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Synthesis of highly cytotoxic tiazofurin mimics bearing a 2,3-anhydro function in the furanose ring

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ABSTRACT

This paper describes a divergent *de novo* synthesis of 2-(2,3-anhydro-β-D-ribofuranosyl)thiazole-4-carboxamide (2′,3′-anhydro-tiazofurin) and the corresponding α- and β-homo-C-nucleosides. The synthetic approach was based on a multistep transformation of D-glucose into suitably protected aldonthioamides followed by their subsequent cyclocondensation with ethyl bromopyruvate to form the thiazole ring. Antiproliferative activity of the target molecules is reported against several human tumour cell lines.

1. Introduction

C-Nucleosides are important targets in synthetic organic chemistry due to their high potential value as bioactive molecules and biochemical probes.[1] A number of these nucleoside analogues have been found to exhibit potent antiviral or antitumour activities. Remarkable among them is tiazofurin (**1**, Fig. 1), a synthetic C-nucleoside that shows antitumour activity in a variety of tumour systems.[2] In phase II clinical trials, it induced haematological responses in patients with acute myelogenous leukaemia, or chronic myeloid leukaemia in blast crisis.[3] Accordingly, tiazofurin has recently been approved as an orphan drug for treatment of these malignant diseases. The biological activity of tiazofurin derives from a combination of cytotoxicity and maturation-inducing activities.[4] Both effects are attributed to inhibition of inosine 5′-monophosphate dehydrogenase (IMPDH) by the tiazofurin adenine dinucleotide, which induces the shutdown of guanylate synthesis.[5] Despite the remarkable efficacy of **1**, lack of specificity and occasional toxicity remains a problem in its clinical use.[2] In order to provide an access to derivatives of reduced toxicity, a number of tiazofurin analogues have been synthesized and evaluated for their antitumour activities.[6] In the course of our recent program directed towards total syntheses of tiazofurin analogues with modified sugar moieties, we have recently disclosed the synthesis of a series of novel β-D-ribofuranosyl-thiazoles that showed potent and selective antiproliferative activities against a number of tumour cell lines, but were devoid of any significant toxicity against the normal foetal lung fibroblasts (MRC-5).[7] As an extension of these studies, our next endeavour was focused on the synthesis of hitherto unknown tiazofurin derivative **2** (2′,3′-anhydro-tiazofurin), as well as its homologue **3** having the 2′,3′-anhydro function in the furanose ring. Synthesis and biological activity of a number of nucleoside analogues with 2′,3′-anhydrofuranosyl sugar moieties has been reported.[8] Some of the results indicate that 2′,3′-anhydro-nucleosides serve as DNA (or RNA) polymerase termination substrates, that might be of use for development of new antitumour agents. Herein we report on the synthesis of tiazofurin analogues **2** and **3** along with their effects on the proliferation of selected human tumour cell lines.[9]

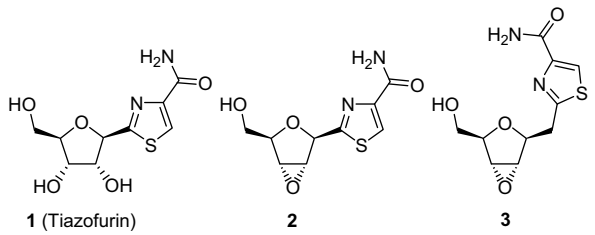

Figure 1. Tiazofurin (**1**) and the targeted analogues **2** and **3**.

2. Results and discussion

Our strategy to synthesise the target C-nucleosides **2** and **3** was to synthesize the ribofuranosyl thioamides **8** (Scheme 1) and **22** (Scheme 3) as key intermediates and then to cyclocondense them with ethyl bromopyruvate to form the thiazole ring. An alternative strategy for the formation of thiazole rings involved direct

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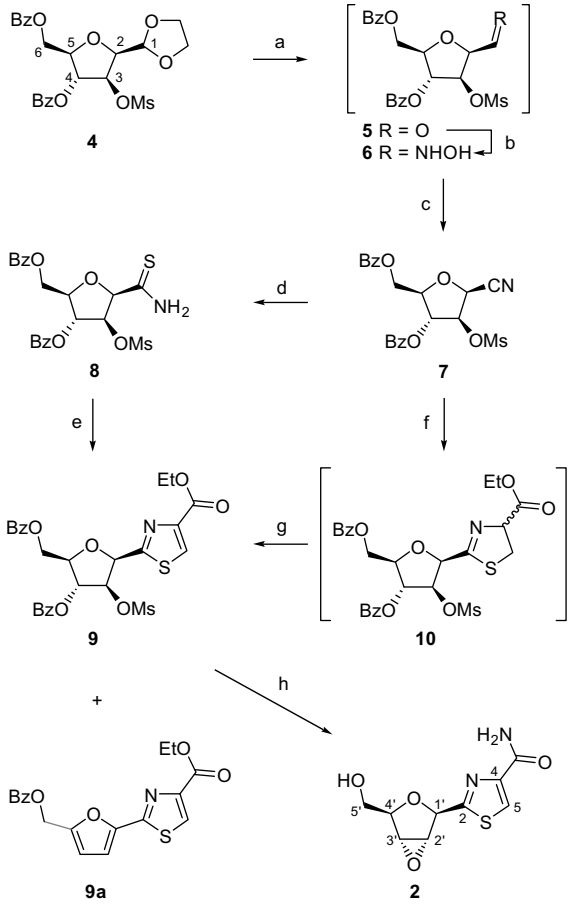
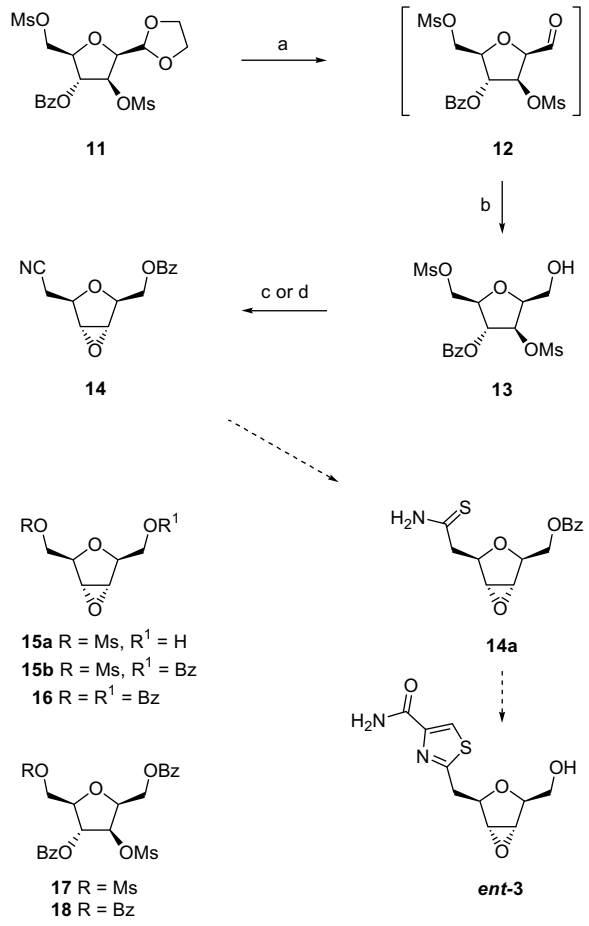
cyclocondensation of cysteine ethyl ester hydrochloride with appropriate aldononitriles in presence of triethylamine according to a previous report.[10]



Scheme 1. Reagents and conditions: (a) 4:1 TFA–6 M HCl, 4 °C, 120 h; (b) $NH_2OH \cdot HCl$, NaOAc, EtOH, CH_2Cl_2, rt, 24 h; (c) MsCl, Py, −15 °C, 0.5 h, then rt, 2 h, 66% from **4**; (d) H_2S, Py, rt, 4 h, 90%; (e) $BrCH_2COCO_2Et$, EtOH, 80 °C, 50 min, 43% of **9**, 10% of **9a**; (f) cysteine ethyl ester hydrochloride, MeOH, Et_3N, rt, 2 h; (g) $BrCCl_3$, DBU, CH_2Cl_2, 0 °C, 5 h, then +4 °C, 3 days, 23% of **9**, 16% of **9a** (both from **7**); (h) NH_3, MeOH, rt, 7 days, 71%.

The synthesis of **2** is outlined in Scheme 1. The sequence started with hydrolytic removal of the dioxolane protection in **4**[11] that was achieved with 4:1 mixture of trifluoroacetic acid and 6 M hydrochloric acid at +4 °C. The resulting unstable aldehyde **5** was not purified, but was immediately treated with hydroxylamine hydrochloride to yield the corresponding oxime **6** as a mixture of the corresponding *E*- and *Z*-isomers. The mixture was not separated but was further treated with mesyl chloride in pyridine to give the corresponding nitrile **7** in 66% yield (with respect to reacted starting compound **4**). Exposure of **7** to hydrogen sulfide gas gave the thioamide **8** (90%). The Hantzsch[12] reaction of **8** with ethyl bromopyruvate afforded the corresponding thiazole **9** (43%), along with a minor amount of the aromatised product **9a** (10%). At this point we wanted to explore an alternative route to thiazole **9** via the key thiazoline intermediate **10** that should be accessible from the nitrile **7** according to an established protocol.[10] Thus, compound **7** was allowed to react with cysteine ethyl ester hydrochloride in the presence of triethylamine at room temperature to afford thiazoline **10** as an inseparable mixture of C-4 epimers. The crude mixture was not separated but was immediately treated with bromotrichloromethane and DBU to give the thiazole **9** in a yield of 23% over the two steps. Oxidation of **10** not only converted the thiazoline ring to a thiazole ring but also concomitantly eliminated the 2′,3′-ester groups to form the aromatised by-product **9a** (16%). It appeared that the former two-step sequence based on the Hantzsch cyclization of thioamide **8** with ethyl bromopyruvate represents a more convenient route towards the key intermediate **9**, since it provided a considerably higher overall yield (39% from **7**) compared to the last method based on the cyclocondensation of cysteine ethyl ester hydrochloride with nitrile **7** (23% from **7**). Treatment of **9** with methanolic ammonia provided the target **2** as a result of successive ester aminolysis and debenzoylation, followed by concomitant epoxide ring closure. Target compound **2** was thus prepared in 18% overall yield calculated from the starting material **4** (6 steps).

For the preparation of homo-C-nucleoside **3** the one carbon homologue of **7** is needed. It was assumed that the requisite intermediate may be accessed by nucleophilic displacement of a primary sulfonyloxy group with the cyanide anion in a suitably functionalized 2,5-anhydro-D-glucitol derivative. Accordingly, the 2,5-anhydride **13** was envisaged not only as a convenient model compound, but also as a possible intermediate for the preparation of the opposite enantiomer of **3** (*ent*-**3**, Scheme 2). The rationale underlying the preparation of *ent*-**3** arises from the fact that enantiomers of certain biologically active nucleoside analogues very often exhibit improved potencies or even novel activities altogether.[13]



Scheme 2. Reagents and conditions: (a) 4:1 TFA–6M HCl, 22 °C, 25 h; (b) NaBH4, MeOH, 0 °C→rt, 2.5 h, 49% (from **11**); (c) KCN, DMSO, 45–49 °C, 76 h, 30% of **14**, 3% of **16**; (d) Bu_4NCN, MeCN, 40 °C, 72 h, 47% of **14**, 10% of **15b**, 5% of **16**; (e) Bu_4NCN, BzCN, MeCN, 40 °C, 76 h, 23% of **14**, 12% of **16**, 12% of **18**.

The sequence commenced from the known dimesylate **11**, which was readily available from glucose monoacetonide over six steps.[11] Hydrolytic removal of the acetal protecting group in **11** gave the unstable aldehyde **12**, which was not purified but was further treated with sodium borohydride in methanol to afford the

corresponding primary alcohol **13** (39% from **11**). Treatment of **13** with potassium cyanide in dry DMSO (45–49 °C) unexpectedly gave a low yield of epoxy-nitrile **14** (30%) as the main reaction product, along with a minor amount of di-*O*-benzoyl derivative **16** (3%).[14] The major product **14** was most likely formed by a sequential three-step process that was promoted by a cyanide anion. The first step of the sequence presumably involved an initial cyanide-catalyzed 4-*O*-debenzoylation[15] of **13** followed by epoxide ring closure to afford **15a**. The benzoyl cyanide thus released subsequently benzoylated[16] the primary hydroxyl group in **15a** to give the intermediate **15b**, which was finally converted to product **14** after nucleophilic displacement of C-5 sulfonyloxy group with the cyanide anion. The postulated intermediates **15a** and **15b** could not be isolated from the reaction mixture. However, when the reaction of **13** was carried out in the presence of tetrabutylammonium cyanide (MeCN, 40 °C, 72 h), apart from the epoxy-nitrile **14** that was obtained in 47% yield and minor amounts of **16** (5%), the intermediate **15b** was isolated in 10% yield. The side-product **16** was presumably formed by a competitive two-step sequence that involved demesylation of intermediate **15b** promoted by cyanide followed by concomitant benzoylation of the liberated primary OH function at C-5 with benzoyl cyanide. This implies that, under these reaction conditions, both epoxide ring closure and *O*-benzoylation steps preceded nucleophilic displacement of the C-6 sulfonyloxy group. However, when the reaction of **13** was carried out in the presence of benzoyl cyanide (Bu_4NCN, MeCN, 40 °C, 72 h) a messy reaction mixture was obtained containing at least three products which were separated with difficulty. A complete conversion of **15b** was observed under these reaction conditions, along with a decreased yield of the epoxy-nitrile **14** (23%) as well as an increased yield of **16** (12%). A minor amount of tribenzoate **18** (12%) was also formed as a result of successive *O*-demesylation of **17**[17] and concomitant benzoylation of the liberated primary OH at C-6. This indicates that under these reaction conditions the removal of the primary *O*-mesyl group with cyanide anion occurs even faster with respect to the competitive epoxide ring closure process.

Compound **14** proved to be crystalline and its structure was conclusively established by X-ray analysis (Fig. 2).

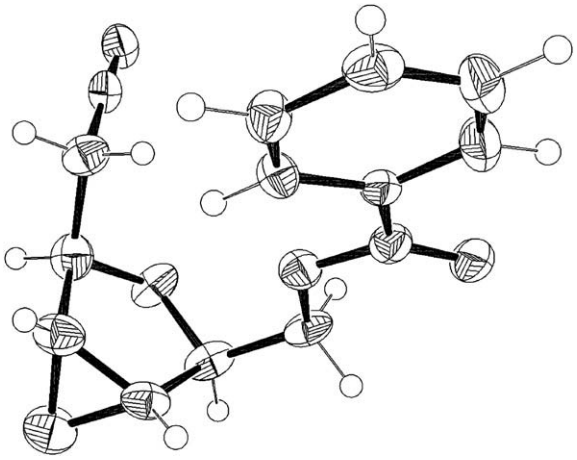
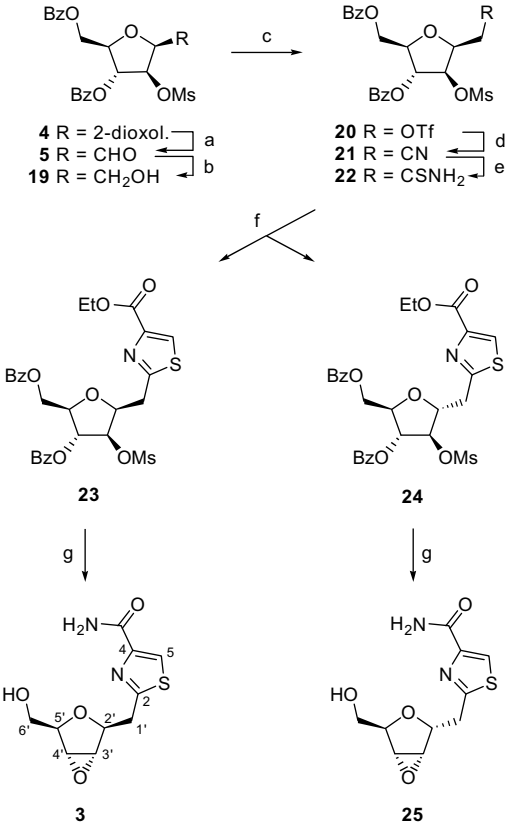


Figure 2. ORTEP presentation of structure **14**.

Unfortunately, reaction of **14** with hydrogen sulfide failed to produce the corresponding thioamide **14a** (Scheme 2). Even after 14 days starting compound **14** remained as a predominant component while only traces of thioamide **14a** could be detected by TLC in the reaction mixture. Attempted cyclocondensation of **14** with cysteine ethyl ester hydrochloride also failed to give the corresponding thiazoline. It appears that the presence of an epoxide group in **14** strongly decreases the reactivity of its nitrile function. In order to avoid the epoxide ring closure process (that obviously preceded the displacement of mesyloxy group in **13**), the triflate ester **20** was envisaged as a convenient intermediate for the preparation of analogue **3** (Scheme 3). Compound **20** contains a much better leaving group at the primary position that would ensure introduction of the nitrile function under mild reaction conditions, hopefully without undesirable epoxide ring closure.



Scheme 3. Reagents and conditions: (a) 4:1 TFA–6 M HCl, 4 °C, 140 h; (b) $NaBH_4$, MeOH, 0 °C, 40 min, then rt, 40 min, 64% from **4**; (c) Tf_2O, Py, CH_2Cl_2, −10 °C, 0.5 h, then rt, 0.5 h; (d) NaCN, DMF, rt, 1.5 h, 73% from **21**; (e) H_2S, Py, rt, 14 days, 78%; (f) $BrCH_2COCO_2Et$, EtOH, 80 °C, 50 min, 32% of **23**, 21% of **24**; (g) NH_3, MeOH, rt, 8 days, 60% of **3**, 65% of **25**.

Compound **4** was hydrolysed under the same reaction conditions as described above, and the resulting crude aldehyde **5** was immediately treated with sodium borohydride in methanol. The corresponding primary alcohol **19** was thus obtained in 64% overall yield. Reaction of **19** with triflic anhydride in pyridine and dichloromethane gave the unstable triflic ester **20** as an oil, which was used in the next step immediately after its isolation from the reaction mixture by solvent extraction. Treatment of crude **20** with NaCN (DMF, rt), or with KCN in the presence of benzo-15-crown-5 ether (MeCN, 0 °C), gave the heptononitrile **21** as the major reaction product (72–73% from **19**). The nitrile **21** was treated with hydrogen sulfide gas under the conditions similar to those already used for the preparation of **8**. However, the conversion of **21** to **22** required 14 days to be complete, whereby the desired thioamide **22** was obtained in 78% yield. The Hantzsch reaction of **22** with ethyl bromopyruvate in ethanol gave the thiazole **23** (32%), accompanied with a minor amount of the C-1′ epimer **24** (21%). The α-anomer **24** was presumably formed from **23** via a ring opening/ring closure process promoted by HBr, which was formed as a by-product in the Hantzsch reaction. Although the acid-catalysed anomerisation of some α-D-ribofuranosyl-C-nucleosides has been reported,[18] this is the first example of such a conversion involving a β-D-arabinofuranosyl-C-nucleoside. Stereochemistry

of **23** and **24** was unambiguously resolved by NOE differential ^{1}H NMR spectroscopy. Designation of the β-anomer **23** was based upon observation of a NOE at H-1′ when H-6′ was irradiated. This effect was not observed in **24**, presumably the α-anomer. However, this stereoisomer exhibited a strong NOE between H-1′ and H-3′, thus implying a spatial vicinity of these protons. Such an arrangement is only possible if the isomer **24** represents the α-anomer. Both isomers **23** and **24** upon treatment with saturated ammonia in methanol gave the expected homo-C-nucleosides **3** and **25** in 60% and 65% yields, respectively.

2.1. Evaluation of cytotoxic activity

Compounds **2**, **3** and **25** were evaluated for their in vitro cytotoxicity towards the following human leukemic and solid tumour cell lines: myelogenous leukaemia K562, promyelocytic leukaemia HL-60, T-cell leukaemia (Jurkat), Burkitt's lymphoma (Raji), colon adenocarcinoma HT-29, estrogen receptor positive breast adenocarcinoma MCF-7 cell line, as well as normal foetal lung fibroblasts (MRC-5). Cytotoxic activity was evaluated by using the standard MTT assay, after exposure of cells to the tested compounds for 72 h. Tiazofurin (**1**) and the commercial antitumour agent doxorubicin (DOX) were used as reference compounds in this bioassay. The results are presented in Table 1.

Table 1
In vitro cytotoxicity of **1**, **2**, **3**, **25** and DOX

Compds	IC_{50}, μM[a]						
	K562	HL-60	Jurkat	Raji	HT-29	MCF-7	MRC-5
Tiazofurin (**1**)	1.89	0.19	0.04	5.28	0.26	1.78	0.36
2	0.64	0.21	1.64	0.18	>100	1.91	>100
3	0.16	33.69	1.68	0.01	0.01	2.67	>100
25	0.05	>100	>100	>100	0.12	10.08	>100
DOX	0.25	0.92	0.03	2.98	0.15	0.20	0.10

[a] IC_{50} is the concentration of compound required to inhibit the cell growth by 50% compared to an untreated control. Values are means of three independent experiments done in quadruplicates. Coefficients of variation were <10%.

Remarkably, all three analogues **2**, **3** and **25** exhibit sub-micromolar cytotoxicity against K562 malignant cells, with IC_{50} values ranging from 0.05 to 0.64 μM. The most active compound against these cells is the α-homo-C-nucleoside **25**, being 38-fold more cytotoxic than tiazofurin, an orphan drug which was approved for treatment of myelogenous leukaemia. At the same time, this molecule demonstrated a 5-fold greater cytotoxicity than DOX towards K562 cell line. Compounds **2** and **3** also efficiently inhibited the growth of K562 cells, with respective IC_{50} values being 3- and 12-fold lower than those observed for the reference compound **1**. The most active compound against HL-60 cells was 2′,3′-anhydrotiazofurin (**2**) that exhibited the same antiproliferative activity as tiazofurin (**1**). However, this molecule was found to be over 4-fold more active than DOX in the same cell line. The β-homo-C-nucleoside **3** showed a moderate cytotoxicity against the HL-60 cells, while the analogue **25** was found to be completely inactive against this cell line. Tiazofurin remains the most potent compound towards the Jurkat T cells and exhibited almost the same cytotoxicity as the commercial antitumour agent doxorubicin (DOX). The analogues **2** and **3**, showed similar and potent antitumour activities in this cell line, but they were over 40-fold less potent than the reference compound **1**. The most potent antiproliferative activity of compounds **2** and **3** was recorded towards Raji malignant cells. Remarkably, the β-homo-C-nucleoside **3** exhibited much more pronounced cytotoxicity against these cells, being approximately 530- and 300-fold more active with respect to both reference compounds **1** and DOX, respectively. At the same time, compound **2** demonstrated a 30- and 16-fold greater cytotoxicity in the same cell line, when compared to **1** and DOX, respectively. Compound **2** was devoid of any cytotoxicity against HT-29 cells, while both homo-C-nucleosides **3** and **25** exhibited sub-micromolar cytotoxicity against these malignant cells. The β-homo-C-nucleoside **3** exhibited the most potent antiproliferative activity, being 26- and 15-fold more active than **1** and DOX, respectively. Compound **25** demonstrated a similar potency as DOX against HT-29 cells, but it was found to be over 2-fold more potent with respect to tiazofurin (**1**) in the same cell line. The analogues **3** and **25** were found to be somewhat less active than the parent compound **1** against the breast adenocarcinoma MCF-7. However, the 2′,3′-anhydro derivative **2** exhibited a similar cytotoxicity towards this cell line as tiazofurin itself. Remarkably, all newly synthesized tiazofurin analogues **2**, **3** and **25** were found to be completely inactive against the normal MRC-5 cells.

3. Conclusions

In summary, three novel tiazofurin derivatives, 2′,3′-anhydrotiazofurin (**2**) and the corresponding β-(**3**) and α-(**25**) homo-C-nucleosides, have been synthesized and evaluated for their in vitro antitumour activity against a number of human neoplastic cell lines. Molecule **2** showed the most pronounced cytotoxic activity against Raji cells, being almost 30-fold more potent than the parent compound, tiazofurin (**1**). Compound **3** exhibited even more potent cytotoxicity towards these cells, being 528-fold more active with respect to the reference compound **1**. The most powerful antitumour activity of compound **25** was recorded in the K562 cell line, being 38-fold more active than tiazofurin. Moreover, none of the synthesized analogues showed any significant cytotoxicity towards the normal foetal lung fibroblasts. Based upon the potent antitumour activities of **2**, **3** and **25**, as well as upon their non-toxicity against normal MRC-5 cells, we believe that these tiazofurin mimics may serve as convenient leads in the synthesis of more potent and selective antitumour agents derived from the parent molecule **1**. Finally, to the best of our knowledge, compounds **2**, **3** and **25** are the first biologically active tiazofurin analogues bearing a 2,3-anhydro ribofuranosyl moiety, while the analogues **3** and **25** represent the first homo-*C*-tiazofurin derivatives that demonstrate antiproliferative activity.

4. Experimental

4.1. General methods

Melting points were determined on a Büchi 510 apparatus and were not corrected. Optical rotations were measured on P 3002 (Krüss) and Polamat A (Carl–Zeiss) polarimeters at room temperature. IR spectra were recorded with Specord 75 (Carl–Zeiss) and Nexus 670 (Thermo Nicolet, DTGS-detector) IR spectrophotometers. NMR spectra were recorded on a Bruker AC 250 E instrument and the chemical shifts (δ-scale) are expressed in ppm values downfield from tetramethylsilane. Chemical ionization low resolution mass spectra were recorded on Finnigan-MAT 8230 spectrometer with isobutane as a reagent gas. High-resolution mass spectra (ESI) were taken on a Micromass LCT KA111 spectrometer. TLC was performed on DC Alufolien Kieselgel 60 F_{254} (E. Merck). Column chromatography was performed on Kieselgel 60 (<0.063 mm, E. Merck). Flash column chromatography was performed using Kieselgel 60 (0.040–0.063, E. Merck). Self-made preparative TLC plates were prepared using Kieselgel 60 G (E. Merck) with Fluorescent Indicator F_{254} as additive. The corresponding bands were scraped and eluted with the respective solvent through short column chromatography. All organic extracts were dried with anhydrous Na_2SO_4 (if not stated otherwise). Organic solutions were concentrated in a rotary evaporator under diminished pressure at a bath temperature below 35 °C.

*4.1.1. 2,5-Anhydro-4,6-di-O-benzoyl-3-O-methanesulfonyl-D-gluconononitrile (**7**)*

A solution of **4** (1.230 g, 2.50 mmol) in a mixture of TFA (6 mL) and 6 M HCl (1.5 mL) was kept at +4 °C for 120 h and then poured into satd aq $NaHCO_3$ (20 mL). The aqueous solution was rendered alkaline with solid $NaHCO_3$ (to pH 8–9) and extracted with CH_2Cl_2 (4×20 mL). The combined extracts were dried (1:1 Na_2SO_4/Na_2CO_3) and evaporated to give crude **5** (1.287 g) as a yellow oil. The crude aldehyde **5** was immediately dissolved in a mixture of dry EtOH (13.5 mL) and CH_2Cl_2 (1.2 mL) and treated with $NH_2OH\cdot HCl$ (0.631 g, 9.08 mmol) and anhydrous NaOAc (0.473 g, 5.77 mmol) while stirring at room temperature for 24 h. The mixture was evaporated, the residue was suspended in water (15 mL) and extracted with CH_2Cl_2 (4×20 mL). The extract was dried (1:1 Na_2SO_4/Na_2CO_3) and evaporated to afford crude oxime **6** (1.069 g) as a mixture of *E*- and *Z*-isomers. ^{1}H NMR ($CDCl_3$): δ 3.08 and 3.12 (2×s, 6H, 2×OMs, *E*/*Z*-isomers), 4.39 and 4.47 (2×m, 2×H-5, *E*/*Z*-isomers), 4.59–4.78 (m, 2×H-6, *E*/*Z*-isomers), 4.83 (dd, $J_{1,2}$=6.7 Hz, $J_{2,3}$=3.7 Hz, H-2, *E*-isomer), 5.27 (t, *J*=3.4 Hz, H-2, *Z*-isomer), 5.32 (d, H-3, *E*-isomer), 5.59 and 5.56 (2×d, H-4, *E*/*Z*-isomers), 5.61 (d, H-3, *Z*-isomer), 7.00 (d, H-1, *Z*-isomer), 7.55 (d, H-1, *E*-isomer), 7.35–8.20 (m, 2×Ph, *E*/*Z*-isomers), 8.60 and 9.11 (2×br s, OH, *E*/*Z*-isomers). ^{13}C NMR ($CDCl_3$): δ 38.5 and 38.6 (2×OMs, *E*/*Z*-isomers), 63.5 (C-6, *E*/*Z*-isomers), 76.0 (C-2, *Z*-isomer), 78.2 (C-2, *E*-isomer), 79.1 and 79.4 (C-4, *E*/*Z*-isomers), 81.7 and 81.8 (C-5, *E*/*Z*-isomers), 82.9 (C-3, *Z*-isomer), 83.5 (C-3, *E*-isomer), 128.3, 128.4, 128.56, 128.61, 129.4, 129.5, 129.7, 129.8, 129.9, 130.0, 133.2, 133.3, 133.9, 140.0 (2×Ph, *E*/*Z*-isomers), 145.8 (C-1, *E*-isomer), 147.4 (C-1, *Z*-isomer), 165.3, 165.4, 166.3 (2×Ph*C*O, *E*/*Z*-isomers). To a cooled (−15 °C) and stirred solution of crude **6** in anhydrous pyridine (7.4 mL) was added dropwise during 30 min a cold solution (−15 °C) of MsCl (1.61 mL, 20.77 mmol) in dry pyridine (4.4 mL). The mixture was stirred at −15 °C for 0.5 h and then at room temperature for the next 2 h. The mixture was poured into ice and 6 M HCl (pH≈2), and the resulting emulsion was extracted with CH_2Cl_2 (4×20 mL). The combined extracts were washed with water (20 mL), satd aq $NaHCO_3$ (20 mL) and again with water (20 mL). The extract was dried (1:1 Na_2SO_4/Na_2CO_3) and evaporated, and the residue (0.984 g) was purified by flash column chromatography (17:3 toluene/EtOAc). **7** (0.607 g, 66% based on reacted **4**) was obtained as a colourless oil homogeneous by TLC, $[\alpha]_D^{23}$ −13.6 (*c* 1.13, $CHCl_3$); R_f=0.45 (17:3 toluene/EtOAc). ^{1}H NMR ($CDCl_3$): δ 3.21 (s, 3H, OMs), 4.51 (ddd, 1H, $J_{5,6a}$=5.0 Hz, $J_{5,6b}$=4.6 Hz, $J_{4,5}$=5.9 Hz, H-5), 4.66 (dd, 1H, $J_{6a,6b}$=12.2 Hz, $J_{5,6a}$=5.0 Hz, H-6a), 4.74 (dd, 1H, $J_{6a,6b}$=12.2 Hz, $J_{5,6b}$=4.6 Hz, H-6b), 5.08 (d, 1H, $J_{2,3}$=4.7 Hz, H-2), 5.51 (dd, 1H, $J_{3,4}$=2.4 Hz, $J_{2,3}$=4.7 Hz, H-3), 5.69 (dd, 1H, $J_{3,4}$=2.4 Hz, $J_{4,5}$=5.9 Hz, H-4), 7.42–8.20 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 39.0 (OMs), 62.9 (C-6), 69.3 (C-2), 77.4 (C-4), 79.7 (C-3), 82.4 (C-5), 113.6 (CN), 127.9, 128.4, 128.9, 129.3, 129.9, 133.4, 134.2 (2×Ph), 165.1 and 166.0 (2×Ph*C*O). No extraneous peaks viewed by NMR. LRMS (CI): *m*/*z* 446 (MH^+). A minor amount of unreacted starting compound **4** (0.215 g, 17%) was recovered.

*4.1.2. 2,5-Anhydro-4,6-di-O-benzoyl-3-O-methanesulfonyl-D-gluconothioamide (**8**)*

Throughout a solution of **7** (0.591 g, 1.33 mmol) in anhydrous pyridine (3 mL) was passed H_2S gas for 4 h at room temperature. The mixture was evaporated and the residue was purified on a column of silica gel (33 g, 4:1 toluene/EtOAc). **8** (0.572 g, 90%) was obtained as a colourless oil homogeneous by TLC, $[\alpha]_D^{23}$ +29.4 (*c* 1.11, $CHCl_3$). R_f=0.6 (7:3 toluene/EtOAc). ^{1}H NMR ($CDCl_3$): δ 3.08 (s, 3H, OMs), 4.59 (ddd, 1H, $J_{4,5}$=1.4 Hz, $J_{5,6a}$=3.2 Hz, $J_{5,6b}$=7.2 Hz, H-5), 4.67 (dd, 1H, $J_{6a,6b}$=11.9 Hz, $J_{5,6a}$=3.2 Hz, H-6a), 4.96 (dd, 1H, $J_{6a,6b}$=11.9 Hz, $J_{5,6b}$=7.2 Hz, H-6b), 5.28 (d, 1H, $J_{2,3}$=3.6 Hz, H-2), 5.51 (d, 1H, $J_{2,3}$=3.6 Hz, H-3), 5.58 (d, 1H, $J_{4,5}$=1.4 Hz, H-4), 7.40–8.14 (m, 10H, 2×Ph), 7.99 and 8.59 (2×br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): δ 38.1 (OMs), 63.8 (C-6), 78.2 (C-4), 83.5 (C-3), 84.9 (C-5), 86.8 (C-2), 128.2, 128.4, 128.6, 128.9, 129.3, 129.9, 133.4 and 134.0 (2×Ph), 165.0 and 167.0 (2×Ph*C*O), 197.7 ($CSNH_2$). No extraneous peaks viewed by NMR. LRMS (CI): *m*/*z* 480 (MH^+).

*4.1.3. Ethyl 2-(3,5-di-O-benzoyl-2-O-methanesulfonyl-β-D-arabinofuranosyl)thiazole-4-carboxylate (**9**)*

Procedure A. A solution of **8** (1.653 g, 3.45 mmol) and ethyl bromopyruvate (0.49 mL, 3.92 mmol) in absolute EtOH (24 mL) was stirred under reflux for 50 min. The solvent was evaporated in vacuum, and the residue was chromatographed through a column of silica gel (100 g, 17:3→7:3 toluene/EtOAc). The aromatised side-product **9a** (0.123 g, 10%) was isolated first as a colourless syrup, R_f=0.64 (17:3 toluene/EtOAc). ^{1}H NMR ($CDCl_3$): δ 1.42 (t, 3H, *J*=7.0 Hz, $CO_2CH_2CH_3$), 4.43 (q, 2H, *J*=7 Hz, $CO_2CH_2CH_3$), 5.36 (s, 2H, H-5′), 6.64 and 7.16 (2×d, 2H, $J_{2',3'}$=3.3 Hz, H-2′ and H-3′), 7.37–8.10 (m, 5H, Ph), 8.13 (s, 1H, H-5). ^{13}C NMR ($CDCl_3$): δ 14.2 ($CO_2CH_2CH_3$), 58.2 (C-5′), 61.5 ($CO_2CH_2CH_3$), 111.1 and 113.3 (C-2′ and C-3′), 126.3 (C-5), 128.3, 128.4, 129.8 and 133.2 (Ph), 147.9 (C-4), 151.3 and 158.2 (C-1′ and C-4′), 161.1 (C-2), 166.0 (Ph*C*O), 170.1 (*C*O_2Et). No extraneous peaks viewed by NMR. The major product **9** (0.844 g, 43%) was isolated as a pale yellow oil, homogeneous by TLC, $[\alpha]_D^{23}$ +3.4 (*c* 1.37, MeOH); R_f=0.47 (17:3 toluene/EtOAc).

Procedure B. To a stirred solution of **7** (0.591 g, 1.33 mmol) in dry MeOH (20 mL) was added L-cysteine ethyl ester hydrochloride (0.371 g, 2 mmol) followed by Et_3N (0.28 mL, 2.0 mmol) at room temperature. The reaction mixture was stirred for 2 h and evaporated. The residue was dissolved in CH_2Cl_2 (75 mL) and washed with water (30 mL), satd $NaHCO_3$ solution (30 mL), and brine (30 mL). The organic layer was dried, filtered and evaporated to give crude **10** (0.805 g) as a colourless foam. To a stirred solution of crude **10** (0.805 g, 1.39 mmol) in anhydrous CH_2Cl_2 was added DBU (0.42 mL, 2.78 mmol). The solution was cooled to 0 °C and $BrCCl_3$ (0.16 mL, 1.67 mmol) was added. The reaction mixture was stirred for 5 h at 0 °C and then stored at +4 °C for 3 days. The mixture was evaporated and the residue was purified by preparative TLC (4:1 toluene/EtOAc, 2 successive developments, eluted with EtOAc) to give pure by-product **9a** (0.076 g, 16%) and slightly impure thiazole **9**. Fractions containing **9** were combined and re-chromatographed on preparative TLC plates (7:3 cyclohexane/Me_2CO, 3 successive developments, eluted with EtOAc) to afford **9** (0.177 g, 23%) as a pale yellow oil homogeneous by TLC, $[\alpha]_D^{23}$ +3.4 (*c* 1.37, MeOH); R_f=0.47 (17:3 toluene/EtOAc). IR (neat): ν_{max} 1723 (C=O), 1368 (as. SO_2), 1179 (sym. SO_2). ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, CH_3CH_2), 2.82 (s, 3H, OMs), 4.39 (q, 2H, CH_3CH_2), 4.60 (td, 1H, $J_{3',4'}$=2.3 Hz, $J_{4',5a'}$=4.9 Hz, $J_{4',5b'}$=4.8 Hz, H-4′), 4.74 (dd, 1H, $J_{5a',5b'}$=11.9 Hz, $J_{4',5a'}$=4.9 Hz, H-5a′), 4.83 (dd, 1H, $J_{5a',5b'}$=11.9 Hz, $J_{4',5b'}$=4.8 Hz, H-5b′), 5.58 (d, 1H, $J_{1',2'}$=3.4 Hz, H-2′), 5.70 (d, 1H, $J_{3',4'}$=2.3 Hz, H-3′), 5.81 (d, 1H, $J_{1',2'}$=3.4 Hz, H-1′), 7.38–8.18 (m, 10H, 2×Ph), 8.23 (s, 1H, H-5). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3CH_2), 38.0 (OMs), 61.5 (CH_3CH_2), 63.2 (C-5′), 80.3 (C-3′), 82.7 (C-2′), 82.9 (C-4′), 128.6 (C-5), 128.28, 128.34, 129.3, 129.7, 129.8, 130.0, 133.2, and 133.4 (2×Ph), 146.8 (C-4), 160.9 (C-2), 165.1 and 166.2 (2×Ph*C*O), 171.1 (*C*O_2Et). No extraneous peaks viewed by NMR. LRMS (CI): *m*/*z* 576 (MH^+).

*4.1.4. 2-(2,3-Anhydro-β-D-ribofuranosyl)thiazole-4-carboxamide (**2**)*

A solution of **9** (0.153 g, 0.27 mmol) in saturated methanolic ammonia (8 mL) was kept at room temperature for 7 days, and then evaporated. The residue was purified by preparative TLC (9:1 CH_2Cl_2/MeOH, eluted with 1:1 ^{i}PrOH/EtOAc) to afford pure **2** (0.046 g, 71%) as a white solid. Recrystallization from MeOH gave an analytical sample **16** as colourless crystals, mp 120–121 °C, $[\alpha]_D^{23}$ +32.8 (*c* 1.18, MeOH), R_f=0.35 (9:1 CH_2Cl_2/MeOH). ^{1}H NMR (methanol-d_4): δ 3.36 (dd, 1H, $J_{5a',5b'}$=11.4 Hz, $J_{4',5a'}$=6.5 Hz, H-5a′), 3.45 (dd, 1H, $J_{5a',5b'}$=11.4 Hz, $J_{4',5b'}$=5.5 Hz, H-5b′), 3.75 (d, 1H,

$J_{2',3'}$=2.8 Hz, H-3′), 4.05 (dd, 1H, $J_{4',5a'}$=6.5 Hz, $J_{4',5b'}$=5.5 Hz, H-4′), 4.11 (d, 1H, $J_{2',3'}$=2.8 Hz, H-2′), 5.10 (s, 1H, H-1′), 8.21 (s, 1H, H-5). NOE contact: H-1′ and H-4′. ^{13}C NMR (methanol-d_4): δ 59.9 (C-3′), 61.0 (C-2′), 63.3 (C-5′), 79.0 (C-1′), 82.1 (C-4′), 126.1 (C-5), 151.2 (C-4), 165.5 (C-2), 172.1 ($CONH_2$). LRMS (CI): *m*/*z* 243 (MH^+). Anal. Found: C, 43.00; H, 4.34; N, 11.42; S, 12.81. Calcd for $C_9H_{10}N_2O_4S\times0.5H_2O$: C, 43.02; H, 4.41; N, 11.15; S, 12.76.

4.1.5. 2,5-Anhydro-4-O-benzoyl-3,6-di-O-methanesulfonyl-D-glucitol (**13**)

A solution of **11** (3.344 g, 7.18 mmol) in a mixture of TFA (32 mL) and 6 M HCl (8 mL) was kept at 22 °C for 25 h. The workup as described above (preparation of **5**) gave crude **12** (3.032 g) as a brown oil. To a stirred and cooled (0 °C) solution of **12** in MeOH (15 mL), was added $NaBH_4$ (0.360 g, 9.52 mmol) in portions over 0.5 h. The cooling bath was removed and the stirring was continued at room temperature for 2.5 h. The mixture was poured into saturated aq NaCl (20 mL) and the resulting emulsion was extracted with CH_2Cl_2 (4×25 mL). The combined extracts were washed with satd aq NaCl, dried and evaporated. The remaining crude mixture was purified by preparative TLC (87 plates, 7:3 toluene/EtOAc, eluted with 1:1 ^{i}PrOH/EtOAc) to give pure **13** (1.484 g, 49% from **11**) that was isolated as a colourless oil, $[\alpha]_D^{23}$ +6.6 (*c* 1.88, $CHCl_3$), R_f=0.6 (2:1 CH_2Cl_2/EtOAc). ^{1}H NMR ($CDCl_3$): δ 2.85 (br s, 1H, exchangeable with D_2O, OH), 3.09 and 3.24 (2×s, 3H each, 2×OMs), 3.93 (d, 2H, $J_{1,2}$=6.0 Hz, 2×H-1), 4.33 (m, 2H, H-2 and H-5), 4.49 (dd, 1H, $J_{6a,6b}$=11.4 Hz, $J_{5,6a}$=4.5 Hz, H-6a), 4.55 (dd, 1H, $J_{6a,6b}$=11.4 Hz, $J_{5,6b}$=4.2 Hz, H-6b), 5.27 (dd, 1H, $J_{3,4}$=0.8 Hz, $J_{2,3}$=3.4 Hz, H-3), 5.45 (dd, 1H, $J_{3,4}$=0.8 Hz, $J_{4,5}$=3.2 Hz, H-4), 7.44–8.11 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 37.5 and 38.3 (2×OMs), 59.4 (C-1), 67.9 (C-6), 78.3 (C-4), 80.87 and 80.91 (C-2, C-5), 81.7 (C-3), 128.2, 128.6, 129.8 and 134.0 (Ph), 165.5 (Ph*C*O). LRMS (CI): *m*/*z* 425 (MH^+). Anal. Found: C, 42.03; H, 4.87; S, 15.39. Calcd for $C_{15}H_{20}O_{10}S_2$: C, 42.45; H, 4.75; S, 15.11.

4.1.6. 3,6:4,5-Dianhydro-7-O-benzoyl-2-deoxy-L-alo-heptononitrile (**14**)

Procedure A. A suspension composed of **13** (0.319 g, 0.75 mmol) and KCN (0.151 g, 2.32 mmol) in DMSO (8 mL) was stirred at 45–49 °C for 76 h. The solvent was removed and the residue was extracted with CH_2Cl_2. The organic solution was evaporated and the oily residue was purified by preparative TLC (7 plates, 10:1 CH_2Cl_2/EtOAc, eluted with 1:1 CH_2Cl_2/EtOAc) to furnish **14** (0.058 g, 30%) as a colourless solid. Crystallization from a mixture of $CHCl_3$/hexane gave an analytical sample of **14**. A minor amount of **16** (0.007 g; 3%) was also isolated as colourless oil.

Procedure B. A solution of **13** (0.208 g; 0.49 mmol) and Bu_4NCN (0.254 g; 0.94 mmol) in dry MeCN (8.4 mL) was stirred at 40 °C for 72 h. The mixture was evaporated and purified by preparative TLC (4 plates, 10:1 CH_2Cl_2/EtOAc, eluted with 1:1 CH_2Cl_2/EtOAc) to give **14** (0.0597 g; 47%). A minor amount of **15b** (0.016 g; 10%) was isolated as a colourless solid. A minor amount of **16** (0.009 g; 5%) was also isolated as colourless oil.

Procedure C. A solution of **13** (0.202 g; 0.48 mmol), Bu_4NCN (0.254 g; 0.94 mmol) and BzCN (0.0837 g; 0.64 mmol) in dry MeCN (8.2 mL) was stirred at 40 °C for 76 h. The mixture was evaporated and purified by preparative TLC as described above (Section B) to give pure **14** (0.028 g; 23%) as colourless crystals. A minor amounts of **16** (0.020 g; 12%) and **18** (0.032 g; 12%) were isolated as colourless oils.

Compound **14**: mp 144–148 °C ($CHCl_3$/hexane), $[\alpha]_D^{20}$ +19.0 (*c* 0.76, $CHCl_3$), R_f=0.69 (10:1 CH_2Cl_2/EtOAc). IR (KBr): ν_{max} 2249 (CN), 1718 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.62 (dd, 1H, $J_{2a,2b}$=16.8 Hz, $J_{2a,3}$=7.1 Hz, H-2a), 2.70 (dd, 1H, $J_{2a,2b}$=16.8 Hz, $J_{2b,3}$=6.3 Hz, H-2b), 3.89 and 3.98 (2×d, 2H, $J_{4,5}$=2.7 Hz, H-4, H-5), 4.41 (dd, 1H, $J_{7a,7b}$=10.8 Hz, $J_{6,7a}$=4.8 Hz, H-7a), 4.42 (dd, 1H, $J_{2a,3}$=7.1 Hz, $J_{2b,3}$=6.3 Hz, H-3), 4.48 (dd, 1H, $J_{6,7a}$=4.8 Hz, $J_{6,7b}$=3.6 Hz, H-6), 4.58 (dd, 1H, $J_{7a,7b}$=10.8 Hz, $J_{6,7b}$=3.6 Hz, H-7b), 7.44–8.08 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 21.8 (C-2), 58.4 and 59.4 (C-4, C-5), 64.3 (C-7), 74.1 (C-3), 77.5 (C-6), 116.1 (CN), 128.7, 129.2, 129.5 and 133.6 (Ph), 165.9 (Ph*C*O). HRMS (ESI): Found: 282.0735 (MNa^+). Calcd for $C_{14}H_{13}NO_4Na$: 282.0742.

Compound **15b**: mp 96 °C (CH_2Cl_2/hexane), $[\alpha]_D^{20}$ +15.8 (*c* 1.17, $CHCl_3$); R_f=0.53 (10:1 CH_2Cl_2/EtOAc). IR (KBr): ν_{max} 1720 (C=O), 1357 (as. SO_2), 1176 (sym. SO_2). ^{1}H NMR ($CDCl_3$): δ 3.05 (s, 3H, OMs), 3.93 (s, 2H, H-3 and H-4), 4.31–4.62 (m, 6H, 2×H-1, 2×H-6, H-2 and H-5), 7.42–8.18 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 37.5 (OMs), 58.2 and 58.4 (C-3 and C-4), 64.1 (C-1), 68.1 (C-6), 128.6, 129.3, 129.6 and 133.4 (Ph), 166.1 (Ph*C*O). HRMS (ESI): Found: 329.0682 (MH^+). Calcd for $C_{14}H_{17}O_7S$: 329.0690.

Compound **16**: R_f=0.84 (2:1 CH_2Cl_2/EtOAc). IR (neat): ν_{max} 1721 (C=O). ^{1}H NMR ($CDCl_3$): δ 3.96 (s, 2H, H-3 and H-4), 4.34–4.55 (m, 6H, H-1, H-6, H-2 and H-5), 7.37–8.11 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): δ 58.5 (C-3 and C-4), 64.1 (C-1 and C-6), 76.9 (C-2 and C-5), 128.5, 129.4, 129.7 and 133.4 (Ph), 166.1 (Ph*C*O). HRMS (ESI): Found: 355.1179 (MH^+). Calcd for $C_{20}H_{19}O_6$: 355.1176.

Compound **18**: $[\alpha]_D^{20}$ +26.1 (*c* 0.27, $CHCl_3$), R_f=0.87 (10:1 CH_2Cl_2/EtOAc). IR (neat): ν_{max} 1720 (C=O), 1367 (as. SO_2), 1178 (sym. SO_2). ^{1}H NMR ($CDCl_3$): δ 3.18 (s, 3H, Ms), 4.48 (m, 1H, $J_{4,5}$=3.2 Hz, $J_{5,6}$=4.3 Hz, $J_{5,6}$=4.9 Hz, H-5), 4.58 (m, 1H, $J_{2,3}$=3.4 Hz, $J_{1,2}$=6.1 Hz, H-2), 4.62–4.75 (m, 4H, H-1 and H-6), 5.37 (d, 1H, $J_{2,3}$=3.4 Hz, H-3), 5.57 (d, 1H, $J_{4,5}$=3.2 Hz, H-4), 7.30–8.21 (m, 15H, Ph). ^{13}C NMR ($CDCl_3$): δ 38.7 (OMs), 61.5 and 63.5 (C-1 and C-6), 78.3, 79.1, 81.6 and 82.4 (C-2, C-4, C-5 and C-3), 128.37, 128.43, 128.6, 129.56, 129.64, 129.67, 129.79, 129.84, 133.2, 133.3, 134.0 (Ph), 165.5, 166.1 and 166.2 (3×Ph*C*O). HRMS (ESI): Found: 555.1319 (MH^+). Calcd for $C_{28}H_{27}O_{10}S$: 555.1319.

4.1.7. 2,5-Anhydro-4,6-di-O-benzoyl-3-O-methanesulfonyl-D-glucitol (**19**)

A solution of **4** (5.6 g, 11.38 mmol) in a mixture of TFA (27.3 mL) and 6 M HCl (6.8 mL) was kept at +4 °C for 140 h. The workup as described above (Section 4.1.1.) gave crude **5** (5.857 g) as a yellow oil. The crude aldehyde **5** (5.857 g, 13.07 mmol) was immediately dissolved in MeOH (22 mL) cooled to 0 °C and treated with $NaBH_4$ (0.49 g, 12.95 mmol) for 40 min. The cooling bath was removed and the stirring was continued at room temperature for 40 min, then quenched with saturated NH_4Cl (40 mL), and extracted with EtOAc (4×25 mL). The combined organic phases were dried and evaporated, and the residue was purified by flash column chromatography (7:3 toluene/EtOAc). The unchanged starting compound **4** (1.426 g, 25%) was first eluted, followed by pure **19** (2.440 g, 64% on the basis of the recovered **4**) isolated as a colourless oil, $[\alpha]_D^{23}$ +20.0 (*c* 1.3, $CHCl_3$), R_f=0.61 (2:1 CH_2Cl_2/EtOAc). ^{1}H NMR ($CDCl_3$): δ 2.94 (br s, 1H, exchangeable with D_2O, OH), 3.15 (s, 3H, OMs), 3.93 (d, 2H, $J_{1,2}$=6.0 Hz, 2×H-1), 4.30 (td, 1H, $J_{1,2}$=6.0 Hz, $J_{2,3}$=3.6 Hz, H-2), 4.40 (m, 1H, H-5), 4.59 and 4.64 (2×dd, 2H, J_{gem}=11.9 Hz, $J_{5,6}$=4.6 Hz, 2×H-6), 5.25 (d, 1H, $J_{3,4}$=1.0 Hz, H-3), 5.49 (dd, 1H, $J_{3,4}$=1.0 Hz, $J_{4,5}$=3.7 Hz, H-4), 7.36–8.10 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 38.2 (CH_3SO_2), 59.5 (C-1), 63.6 (C-6), 79.1 (C-4), 80.8 (C-2), 80.9 (C-5), 82.6 (C-3), 128.3, 129.3, 129.48, 129.54, 129.6, 129.7, 133.2, 133.8 (2×Ph), 165.5 and 166.2 (2×Ph*C*O). LRMS (CI): *m*/*z* 451 (MH^+). Anal. Found: C, 54.60; H, 5.03; S, 7.00. Calcd for $C_{21}H_{22}O_9S\times0.5H_2O$: C, 54.89; H, 5.05; S, 6.98.

4.1.8. 3,6-Anhydro-5,7-di-O-benzoyl-2-deoxy-4-O-methanesulfonyl-D-gluco-heptononitrile (**21**)

Procedure A. To a cooled (−10 °C) and stirred solution of **19** (1.245 g, 2.77 mmol) in dry pyridine (0.96 mL, 11.92 mmol) and CH_2Cl_2 (25 mL), was added a cooled (−10 °C) solution of Tf_2O (0.71 mL, 3.58 mmol) in dry CH_2Cl_2 (9.5 mL). The mixture was first stirred at −10 °C for 0.5 h, then at room temperature for 0.5 h, and

then diluted with CH_2Cl_2 (50 mL). The organic solution was washed successively with 10% aq HCl (50 mL), and water (50 mL). The organic phase was dried and evaporated to give crude **20** (1.726 g) as an unstable pale yellow syrup that was used in the next synthetic step immediately after its brief isolation. ^{1}H NMR ($CDCl_3$): δ 3.18 (s, 3H, OMs), 4.51 (m, 1H, H-5), 4.57 (m, 1H, H-2), 4.63 (m, 2H, J_{gem}=11.6 Hz, 2×H-6), 4.75 (dd, 1H, $J_{1a,1b}$=10.9 Hz, $J_{1a,2}$=4.1 Hz, H-1a), 4.83 (dd, 1H, $J_{1a,1b}$=10.9 Hz, $J_{1b,2}$=6.7 Hz, H-1b), 5.34 (dd, 1H, $J_{2,3}$=3.6 Hz, $J_{3,4}$=1.0 Hz, H-3), 5.54 (dd, 1H, $J_{3,4}$=1.0 Hz, $J_{4,5}$=3.7 Hz, H-4), 7.36–8.15 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 38.3 (OMs), 63.1 (C-6), 72.9 (C-1), 77.4 (C-2), 78.6 (C-4), 81.4 (C-5), 81.6 (C-3), 118.4 (q, $J_{C,F}$=319.8 Hz, CF_3), 128.4, 128.5, 129.2, 129.3, 129.4, 129.7, 133.2 and 134.0 (2×Ph), 165.4 and 166.0 (2×Ph*C*O). To a solution of crude **20** (1.779 g, 3.06 mmol) in DMF (27.5 mL) was added NaCN (0.374 g, 7.64 mmol) and the resulting suspension was stirred at room temperature for 1.5 h. The mixture was diluted with water (50 mL) and extracted with a 1:1 mixture of benzene and hexane (4×60 mL). The combined extract was washed with water (1×50 mL), dried and evaporated. Flash column chromatography (9:1 toluene/EtOAc) of the residue gave **21** (0.957 g, 73% from **19**) as a colourless oil, $[\alpha]_D^{23}$ +19.6 (*c* 2.4, $CHCl_3$), R_f=0.71 (9:1 CH_2Cl_2/EtOAc).

Procedure B. To a suspension of crude **20** (0.541 g, 0.93 mmol) in dry MeCN (2 mL) was added KCN (0.058 g, 0.89 mmol) and a solution of benzo-15-crown-5 (0.727 g, 2.71 mmol) in dry MeCN (10 mL). The mixture was stirred at 0 °C for 1 h and then evaporated. The residue was dissolved in CH_2Cl_2 (25 mL) and washed with satd aq NaCl (2×10 mL). The organic solution was separated, dried and evaporated. Chromatographic purification of the residue by preparative TLC (9:1 CH_2Cl_2/EtOAc, eluted with 1:1 CH_2Cl_2/EtOAc) gave **21** (0.315 g, 74% from **19**) as a colourless oil, $[\alpha]_D^{23}$ +19.6 (*c* 2.4, $CHCl_3$), R_f=0.71 (9:1 CH_2Cl_2/EtOAc). IR (neat): ν_{max} 2260 (CN), 1726.67 (C=O), 1366.67 (as. SO_2), 1186.67 (sym. SO_2). ^{1}H NMR ($CDCl_3$): δ 2.83 (dd, 1H, $J_{1a,2}$=6.0 Hz, $J_{1a,1b}$=17.2 Hz, H-1a), 2.90 (dd, 1H, $J_{1a,1b}$=17.2 Hz, $J_{1b,2}$=6.6 Hz, H-1b), 3.21 (s, 3H, OMs), 4.48 (m, 2H, H-2 and H-5), 4.63 (pseudo d, 2H, $J_{5,6}$=4.6 Hz, 2×H-6), 5.20 (d, 1H, $J_{2,3}$=3.5 Hz, H-3), 5.51 (d, 1H, $J_{4,5}$=3.4 Hz, H-4), 7.36–8.15 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 18.4 (C-1), 38.5 (OMs), 63.2 (C-6), 75.9 (C-2), 79.0 (C-4), 81.5 (C-5), 82.5 (C-3), 116.3 (CN), 128.1, 128.4, 128.6, 129.3, 129.7, 129.8, 133.3 and 134.1 (2×Ph), 165.4 and 166.1 (2×Ph*C*O). LRMS (CI): *m*/*z* 460 (MH^+). Anal. Found: C, 57.29; H, 4.31; N, 2.67; S, 6.69. Calcd for $C_{22}H_{21}NO_8S$: C, 57.51; H, 4.61; N, 3.05; O, S, 6.98.

4.1.9. 3,6-Anhydro-5,7-di-O-benzoyl-2-deoxy-4-O-methanesulfonyl-D-gluco-heptonthioamide (22)

Through a solution of **21** (0.50 g, 1.09 mmol) in dry pyridine (3 mL) was passed H_2S gas at room temperature for 14 days. After workup as described above (Section 4.1.2.) followed by chromatographic purification on a column of flash silica (4:1 toluene/EtOAc) pure **22** (0.420 g, 78%) was obtained as a colourless syrup, $[\alpha]_D^{23}$ −12.8 (*c* 1.76, $CHCl_3$), R_f=0.39 (7:3 toluene/EtOAc). ^{1}H NMR ($CDCl_3$): δ 3.11 (d, 2H, $J_{2,3}$=6.2 Hz, 2×H-2), 3.16 (s, 3H, OMs), 4.43 (m, 1H, $J_{6,7}$=4.5 Hz, H-6), 4.64 (d, 2H, 2×H-7), 4.78 (td, 1H, $J_{2,3}$=6.2 Hz, $J_{3,4}$=3.3 Hz, H-3), 5.24 (d, 1H, $J_{3,4}$=3.3 Hz, H-4), 5.48 (d, 1H, $J_{5,6}$=3.3 Hz, H-5), 7.40–8.15 (m, 10H, 2×Ph), 7.80–8.00 (2×br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): δ 38.4 (OMs), 43.9 (C-2), 63.4 (C-7), 79.1 (C-5), 79.6 (C-3), 81.3 (C-6), 83.7 (C-4), 128.1, 128.2, 129.0, 129.3, 129.6, 129.8, 133.3 and 133.9 (2×Ph), 165.6 and 166.3 (2×Ph*C*O), 204.8 ($CSNH_2$). Anal. Found: C, 50.90; H, 4.81; N, 2.63; S, 11.16. Calcd for $C_{22}H_{23}NO_8S_2\times1.5H_2O$: C, 50.76; H, 5.03; N, 2.69; S, 12.32.

4.1.10. Ethyl 2-(2,5-anhydro-4,6-di-O-benzoyl-1-deoxy-3-O-methanesulfonyl-D-glucitol-1-C-yl)thiazole-4-carboxylate (23) and ethyl 2-(2,5-anhydro-4,6-di-O-benzoyl-1-deoxy-3-O-methanesulfonyl-D-mannitol-1-C-yl)thiazole-4-carboxylate (24)

A solution of **22** (0.485 g, 0.984 mmol) and ethyl bromopyruvate (0.15 mL, 1.18 mmol) in absolute ethanol (7 mL), was refluxed for 50 min. After workup as described above (Section 4.1.3A), the crude mixture was first purified by flash column chromatography (4:1 toluene/EtOAc), and then by preparative TLC (7:3 toluene/EtOAc, **3** successive developments, eluted with EtOAc) to afford pure **23** (0.186 g, 32%) as a colourless syrup, and pure **24** (0.123 g, 21%) as a colourless oil.

Compound **23**: $[\alpha]_D^{23}$ −3.0 (*c* 1.39, $CHCl_3$), R_f=0.55 (7:3 toluene/EtOAc, 2×developed). ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, *J*=7.3 Hz, *C*H_3CH$_2$), 3.20 (s, 3H, OMs), 3.48 and 3.58 (2×dd, 2H, J_{gem}=15.4 Hz, $J_{1',2'}$=8.1 and 4.8 Hz, 2×H-1′), 4.39 (m, 3H, CH$_3$C*H*$_2$ and H-5′), 4.63 (d, 2H, $J_{5',6'}$=4.7 Hz, H-6′), 4.71 (m, 1H, $J_{2',3'}$=3.4 Hz, H-2′), 5.22 (d, 1H, H-3′), 5.54 (d, 1H, H-4′), 7.40–8.17 (m, 10H, 2×Ph), 8.07 (s, 1H, H-5). NOE contacts: CH_3SO_2 and H-4′, CH_3SO_2 and C*H*$_2$CH$_3$, H-6′ and H-4′, H-6′ and H-1′. ^{13}C NMR ($CDCl_3$): δ 14.2 (*C*H$_3$CH$_2$), 32.9 (C-1′), 38.6 (OMs), 61.3 (CH$_3$*C*H$_2$), 63.4 (C-6′), 79.3 (C-4′), 79.4 (C-2′), 81.4 (C-5′), 83.5 (C-3′), 127.7 (C-5), 128.3, 128.4, 128.5, 129.5, 129.7, 129.8, 133.1 and 133.8 (2×Ph), 146.9 (C-4), 161.1 (C-2), 165.4, 166.1 and 166.2 (2×Ph*C*O and *C*O$_2$Et). LRMS (CI): *m*/*z* 590 (MH^+). Anal. Found: C, 55.04; H, 4.34; N, 2.21; S, 10.54. Calcd for $C_{27}H_{27}NO_{10}S_2$: C, 55.00; H, 4.62; N, 2.38; S, 10.88.

Compound **24**: $[\alpha]_D^{23}$ −5.8 (*c* 1.6, $CHCl_3$), R_f=0.63 (7:3 toluene/EtOAc, 2×developed). ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, *C*H_3CH$_2$), 3.15 (s, 3H, OMs), 3.49 and 3.62 (2×dd, 2H, $J_{1',2'}$=7.7 and 5.2 Hz, J_{gem}=15.3 Hz, 2×H-1′), 4.37 (q, 2H, CH$_3$C*H*$_2$), 4.51–4.73 (m, 3H, $J_{4',5'}$=2.4 Hz, 2×H-6′ and H-5′), 4.79 (m, 1H, $J_{2',3'}$=3.9 Hz, H-2′), 5.28 (dd, 1H, $J_{3',4'}$=2.4 Hz, H-3′), 5.63 (t, 1H, H-4′), 7.40–8.12 (m, 10H, 2×Ph), 8.09 (s, 1H, H-5). NOE contact: H-3′ and H-1′. ^{13}C NMR ($CDCl_3$): δ 14.2 (*C*H$_3$CH$_2$), 35.6 (C-1′), 38.4 (OMs), 61.3 (CH$_3$*C*H$_2$), 63.7 (C-6′), 79.4 (C-4′), 81.1 (C-5′), 81.3 (C-2′), 84.7 (C-3′), 128.1 (C-5), 128.4, 128.48, 128.54, 129.4, 129.7, 129.8, 133.2 and 133.8 (2×Ph), 146.8 (C-4), 161.0 (C-2), 165.5, 165.6 and 166.1 (2×Ph*C*O and *C*O$_2$Et). LRMS (CI): *m*/*z* 590 (MH^+). Anal. Found: C, 55.14; H, 4.42; N, 2.19; S, 11.17. Calcd for $C_{27}H_{27}NO_{10}S_2$: C, 55.00; H, 4.62; N, 2.38; S, 10.88.

4.1.11. 2-(2,5:3,4-Dianhydro-1-deoxy-D-allitol-1-C-yl)thiazole-4-carboxamide (3)

A solution of **23** (0.117 g, 0.2 mmol) in saturated methanolic ammonia (5 mL), was stored at room temperature for 8 days. After workup as described above (Section 4.1.4.), the mixture was purified by preparative TLC (5:1 $CHCl_3$/MeOH, eluted with 1:1 ^{i}PrOH/EtOAc) to give pure **3** (0.030 g, 60%) as colourless crystals, mp 141–141.5 °C, $[\alpha]_D^{23}$ +53.3 (*c* 0.45, MeOH), R_f=0.6 (5:1 $CHCl_3$/MeOH). ^{1}H NMR (methanol-d_4): δ 3.35 (d, 2H, $J_{1',2'}$=7.0 Hz, 2×H-1′), 3.60 (dd, 1H, $J_{6a',6b'}$=11.8 Hz, $J_{5',6a'}$=5.2 Hz, H-6a′), 3.68 (dd, 1H, $J_{6a',6b'}$=11.8 Hz, $J_{5',6b'}$=4.1 Hz, H-6b′), 3.90 (d, 1H, $J_{3',4'}$=2.8 Hz, H-4′), 3.96 (d, 1H, $J_{3',4'}$=2.8 Hz, H-3′), 4.10 (dd, 1H, $J_{5',6a'}$=5.2 Hz, $J_{5',6b'}$=4.1 Hz, H-5′), 4.44 (t, 1H, $J_{1',2'}$=7.0 Hz, H-2′), 8.13 (s, 1H, H-5). NOE contacts: H-1′ and H-6′, H-1′ and H-3′. ^{13}C NMR (methanol-d_4): δ 37.3 (C-1′), 59.8 (C-4′), 60.9 (C-3′), 63.3 (C-6′), 78.9 (C-2′), 81.3 (C-5′), 126.0 (C-5), 150.2 (C-4), 159.2 (C-2), 168.8 ($CONH_2$). LRMS (CI): *m*/*z* 257 (MH^+). Anal. Found: C, 46.90; H, 4.85; N, 10.81; S, 12.55. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.86; H, 4.69; N, 10.93; S, 12.53.

4.1.12. 2-(2,5:3,4-Dianhydro-1-deoxy-D-altritol-1-C-yl)thiazole-4-carboxamide (25)

A solution of **24** (0.074 g, 0.12 mmol) in saturated methanolic ammonia (3 mL) was kept at room temperature for 8 days. After workup as described above (Section 4.1.4.), the mixture was purified by preparative TLC (5:1 $CHCl_3$/MeOH, eluted with 1:1 ^{i}PrOH/EtOAc) to afford pure **25** (0.021 g, 65%) as colourless crystals, mp 200 °C, $[\alpha]_D^{23}$ +4.0 (*c* 0.47, DMSO), R_f=0.55 (5:1 $CHCl_3$/MeOH). ^{1}H NMR (DMSO-d_6): δ 3.15 (dd, 1H, $J_{1a',1b'}$=14.9 Hz, $J_{1a',2'}$=7.3 Hz, H-1a′), 3.28 (dd, 1H, $J_{1a',1b'}$=14.9 Hz, $J_{1b',2'}$=5.7 Hz, H-1b′), 3.45 (m, 2H, $J_{5',6'}$=4.6 Hz, 2×H-6′), 3.79 (d, 1H, $J_{3',4'}$=3.0 Hz, H-4′), 3.96 (d, 1H, $J_{3',4'}$=3.0 Hz, H-3′), 3.99 (t, 1H, $J_{5',6'}$=4.6 Hz, H-5′), 4.37 (dd, 1H, $J_{1a',2'}$=7.3 Hz, $J_{1b',2'}$=5.7 Hz, H-2′), 4.94 (br t, 1H, exchangeable with

D_2O, OH), 7.52 and 7.71 (2×br s, 2H, NH_2), 8.10 (s, 1H, H-5). NOE contact: H-6′ and H-4′. ^{13}C NMR (DMSO-d_6): δ 34.6 (C-1′), 57.7 (C-3′), 58.0 (C-4′), 61.5 (C-6′), 76.3 (C-2′), 79.1 (C-5′), 124.7 (C-5), 149.7 (C-4), 162.8 (C-2), 167.2 ($CONH_2$). LRMS (CI): m/z 257 (MH^+). Anal. Found: C, 46.96; H, 4.91; N, 10.65; S, 12.28. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.86; H, 4.69; N, 10.93; S, 12.53.

4.2. Single crystal X-ray analysis[19]

Single crystals of compound **14** were grown from slow evaporation of a solution of the compound in a mixture of $CHCl_3$ and hexane. Crystallographic data were measured on a Nonius Kappa CCD area-detector diffractometer using ω- and ψ-scans and Mo Kα radiation (λ=0.71073 Å). Experimental details from the structure determinations are given in Table 2. The structure was resolved by direct method (SHELXS-97[20]) and refined by full matrix least-squares on F^2 (SHELXL-97[21])

Table 2
Crystallographic data and structure refinement of **14**

Crystallographic parameter	
Empirical formula	$C_{14}H_{13}NO_4$
Formula weight	259.25
Temperature (K)	150(2)
Wavelength (Å)	0.71073 [Mo Kα]
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a=5.5071(9) b=9.4337(11) c=23.674(3)
Volume (Å^3)	1229.9(3)
Z	4
Density (calculated)	1.4 mg/m^3
Absorption coefficient (mm^{-1})	0.104
F(000)	544
Crystal size	0.30 mm×0.20 mm×0.20 mm
Data collection range	$1.72 \le \Theta \le 24.55^\circ$
Index ranges	$-6 \le h \le 5$, $-11 \le k \le 11$, $-27 \le l \le 27$
Reflections collected	2368
Independent reflections	1936 [R(int)=0.0343]
Observed reflections	1518 [$I>2\sigma(I)$]
Absorption correction	Multi-scan
Max. and min. transmission	0.9907 and 0.9676
Refinement method	Full
Data/restraints/parameters	1936/0/172
Goodness-of-fit on $F2$	1.123
Final R indices [$I>2\sigma(I)$]	R_1=0.0647, wR_2=0.1439
R indices (all data)	R_1=0.0919, wR_2=0.1671
Largest diff. peak and hole	0.366 and −0.41 e Å^{-3}
Absolute structure parameter	−1(3)

4.3. In vitro antitumour assay

Exponentially growing cells were harvested, counted by trypan blue exclusion and plated into 96-well microtitar plates (Costar) at optimal seeding density of 10^4 (K562, HL-60, Jurkat and Raji) or 5×10^3 (HT-29 and MCF-7) cells per well to assure logarithmic growth rate throughout the assay period. Antiproliferative activity was evaluated by the tetrazolium colorimetric MTT assay following the recently reported procedure.[22]

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