Although the Lewis acidic zinc chloride not only activates acid chlorides but also catalyze iminium ion formation (Paulsen and Pflufhaupt, 1980; Isbell and Frush, 1958) and, thereby, anomerization (Somsák *et al.*, 2008a, b), in our case, the *β*-anomers **6a–f** were solely obtained. Their ^{1}H NMR spectra showed





Scheme 1 Reagents and conditions: (*i*) H_2, 10 % Pd/C, EtOAc, 20 °C, 24 h; (*ii*) DMF, RCOCl, Et_3N, room temperature, 1 h; (*iii*) ammonia/MeOH or MeOH, methanolic NaOMe (1 M), Amberlyst 15 (H^+ form), room temperature; (*iv*) NH_3, CO_2, THF, Ph_3P, 24 h; (*v*) $CHCl_3$, RCOCl, $ZnCl_2$, reflux; (*vi*) MeOH, methanolic NaOMe (1 M), Amberlyst 15 (H^+ form), 0 °C, 20 min or MeOH, Bu_2SnO, reflux, 2 h

Table 1 Cytostatic activity of compounds **3a–f**, **4a–f**, **6a–f** and **7a–f** against murine leukemia (L1210), human lymphocyte (CEM) and human cervix carcinoma (HeLa) cell cultures and primary fibroblasts

Compound	IC_{50}^{a} (μM)			MCC[b] (μM)
	L1210	CEM	HeLa	HEL
3a	≥250	≥250	≥250	>100
3b	106 ± 6	116 ± 9	118 ± 23	>100
3c	139 ± 8	180 ± 100	≥250	>100
3d	110 ± 6	99 ± 15	124 ± 18	>100
3e	184 ± 2	118 ± 5	≥250	>100
3f	103 ± 1	110 ± 5	64 ± 16	>100
4a	134 ± 1	192 ± 82	84 ± 21	>100
4b	>250	>250	>250	>100
4c	>250	>250	>250	>100
4d	>250	>250	>250	>100
4e	>250	>250	>250	>100
4f	>250	>250	>250	>100
6a	91 ± 15	110 ± 29	100 ± 14	>100
6b	78 ± 0	38 ± 10	66 ± 12	>100
6c	>250	>250	>250	>100
6d	24 ± 0	16 ± 1	44 ± 24	>100
6e	71 ± 16	41 ± 4	88 ± 17	>100
6f	47 ± 8	32 ± 1	39 ± 23	>100
7a	206 ± 44	141 ± 5	>250	>100
7b	>250	>250	>250	>100
7c	9.0 ± 5.9	24 ± 1	19 ± 3	>100
7d	25 ± 2	22 ± 4	45 ± 27	>100
7e	>250	>250	>250	>100
7f	>250	>250	>250	>100
5-Fluorouracil	0.33 ± 0.17	18 ± 5	0.54 ± 0.12	–
6-Mercaptopurine	2.8 ± 1.1	2.8 ± 1.3	1.1 ± 0.1	–

[a] 50 % inhibitory concentration or compound concentration required to inhibit cell proliferation by 50 %

[b] Minimal cytotoxic concentration or compound concentration required to affect and alter microscopically detectable human lung fibroblast HEL cell morphology

large coupling constants for H-1, H-2, H-3, H-4 and H-5 ($J_{1,2} \geq 9.4$ Hz, $J_{2,3} \geq 8.5$ Hz, $J_{3,4} \geq 8.9$ Hz and $J_{4,5} \geq 9.4$ Hz) arising from the trans-diaxial orientation of these consecutive protons, indicating the *β*-configuration of the sugar moiety and equatorially oriented acetyl groups.

Subsequent deacetylation of analogues **6a–f** under Zemplén conditions (Agoston *et al.*, 2001) at 0 °C for 20 min afforded the fully deprotected derivatives **7a,b,d,e,f** after flash chromatography, in good yields (72–82 %). Deprotection of acyl urea **6c** either with basic or acidic transesterification conditions (sodium methoxide, methanolic ammonia, methanolic hydrogen chloride) was unsuccessful, due to faster cleavage of the *N*-acyl moiety than removal of the *O*-protecting groups. In order to overcome this difficulty and to successfully synthesize compound **7c**, we sought to couple the free glucosyl urea (McKay and Nguyen, 2014; Helm and Kakhesy, 1989) with the desired acyl chloride RCOCl (**c**) in the presence of $ZnCl_2$, but unfortunately only the starting materials were recovered. To our delight, when the acyl urea **6c** was stirred in methanol in the presence of 0.5 eq dibutyltin oxide (Bu_2SnO) at reflux (Liu *et al.*, 2002), the acetyl groups were smoothly deprotected and derivative **7c** was isolated after flash chromatography, in 83 % yield (Scheme 1).

All compounds were well characterized by ^{1}H and ^{13}C NMR, mass spectrometry and elemental analysis and gave satisfactory analytical and spectroscopic data, which were in full accordance with their depicted structure. During the spectroscopic characterization, compound **6f** appeared to

Table 2 Cytotoxicity and antiviral activity of **6f** in Vero cell cultures

Compound	IC_{50}^{b} (μM)					
	Minimum cytotoxic concentration[a] (μM)	Parainfluenza-3 virus	Reovirus-1	Sindbis virus	Coxsackie virus B4	Punta Toro virus
6f	>100	45	>100	58	58	100
DS-10.000 (μg/mL)	>100	>100	>100	20	100	100
Ribavirin	>250	250	>250	>250	>250	146

[a] Required to cause a microscopically detectable alteration of normal cell morphology

[b] Required to reduce virus-induced cytopathicity by 50 %

consist of two rotamers, judged from their ^{1}H NMR spectra, which is probably due to hindered rotation of the amide bond.

Anticancer activity

The cytostatic activity of **3a–f**, **4a–f**, **6a–f** and **7a–f** was determined against murine leukemia (L1210), human lymphocyte (CEM) and human cervix carcinoma (HeLa) cell cultures, and the results are summarized in Table 1.

From the overall results obtained, it was clear that the acetylated *N*-acyl-*β*-D-glucopyranosylamines (**3b–f**) and ureas (**6a**, **b**, **e**, **f**) showed a better cytostatic profile than their corresponding unprotected derivatives **4b–f** and **7a**, **b**, **e**, **f**, respectively (Table 1). Exceptions were analogues **4a** and **7c**, which proved to be more cytostatic than their corresponding acetylated congeners **3a** and **6c**; in particular derivative **7c** proved to be the most cytotoxic for all three tumor cell lines (IC_{50} of 9, 24 and 19 μM, respectively). The cytostatic potential of **7c** was only 5- to 15-fold lower than the established 6-mercaptopurine anticancer drug. Finally, the acetylated analogue **6d** and the unprotected **7d** exhibited a comparable degree of cellular cytotoxicity (IC_{50} of 16–45 μM). Also, the tested compounds were not cytotoxic in normal (primary) confluent human lung fibroblast (HEL) cell cultures ($MCC_{50} > 100$ μM).

Broad-spectrum evaluation for potential antiviral activity

Compounds **3a–f**, **4a–f**, **6a–f** and **7a–f** have been evaluated against a broad panel of DNA and RNA viruses, including herpes simplex virus type 1 [HSV-1(KOS)], HSV-2 (G), vaccinia virus and vesicular stomatitis virus (VSV) in HEL cultures; VSV, Coxsackie virus B4 and respiratory syncytial virus (RSV) in HeLa cell cultures; parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4 and Punta Toro virus in Vero cell cultures; influenza virus A (H1N1, H3N2) and influenza virus B in MDCK cell cultures, feline corona virus (FIPV) and feline herpes virus in CRFK cell cultures and human inmmunodeficiency virus ($HIV\text{-}1III_{B}$ and HIV-2ROD) in CEM T cell cultures.

Only the acetylated glucopyranosyl urea **6f** was found to inhibit the proliferation of parainfluenza-3 virus, Sindbis virus and Coxsackie virus B4 in Vero cells at the concentration of 45 and 58 μM (*vide* IC_{50}), respectively, whereas the well-described antiviral drug ribavirin showed no activity at all (≥250 μM). The polyanionic compound dextran sulfate (DS) (mw 10,000) was also included as a control compound (Table 2).

Conclusion

In this study, we report the synthesis of novel acetylated as well as fully deprotected *N*-acyl-*β*-D-glucopyranosylamines and ureas as potential cytotoxic agents. Since the *N*-acyl-*β*-D-glucopyranosylureas proved to be more cytostatic than the corresponding amines and the final analogues were less potent than their acetylated congeners, it seems that the cytostatic activity of compounds is associated with the type of the linker, while the acetyl moiety may also contribute to the antitumor effect. Derivative **7c** exhibited the most enhanced cytostatic activity (IC_{50} of 9, 24 and 19 μM, respectively) and might be the basis for preparing structure-related derivatives with improved cytostatic potential, while analogue **6f** inhibited the proliferation of parainfluenza-3 virus, Sindbis virus and Coxsackie virus B4 in Vero cell cultures at the concentration of 45, 58 and 58 μM (vide IC_{50}), respectively, as compared to ribavirin (≥250 μM).

Experimental

Chemistry

Thin layer chromatography (TLC) was performed on Merck precoated 60F254 plates. Reactions were monitored by TLC

on silica gel, with detection by UV light (254 nm) or by charring with sulfuric acid. Flash chromatography was performed using silica gel (240–400 mesh, Merck). ^{1}H NMR and ^{13}C NMR spectra were obtained at room temperature with a Bruker 300 spectrometer at 300 and 75.5 MHz, respectively, using chloroform-*d* ($CDCl_3$) and methanol-d_4 (CD_3OD) with internal tetramethylsilane (TMS). The ^{1}H assignments of compounds 6 were based on ^{1}H–^{1}H COSY experiments executed using standard Varian software. Chemical shifts (δ) were given in ppm measured downfield from TMS, and spin–spin coupling constants are in Hz. Mass spectra were obtained on a ThermoQuest Finnigan AQA Mass Spectrometer (electrospray ionization). Optical rotations were measured using an Autopol I polarimeter.

All reactions sensitive to oxygen or moisture were carried out under nitrogen atmosphere using oven-dried glassware. Chloroform ($CHCl_3$) was distilled from phosphorus pentoxide and stored over 4E molecular sieves. Methanol (MeOH) was stored over 3E molecular sieves. 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (**1**) (Tropper *et al.*, 1992), 2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosylamine (**2**), *N*-acyl-β-D-glucopyranosylamines **3a–f** and **4a–f** (Parmenopoulou *et al.*, 2014) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylurea (**5**) (Pinter *et al.*, 1995) were prepared according to the procedures described in literature, and their chemical and physical properties were in agreement with previous data.

*General procedure for preparation of the N-acyl-N′-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylureas (**6a–f**)*

To a solution of an acyl chloride (18 mmol) in 20 mL of dry $CHCl_3$, anhydrous $ZnCl_2$ (0.59 mmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylurea (**5**) (2.56 mmol) were added with stirring. The reaction mixture was refluxed until TLC showed the complete transformation of the urea. Then, the reaction mixture was poured into ice water and was extracted with chloroform (2×). The organic phases were collected and washed with sat. aq. $NaHCO_3$ solution and water. After drying, the solvent was evaporated under vacuo and the residue was purified by flash chromatography (*n*-hexane/EtOAc 1:1).

*N-(E)-3-(Biphenyl-4-yl)acryloyl-N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-urea (**6a**)*

White foam, yield 44 %; *Rf* = 0.28 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{22} = +4$ ($c = 0.20$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.37 (d, 1H, $J = 9.0$ Hz, NH), 9.10 (s, 1H, NH), 7.86 (d, 1H, $J = 15.6$ Hz, CH=CH), 7.68–7.38 (m, 9H, ArH), 6.51 (d, 1H, CH=CH), 6.39–5.29 (2pseudo t, 2H, $J = 9.6$, 9.4 Hz, H-1, H-3), 5.17–5.08 (2pseudo t, 2H, $J = 9.4$, 9.5 Hz, H-4, H-2), 4.25 (dd, 1H, $J = 4.3$, 12.5 Hz, H-6a), 4.10 (dd, 1H, $J = 1.9$, 12.5 Hz, H-6b), 3.83 (ddd, 1H, $J = 2.1$, 4.1, 10.0 Hz, H-5), 2.06, 2.05, 2.03, 2.01 (4s, 12H, 4OAc); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.6, 170.1, 169.8, 169.4, 166.4, 154.8 (CO), 145.4, 143.7, 139.9, 132.8, 128.9, 128.8, 128.0, 127.7, 127.0, 118.3 (CH=CH and Ar–C), 79.0, 73.6, 73.0, 70.0, 68.2, 61.6 (C-1–C-6), 20.7, 20.6, 20.5 ($OCOCH_3$); ESI–MS: *m/z*, 597.24 $[M + H]^+$. Anal. calcd for $C_{30}H_{32}N_2O_{11}$: C, 60.40; H, 5.41; N, 4.70; Found: C, 60.17; H, 5.59; N, 4.83.

*N-4-(5,6,7,8-Tetrahydronaphthalen-2-yl)butanoyl-N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-urea (**6b**)*

Yellow foam, Yield 38 %; *Rf* = 0.38 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{22} = +2$ ($c = 0.20$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99–6.86 (m, 4H, ArH, NH), 6.13 (d, 1H, $J = 9.2$ Hz, NH), 5.34–5.25 (2pseudo t, 2H, $J = 9.4$, 8.9 Hz, H-1, H-3), 5.06 (t, 1H, $J = 9.9$ Hz, H-4), 4.90 (t, 1H, $J = 9.6$ Hz, H-2), 4.30 (dd, 1H, $J = 3.8$, 12.5 Hz, H-6a), 4.08 (dd, 1H, $J = 1.1$, 12.5 Hz, H-6b), 3.82 (ddd, 1H, $J = 1.8$, 3.8, 10.3 Hz, H-5), 2.73 (m, 4H, tetrahydronaphthalene moiety), 2.60 (t, 2H, $J = 7.4$ Hz, CH_2), 2.38 (t, 2H, $J = 7.4$ Hz, CH_2), 2.07, 2.03, 2.02, 2.01 (4s, 12H, 4OAc), 1.95–1.88 (m, 2H, CH_2), 1.79 (m, 4H, tetrahydronaphthalene moiety); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.8, 170.5, 169.9, 169.7, 169.4, 152.9 (CO), 137.7, 137.3, 135.2, 129.3, 129.1, 125.6 (Ar–C), 79.1, 73.7, 73.2, 70.4, 68.4, 61.8 (C-1–C-6), 36.4, 34.4, 29.4, 29.1, 26.0, 23.3, 23.2 (3CH_2 and 4CH_2 of tetrahydronaphthalene moiety), 20.7, 20.5, 20.4 ($OCOCH_3$); ESI–MS: *m/z*, 591.21 $[M + H]^+$. Anal. calcd for $C_{29}H_{38}N_2O_{11}$: C, 58.97; H, 6.49; N, 4.74; Found: C, 59.31; H, 6.67; N, 4.53.

*N-2-(Biphenyl-4-yloxy)acetyl-N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-urea (**6c**)*

Yellow foam, Yield 62 %; *Rf* = 0.32 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{22} = + 16$ ($c = 0.20$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (d, 1H, $J = 9.0$ Hz, NH), 8.51 (s, 1H, NH), 7.58–7.30 (m, 7H, ArH), 7.00 (d, 2H, $J = 8.6$ Hz, ArH), 7.35–5.25 (2pseudo t, 2H, $J = 9.4$, 9.2 Hz, H-1, H-3), 5.14–5.06 (2pseudo t, 2H, $J = 9.7$, 9.5 Hz, H-4, H-2), 4.63, 4.58 (q, AB-system, 2H, $J = 16.3$ Hz, CH_2), 4.28 (dd, 1H, $J = 4.4$, 12.5 Hz, H-6a), 4.13 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6b), 3.83 (ddd, 1H, $J = 2.2$, 4.3, 10.1 Hz, H-5), 2.09, 2.04, 2.03, 2.02 (4s, 12H, 4OAc); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7, 170.0, 169.8, 169.5, 169.4, 169.3 (CO), 157.4, 140.6, 134.8, 128.8, 128.4, 128.2, 126.8, 114.9 (Ar–C), 77.9, 75.0, 72.9, 70.1, 68.0, 67.5, 61.4 (CH_2 and C1–C6), 20.7, 20.6, 20.5 ($OCOCH_3$); ESI–MS: *m/z*, 601.22 $[M + H]^+$. Anal. calcd for $C_{29}H_{32}N_2O_{12}$: C, 58.00; H, 5.37; N, 4.66; Found: C, 57.88; H, 5.73; N, 5.06.

*N-(E)-3-(4-Isopropylphenyl)acryloyl-N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-urea (**6d**)*

White foam, Yield 67 %; Rf = 0.36 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{22}$ = -4 (c = 0.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.32 (d, 1H, J = 9.0 Hz, NH), 8.59 (s, 1H, NH), 7.80 (d, 1H, J = 15.6 Hz, CH=CH), 7.47 (d, 2H, J = 8.1 Hz, ArH cumenyl), 7.28 (d, 2H, J = 10.1 Hz, ArH cumenyl), 6.39 (d, 1H, CH=CH), 5.37–5.27 (2pseudo t, 2H, J = 9.4, 9.8 Hz, H-1, H-3), 5.15–5.08 (2pseudo t, 2H, J = 9.4, 9.6 Hz, H-4, H-2), 4.26 (dd, 1H, J = 4.4, 12.4 Hz, H-6a), 4.15–4.08 (dd, 1H, J = 1.6, 12.4 Hz, H-6b), 3.83 (ddd, 1H, J = 2.1, 4.1, 10.0 Hz, H-5), 2.99–2.90 (m, 1H, CH_3–CH–CH_3), 2.05, 2.03 (2s, 12H, 4OAc), 1.27 (d, 6H, J = 6.9 Hz, CH_3–CH–CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7, 170.1, 169.9, 169.4, 166.3, 154.4 (CO), 152.5, 146.1, 131.4, 128.5, 127.2, 117.3 (CH=CH and Ar–C), 79.0, 73.6, 73.0, 70.1, 68.1, 61.6 (C-1–C-6), 34.2, 23.7 (CH_3–CH–CH_3), 20.7, 20.6, 20.5 ($OCOCH_3$); ESI–MS: *m/z*, 563.21 $[M + H]^+$. Anal. calcd for $C_{27}H_{34}N_2O_{11}$: C, 57.64; H, 6.09; N, 4.98; Found: C, 57.46; H, 6.34; N, 5.29.

*N-(R)-3-(4-Ethylphenyl)butanoyl-N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-urea (**6e**)*

Yellow foam, Yield 44 %; Rf = 0.28 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{22}$ = -10 (c = 0.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.05 (d, 1H, J = 8.2 Hz, NH), 8.28 (s, 1H, NH), 7.19–711 (m, 4H, ArH), 5.31–5.16 (2pseudo t, 2H, J = 9.4, 9.2 Hz, H-1, H-3), 5.12–5.02 (2pseudo t, 2H, J = 9.5, 10.0 Hz, H-4, H-2), 4.25 (dd, 1H, J = 4.3, 12.4 Hz, H-6a), 4.11 (dd, 1H, J = 2.0, 12.4 Hz, H-6b), 3.80 (ddd, 1H, J = 2.1, 4.0, 10.7 Hz, H-5), 3.35–3.22 (m, 1H, CH), 3.69–3.54 (m, 4H, CH_2, CH_2CH_3), 2.07, 2.02, 2.01, 1.98 (4s, 12H, 4OAc), 1.34 (d, 3H, J = 6.8 Hz, CH_3), 1.20 (t, 3H, J = 7.6 Hz, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.9, 172.3, 171.5, 170.1, 169.8, 154.4 (CO), 142.5, 142.4, 128.7, 126.6 (Ar–C), 77.9, 73.3, 72.4, 70.7, 68.2, 61.6 (C-1–C-6), 45.5, 42.3, 36.0 (CH and 2CH_2), 27.7, 21.0, 20.8, 20.7, 15.1 ($OCOCH_3$, $CHCH_3$, CH_2CH_3); ESI–MS: *m/z*, 565.20 $[M + H]^+$. Anal. calcd for $C_{27}H_{36}N_2O_{11}$: C, 57.44; H, 6.43; N, 4.96; Found: C, 57.34; H, 6.72; N, 4.57.

*N-(S)-3-(4-Isopropylphenyl)-2-methylpropanoyl-N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-urea (**6f**)*

Yellow foam, Yield 35 %; Rf = 0.33 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{22}$ = + 4 (c = 0.20, $CHCl_3$); The ^1H NMR spectrum showed hindered rotation around the amide bond. ^1H NMR (300 MHz, $CDCl_3$): δ 9.11 (t, 1H, J = 10.1 Hz, NH), 8.10 (2br s, 1H, NH), 7.17–7.05 (m, 4H, ArH cumenyl), 5.32–5.18 (2pseudo t, 2H, J = 9.4, 9.1 Hz, H-1, H-3), 5.12–5.03 (2pseudo t, 2H, J = 9.4, 8.5 Hz, H-4, H-2), 4.26 (dd, 1H, J = 4.3, 12.5 Hz, H-6a), 4.09 (dd, 1H, J = 1.6, 12.5 Hz, H-6b), 3.77 (ddd, 1H, J = 2.0, 4.0, 10.1 Hz, H-5), 3.05–2.83 (m, 2H, CH_2), 2.69–2.58 (m, 2H, CH, CH_3-CH–CH_3), 2.08, 2.07, 2.02, 2.01 (4s, 12H, 4OAc), 1.24, 1.23 (2d, 6H, J = 6.9 Hz, CH_3–CH–CH_3), 1.19 (2d, 3H, J = 6.5 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.2, 170.5, 170.0, 169.5, 169.3, 153.8 (CO), 147.4, 135.8, 128.8, 126.7 (Ar–C), 79.1, 73.8, 73.2, 70.4, 68.4, 61.8 (C-1–C-6), 43.9, 39.1, 33.7 (2CH and CH_2), 23.9, 20.6, 20.5, 20.4, 16.8 (CH_3–CH–CH_3, $OCOCH_3$, $CHCH_3$); ESI–MS: *m/z*, 579.25 $[M + H]^+$. Anal. calcd for $C_{28}H_{38}N_2O_{11}$: C, 58.12; H, 6.62; N, 4.84; Found: C, 58.26; H, 6.35; N, 4.72.

*General procedure for the preparation of the N-acyl-N′-β-D-glucopyranosylureas **7a,b,d,e,f***

The protected ureas **6a,b,d,e,f** (0.18 mmol) were dissolved in dry MeOH (1 mL), 1–2 drops of 1 M methanolic sodium methoxide (NaOMe) solution were added and the reaction mixture was kept at 0 °C until completion of the transformation (20 min, TLC, EtOAc/MeOH 4:1). Amberlyst 15 (H^+ form) was then added to remove sodium ions, the resin was filtered off, the solvent was removed and the residue was purified by flash chromatography (EtOAc/MeOH 4:1) to afford pure **7a,b,d,e,f**.

*N-(E)-3-(Biphenyl-4-yl)acryloyl-N′-(β-D-glucopyranosyl)-urea (**7a**)*

White syrup, Yield 72 %; *Rf* = 0.22 (EtOAc/MeOH 4:1); $[\alpha]_D^{22}$ = + 2 (c = 0.20, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 7.83 (d, 1H, J = 15.7 Hz, CH=CH), 7.71–7.65 (m, 6H, ArH), 7.51–7.36 (m, 3H, ArH), 6.76 (d, 1H, CH=CH), 4.98 (d, 1H, J = 8.9 Hz, H-1), 3.88 (dd, 1H, J = 1.5, 11.8 Hz, H-6b), 3.71 (dd, 1H, J = 4.4, 11.8 Hz, H-6a), 3.50–3.37 (m, 4H, H-2–H-5); ^{13}C NMR (75.5 MHz, CD_3OD) δ 168.8, 156.3 (CO), 145.6, 144.9, 141.4, 134.7, 130.0, 129.9, 129.0, 128.6, 128.0, 120.2 (CH=CH and Ar–C), 82.2, 79.8, 79.1, 74.6, 71.6, 62.9 (C-1–C-6); ESI–MS: *m/z*, 429.17 $[M + H]^+$. Anal. calcd for $C_{22}H_{24}N_2O_7$: C, 61.67; H, 5.65; N, 6.54; Found: C, 61.39; H, 5.48; N, 6.65.

*N-4-(5,6,7,8-Tetrahydronaphthalen-2-yl)butanoyl-N′-(β-D-glucopyranosyl)-urea (**7b**)*

Yellow syrup, Yield 82 %; *Rf* = 0.25 (EtOAc/MeOH 4:1); $[\alpha]_D^{22}$ = + 22 (c = 0.20, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 6.94–6.85 (m, 3H, ArH), 4.90 (d, 1H,

$J = 9.0$ Hz, H-1), 3.83 (dd, 1H, $J = 1.3$, 11.8 Hz, H-6b), 3.66 (dd, 1H, $J = 4.4$, 11.8 Hz, H-6a), 3.44–3.35 and 3.28–3.22 (2 m, 4H, H-2–H-5), 2.71 (m, 4H, tetrahydronaphthalene moiety), 2.56 (t, 2H, $J = 7.5$ Hz, CH_2), 2.33 (t, 2H, $J = 7.3$ Hz, CH_2), 1.95–1.85 (m, 2H, CH_2), 1.78 (m, 4H, tetrahydronaphthalene moiety); ^{13}C NMR (75.5 MHz, CD_3OD) δ 177.2, 156.0 (CO), 139.7, 138.1, 135.8, 130.1, 126.7 (Ar–C), 82.1, 79.8, 79.1, 74.5, 71.6, 62.9 (C-1–C-6), 36.8, 35.6, 30.4, 30.1, 27.7, 24.6, 24.5 ($3CH_2$ and $4CH_2$ of tetrahydronaphthalene moiety); ESI–MS: *m/z*, 423.18 $[M + H]^+$. Anal. calcd for $C_{21}H_{30}N_2O_7$: C, 59.70; H, 7.16; N, 6.63; Found: C, 59.85; H, 7.01; N, 6.49.

*N-2-(Biphenyl-4-yloxy)acetyl-N′-(β-D-glucopyranosyl)-urea (**7c**)*

The protected derivative **6c** (1 mmol) was heated under reflux in dry MeOH (4 mL) containing Bu_2SnO (0.5 mmol) for 2 h and the fully deprotected compound **7c** was obtained as a yellow syrup after flash chromatography using EtOAc/MeOH 4:1 as eluting solvents. Yield 83 %; $Rf = 0.18$ (EtOAc/MeOH 4:1); $[\alpha]_D^{22} = -8$ ($c = 0.20$, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 7.59–7.56 (m, 4H, ArH), 7.40, 7.28 (2t, 3H, $J = 7.6$ Hz, ArH), 7.10 (d, 2H, $J = 8.7$ Hz, ArH), 5.04 (d, 1H, $J = 8.6$ Hz, H-1), 4.63, 4.60 (q, AB-system, 2H, $J = 15.0$ Hz, CH_2), 3.84 (dd, 1H, $J = 1.3$, 11.8 Hz, H-6b), 3.68 (dd, 1H, $J = 4.4$, 11.8 Hz, H-6a), 3.46–3.36 (m, 4H, H-2–H-5); ^{13}C NMR (75.5 MHz, CD_3OD) δ 172.1, 158.7 (CO), 141.9, 136.2, 129.8, 129.2, 127.9, 127.6, 116.3 (Ar–C), 80.9, 79.5, 79.0, 73.9, 71.3, 68.4, 62.6 (C1–C6, CH_2); ESI–MS: *m/z*, 433.18 $[M + H]^+$. Anal. calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.59; N, 6.48; Found: C, 58.67; H, 5.32; N, 6.23.

*N-(E)-3-(4-Isopropylphenyl)acryloyl-N′-(β-D-glucopyranosyl)-urea (**7d**)*

White syrup, Yield 76 %; $Rf = 0.29$ (EtOAc/MeOH 4:1); $[\alpha]_D^{22} = +20$ ($c = 0.20$, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 7.74 (d, 1H, $J = 15.7$ Hz, CH=CH), 7.53, 7.29 (2d, 4H, $J = 8.2$ Hz ArH cumenyl), 6.64 (d, 1H, CH=CH), 4.94 (d, 1H, $J = 9.0$ Hz, H-1), 3.85 (dd, 1H, $J = 1.8$, 11.6 Hz, H-6b), 3.67 (dd, 1H, $J = 4.4$, 11.6 Hz, H-6a), 3.46–3.34 (m, 4H, H-2–H-5), 2.97–2.88 (m, 1H, CH), 1.25 (d, 6H, $J = 6.9$ Hz, CH_3–CH–CH_3); ^{13}C NMR (75.5 MHz, CD_3OD) δ 168.9, 156.4 (CO), 153.5, 146.2, 133.4, 129.6, 128.2, 119.3 (CH=CH and Ar–C), 82.2, 79.8, 79.1, 74.6, 71.6, 62.9 (C-1–C-6), 35.4, 24.1 (CH_3–CH–CH_3); ESI–MS: *m/z*, 395.20 $[M + H]^+$. Anal. calcd for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.64; N, 7.10; Found: C, 57.69; H, 6.29; N, 7.23.

*N-(R)-3-(4-Ethylphenyl)butanoyl-N′-(β-D-glucopyranosyl)-urea (**7e**)*

Yellow syrup, Yield 74 %; $Rf = 0.37$ (EtOAc/MeOH 4:1); $[\alpha]_D^{22} = +20$ ($c = 0.20$, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 7.13–7.09 (m, 4H, ArH), 4.88 (d, 1H, $J = 9.0$ Hz, H-1), 3.83 (dd, 1H, $J = 4.5$, 11.8 Hz, H-6a), 3.70–3.62 (m, 1H, H-6b), 3.42–3.34 and 3.26–3.19 (2 m, 4H, H-2–H-5), 2.64–2.53 (m, 5H, CH, CH_2, CH_2CH_3), 1.29–1.24 (m, 6H, $CHCH_3$, CH_2CH_3); ^{13}C NMR (75.5 MHz, CD_3OD) δ 176.0, 155.9 (CO), 145.7, 143.7, 129.0, 127.8 (Ar–C), 82.1, 79.8, 79.0, 74.5, 71.5, 62.8 (C-1–C-6), 45.9, 37.2, 29.4 (CH and $2CH_2$), 22.3, 16.1 ($CHCH_3$, CH_2CH_3); ESI–MS: *m/z*, 397.16 $[M + H]^+$. Anal. calcd for $C_{19}H_{28}N_2O_7$: C, 57.56; H, 7.12; N, 7.07; Found: C, 57.73; H, 6.86; N, 6.70.

*N-(S)-3-(4-Isopropylphenyl)-2-methylpropanoyl-N′-(β-D-glucopyranosyl)-urea (**7f**)*

Yellow syrup, Yield 72 %; $Rf = 0.35$ (EtOAc/MeOH 4:1); $[\alpha]_D^{22} = +36$ ($c = 0.20$, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 7.15–7.08 (m, 4H, ArH cumenyl), 4.90 (d, 1H, $J = 9.0$ Hz, H-1), 3.84 (m, 1H, H-6b), 3.68 (dd, 1H, $J = 4.3$, 12.0 Hz, H-6a), 3.46–3.35 (m, 4H, H-2–H-5), 3.00–2.83 and 2.81–2.57 (2 m, 4H, CH_2, CH, CH_3–CH–CH_3), 1.22 (d, 6H, $J = 6.9$ Hz, CH_3–CH–CH_3), 1.14 (d, 3H, $J = 6.8$ Hz, CH_3); ^{13}C NMR (75.5 MHz, CD_3OD) δ 180.3, 156.1 (CO), 148.2, 137.8, 130.0, 127.5 (Ar–C), 82.0, 79.8, 79.0, 74.4, 71.3, 62.7 (C-1–C-6), 44.4, 40.0, 35.1 (2CH and CH_2), 24.5, 17.8 (CH_3–CH–CH_3, $CHCH_3$); ESI–MS: *m/z*, 411.19 $[M + H]^+$. Anal. calcd for $C_{20}H_{30}N_2O_7$: C, 58.52; H, 7.37; N, 6.82; Found: C, 58.33; H, 7.63; N, 6.42.

Antiviral activity assays (Kokosza *et al.*, 2013; Novikov *et al.*, 2013)

The antiviral assays, other than the anti-HIV assays, were based on the inhibition of virus-induced cytopathicity or plaque formation in HEL [herpes simplex virus type 1 (HSV-1) (KOS), HSV-2 (G), vaccinia virus, vesicular stomatitis virus, human cytomegalovirus (HCMV), and varicella-zoster virus (VZV)], Vero (parainfluenza-3, reovirus-1, Sindbis virus, and Coxsackie B4), HeLa (vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus) or MDCK [influenza A (H1N1; H3N2) and influenza B] cell cultures. The confluent cell cultures (or nearly confluent for MDCK cells) in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50 % of the cell cultures) or with 20 plaque-forming units (PFU) (for VZV) in the

presence of varying concentrations (100, 20, etc., μM) of the test compounds. The viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. The antiviral activity was expressed as the EC_{50} or the compound concentration required to reduce virus-induced cytopathogenicity or viral plaque (VZV) plaque formation by 50 %. The minimal cytotoxic concentration (MCC) of the compounds was defined as the compound concentration that caused a microscopically visible alteration of cell morphology. Alternatively, the cytostatic activity of the test compounds was measured based on the inhibition of cell growth. HEL cells were seeded at a rate of 5 × 103 cells/well into 96-well microtiter plates and allowed to proliferate for 24 h. Then, the medium containing different concentrations of the test compounds was added. After three days of incubation at 37 °C, the cell number was determined with a Coulter counter. The cytostatic concentration was calculated as the CC_{50}, or the compound concentration required to reduce cell proliferation by 50 % relative to the number of cells in the untreated controls. The methodology of the anti-HIV assays was as follows: human CEM ($\sim 3 \times 105$ cells/cm^3) cells were infected with 100 $CCID_{50}$ of HIV-1IIIB or HIV-2ROD and seeded in 200-μL wells of a microtiter plate containing appropriate dilutions of the test compounds. After 4 days of incubation at 37 °C, the HIV-induced CEM giant cell formation was examined light microscopically.

Antiproliferative assays (Kokosza *et al.*, 2013; Novikov *et al.*, 2013)

The cytostatic effects of the test compounds on murine leukemia cells (L1210), human T-lymphocyte cells (CEM), and human cervix carcinoma cells (HeLa) were evaluated as follows: an appropriate number of cells suspended in growth medium were allowed to proliferate in 200-μL-wells of 96-well microtiter plates in the presence of variable amounts of test compounds at 37 °C in a humidified CO_2-controlled atmosphere. After 48 h (L1210), 72 h (CEM) or 96 h (HeLa), the number of cells was determined in a Coulter counter. The IC_{50} value was defined as the compound concentration required to inhibit cell proliferation by 50 %.

Cytotoxic activity assay (Kokosza *et al.*, 2013; Novikov *et al.*, 2013)

Confluent human lung fibroblast (HEL) cultures in 96-well microtiter plate were exposed to serial dilutions of the test compounds (i.e., 100, 20, 4, 0.8 μM). After 3 days of incubation at 37 °C, microscopical detectable alterations of cell morphology were examined.

Acknowledgments This work was supported in part by the Postgraduate Programmes “Biotechnology-Quality assessment in Nutrition and the Environment,” “Application of Molecular Biology-Molecular Genetics-Molecular Markers,” Department of Biochemistry and Biotechnology, University of Thessaly, and the KU Leuven (GOA 10/14). We thank Lizette van Berckelaer, Leen Ingels, Leentje Persoons and Frieda De Meyer for excellent technical assistance in the evaluation of these compounds in the cellular assays.

References

Agoston K, Dobó A, Rákó J, Kerékgyártó J, Szurmai Z (2001) Anomalous Zemplén deacylation reactions of alpha- and beta-D-mannopyranoside derivatives. Carbohydr Res 330:183–190

Blanc J, Geney R, Menet C (2013) Type II kinase inhibitors: an opportunity in cancer for rational design. Anti-Cancer Agents Med Chem 13:731–747

Davis MI, Hunt JP, Herrgard S, Ciceri P, Wodicka LM, Pallares G, Hocker M, Treiber DK, Zarrinkar PP (2011) Comprehensive analysis of kinase inhibitor selectivity. Nat Biotechnol 29:1046–1051

Dimopoulou A, Manta S, Kiritsis C, Gkaragkouni DN, Papasotiriou I, Balzarini J, Komiotis D (2013) Rapid microwave-enhanced synthesis of C5-alkynyl pyranonucleosides as novel cytotoxic antitumor agents. Bioorg Med Chem Lett 23:1330–1333

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386

Helm RF, Kakhesy JJ (1989) Carbohydrate–urea–phenol-based adhesives: transient formation of mono- and di-D-glucosylurea. Carbohydr Res 189:103–112

Isbell HS, Frush HL (1958) Mutarotation, hydrolysis, and rearrangement reactions of glycosylamines. J Org Chem 23:1309–1319

Jänne PA, Gray N, Settleman J (2009) Factors underlying sensitivity of cancers to small-molecule kinase inhibitors. Nat Rev Drug Discov 8:709–723

Kantsadi AL, Manta S, Psarra AM, Dimopoulou A, Kiritsis C, Parmenopoulou V, Skamnaki VT, Zoumpoulakis P, Zographos SE, Leonidas DD, Komiotis D (2012) The binding of C5-alkynyl and alkylfurano[2,3-*d*]pyrimidine glucopyranonucleosides to glycogen phosphorylase b: synthesis, biochemical and biological assessment. Eur J Med Chem 54:740–749

Kokosza K, Balzarini J, Piotrowska DG (2013) Design, synthesis, antiviral and cytostatic evaluation of novel isoxazolidine nucleotide analogues with a carbamoyl linker. Bioorg Med Chem 21:1097–1108

Liu HM, Yan X, Li W, Huang C (2002) A mild and selective method for cleavage of *O*-acetyl groups with dibutyltin oxide. Carbohydr Res 337:1763–1767

Lu CS, Tang K, Li Y, Jin B, Yin DL, Ma C, Chen XG, Huang HH (2013) Synthesis and in vitro antitumor activities of novel benzyl urea analogues of sorafenib. Yao Xue Xue Bao 48:709–717

Manta S, Parmenopoulou V, Kiritsis C, Dimopoulou A, Kollatos N, Papasotiriou I, Balzarini J, Komiotis D (2012) Stereocontrolled facile synthesis and biological evaluation of (3′S) and (3′R)-3′-amino (and Azido)-3′-deoxy pyranonucleosides. Nucleosides Nucleotides Nucleic Acids 31:522–535

McKay MJ, Nguyen HM (2014) Recent developments in glycosyl urea synthesis. Carbohydr Res 385:18–44

Montagut C, Settleman J (2009) Targeting the RAF–MEK–ERK pathway in cancer therapy. Cancer Lett 283:125–134

Novikov MS, Babkov DA, Paramonova MP, Khandazhinskaya AL, Ozerov AA, Chizhov AO, Andrei G, Snoeck R, Balzarini J, Seley-Radtke KL (2013) Synthesis and anti-HCMV activity of 1-[ω-(phenoxy)-alkyl]uracil derivatives and analogues thereof. Bioorg Med Chem 21:4151–4157

Parmenopoulou V, Kantsadi AL, Tsirkone VG, Chatzileontiadou DS, Manta S, Zographos SE, Molfeta C, Archontis G, Agius L, Hayes JM, Leonidas DD, Komiotis D (2014) Structure based inhibitor design targeting glycogen phosphorylase b. Virtual screening, synthesis, biochemical and biological assessment of novel *N*-acyl-β-D-glucopyranosylamines. Bioorg Med Chem 22:4810–4825

Paulsen H, Pflufhaupt KW (1980) The carbohydrates: chemistry and biochemistry. In: Pigman W, Horton D (eds) 2. Academic Press, New York, pp 881–927

Peterson QP, Hsu DC, Goode DR, Novotny CJ, Totten RK, Hergenrother PJ (2009) Procaspase-3 activation as an anti-cancer strategy: structure-activity relationship of procaspase-activating compound 1 (PAC-1) and its cellular co-localization with caspase-3. J Med Chem 52:5721–5731

Pinter I, Kovacs J, Toth G (1995) Synthesis of sugar ureas via phosphinimines. Carbohydr Res 273:99–108

Putt KS, Chen GW, Pearson JM, Sandhorst JS, Hoagland MS, Kwon JJ, Hwang SK, Jin H, Churchwell MI, Cho MH, Doerge DR, Helferich WG, Hergenrother PJ (2006) Small-molecule activation of procaspase-3 to caspase-3 as a personalized anticancer strategy. Nat Chem Biol 2:543–550

Sausville EA (2000) Protein kinase antagonists: interim challenges and issues. Anticancer Drug Des 15:1–2

Sethi N, Kang Y (2011) Unravelling the complexity of metastasis—molecular understanding and targeted therapies. Nat Rev Cancer 11:735–748

Somsák L, Felföldi N, Kónya B, Hüse C, Telepó K, Bokor E, Czifrák K (2008a) Assessment of synthetic methods for the preparation of *N*-beta-D-glucopyranosyl-*N*′-substituted ureas, -thioureas and related compounds. Carbohydr Res 343:2083–2093

Somsák L, Czifrák K, Tóth M, Bokor E, Chrysina ED, Alexacou KM, Hayes JM, Tiraidis C, Lazoura E, Leonidas DD, Zographos SE, Oikonomakos NG (2008b) New inhibitors of glycogen phosphorylase as potential antidiabetic agents. Curr Med Chem 15:2933–2983

Tropper FD, Andersson FO, Braun S, Roy R (1992) Phase transfer catalysis as a general and stereoselective entry into glycosyl azides from glycosyl halides. Synthesis 7:618–620

Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, Simantov R, Kelley S (2006) Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov 5:835–844

Zhang B, Zhao Y, Zhai X, Wang L, Yang J, Tan Z, Gong P (2012) Design, synthesis and anticancer activities of diaryl urea derivatives bearing *N*-acylhydrazone moiety. Chem Pharm Bull 60:1046–1054