Synthesis of New Series of 2-C-(β-D-glucopyranosyl)-Pyrimidines and Their Evaluation as Inhibitors of Some Glycoenzymes

Eszter Szennyes 1, Gyöngyi Gyémánt 2, László Somsák 1,* and Éva Bokor 1,*

1 Department of Organic Chemistry, University of Debrecen, H-4002 Debrecen, POB 400, Hungary; szeszterke11@gmail.com
2 Department of Inorganic and Analytical Chemistry, University of Debrecen, H-4002 Debrecen, POB 400, Hungary; gyemant@science.unideb.hu
* Correspondence: somsak.laszlo@science.unideb.hu (L.S.); bokor.eva@science.unideb.hu (É.B.); Tel.: + 36-525-129-00 ext 22348 (L.S.); + 36-525-129-00 ext 22474 (É.B.)

Academic Editor: Orazio Nicolotti
Received: 20 December 2019; Accepted: 4 February 2020; Published: 6 February 2020

Abstract: Despite the substantial interest in C-glycosyl heterocycles as mimetics of biologically active native glycans, the appearance of C-glycopyranosyl derivatives of six-membered heterocycles, both in synthetic and biological contexts, is rather scarce. As part of our ongoing research program aimed at preparing hitherto barely known 2-C-glycopyranosyl pyrimidines, the goal of the present study was to synthesize new 5-mono- and multiply substituted derivatives of this compound class. Thus, 2-C-(β-D-glucopyranosyl)-5,6-disubstituted-pyrimidin-4(3H)-ones and 4-amino-2-C-(β-D-glucopyranosyl)-5,6-disubstituted-pyrimidines were prepared by base-mediated cyclocondensations of O-perbenzylated and O-unprotected C-(β-D-glucopyranosyl) formamidine hydrochlorides with methylenemalonic acid derivatives. The 2-C-(β-D-glucopyranosyl)-5-substituted-pyrimidines were obtained from the same amidine precursors upon treatment with vinamidinium salts. The deprotected derivatives of these pyrimidines were tested as inhibitors of some glycoenzymes. None of them showed inhibitory activity towards glycogen phosphorylase and α- and β-glucosidase enzymes, but some members of the sets exhibited moderate inhibition against bovine liver β-galactosidase.

Keywords: C-Glucopyranosyl derivative; pyrimidine; amidine; glycoenzyme; inhibitor

1. Introduction

C-Glycopyranosyl heterocycles [1] are among the widely investigated groups of sugar-based small molecules. The intense interest in such compounds is primarily due to their possible use as glycomimetics [1–3]. The hydrolitically stable C-C linkage between the glycon and the heterocyclic aglycon part, and the ability of the heteroaromatic moiety to strengthen the binding by diverse interactions (e.g., hydrogen bonds, van der Waals interactions, π-π stackings, and coordination to metal ions) to target biomolecules, along with some general advantages derived from the presence of the sugar component (e.g., enhancement of the solubility, the possibility of targeting carbohydrate binding proteins), make these compounds very attractive in drug design [4].

Within this compound class, the most commonly represented ones are C-glycopyranosyl derivatives of five-membered heterocycles, possessing a large variety of biological effects [1]. On the other hand, six-membered C-glycopyranosyl heterocycles have received much less attention [1]. This appears to be surprising given that their C-glycofuranosyl variants, as analogues of nucleosides, belong to an intensively studied class of sugar conjugates [5]. This general tendency also applies to
C-glycosyl pyrimidines: while a great number of C-glycofuranosyl pyrimidines are known [6–11], C-glycopyranosyl analogues are scarcely found in the literature.

For the formation of 2-C-glycopyranosyl pyrimidines, only one example was described [12], wherein a Minisci type radical glycosylation of a protonated pyrimidine resulted in a 2-(3′,4′-di-O-benzoyl-2′-deoxy-β-D-ribopyranosyl)-pyrimidine together with the corresponding 4-C-glycopyranosylated isomer in 3:7 ratio. Some 5-C-glycopyranosyl pyrimidines were produced by ring-closures of C-glycopyranosylated enamino ketones with guanidine or acetamidine [13,14]. In addition, series of 4-C-, 6-C-, and 4,6-bis-C-glycosyl dihydropyrimidines were obtained from C-glycopyranosyl formaldehydes or β-ketoesters by three-component Biginelli-type cyclisations [15,16].

Recently, as part of a systematic study on the syntheses of 2-C-glycopyranosyl pyrimidines (e.g. I and II in Figure 1), we published their first general synthesis from the corresponding O-perbenzylated (I) or O-protected C-glucopyranosyl formamidines (2) as well as in a one-pot threecomponent formation of O-peracylated glycopyranosyl cyanides [17]. Some members of I and II exhibited moderate inhibition of some glycosidase enzymes [17], however, each proved inactive against glycogen phosphorylase [17]. Although these biological effects are not outstanding, these are the first investigations to reveal potential utilities of this novel compound class.

As a continuation of these studies, in this paper, we disclose the preparation of 4,5,6-tri- and 5-monosubstituted 2-C-glucopyranosyl pyrimidines (III, IV and V, respectively) by the reaction of amidines 1 and 2 with methylenemalonic acid derivatives and vinamidinium salts, respectively, and the evaluation of the resulting heterocycles as inhibitors of glycoenzymes.

**Figure 1.** Recent syntheses of 2-C-glucopyranosyl pyrimidines yielding biologically active derivatives and the target compounds of this study.

2. Results and Discussion

2.1. Syntheses

For the synthesis of the target trisubstituted 2-C-glucopyranosyl pyrimidines, the ring-closures of amidine hydrochloride 1 [18,19] with methylenemalonic acid derivatives 3–7 were investigated.
Table 1. Ring-closure of C-[(β-D-glucopyranosyl)]formamidines with methylenemalic acid derivatives.

| Reagent | Product | Yield (%) | R<sup>1</sup> | R<sup>2</sup> | R<sup>3</sup> | 10 from 10 | 11 from 2 |
|---------|---------|-----------|---------------|---------------|-------------|------------|-----------|
| 3       |         |           | H             | CN            | NH<sub>2</sub> | 76         | 73        |
| 4       |         |           | H             | COOEt         | NH<sub>2</sub> | 37         | 51        | 20        |
| 5       |         |           | H             | COOEt         | OH<sup>b</sup> | 30         | n.r.<sup>a</sup> | 45        |
| 6       |         |           | Ph            | CN            | NH<sub>2</sub> | 78         | n.r.<sup>a</sup> | 85        |
| 7       |         |           | Ph            | CN            | COOEt       | 70         | n.r.<sup>a</sup> | 41        |
| 8       |         |           | Ph            | COOMe         | OH<sup>b</sup> | 70         | n.r.<sup>a</sup> | 41        |
| 9       |         |           | Ph            | COOEt         | OH<sup>b</sup> | 70         | n.r.<sup>a</sup> | 41        |

* n.r.: No reaction; <sup>a</sup> In order to depict compounds 10 and 11 in generalizable chemical formulae, the 6-oxo-1,6-dihydropyrimidine derivatives 10<sub>c,d,f,g,h</sub> and 11<sub>c,d,f,g,h</sub> are shown in their tautomeric 6-hydroxy-pyrimidine forms (R<sup>3</sup> = OH).

Due to the different outcome of the ring-closure of 1 with dialkyl benzylidenemalonates 8 and 9, the synthesis of compounds 10<sub>g,h</sub> and 11<sub>g,h</sub> are presented separately in Scheme 1.

first (Table 1). Treatment of 1 with compounds 3–7 in the presence of NaOMe in MeOH at 0 °C gave the desired pyrimidines 10<sub>a–f</sub>, respectively, in good yields. In the reaction of 1 with ethyl 2-cyano-3-ethoxyacrylate 4, the nucleophilic amidine attacked both the cyano and the ester groups of the
Thus, this cyclocondensation led to the formation of a mixture of ethyl 4-amino-pyrimidine-5-carboxylate 10b and 6-oxo-1,6-dihydropyrimidine-5-carbonitrile 10c. Surprisingly, the same reaction of 1 with ethyl 2-cyano-2-phenylacrylate 7 afforded only one product 11f, derived from a ring-closure involving the ester group of the reagent.

For the O-debenzylation of the new 2-glucosyl pyrimidines 10a–f, catalytic hydrogenolysis in an acidified EtOAc-EtOH solvent mixture at ambient temperature was attempted. Under the applied reductive conditions, the deprotection of compounds 10b and 10d was smoothly affected to get the test compounds 11b and 11d, respectively, in acceptable yields. Unfortunately, pyrimidines 10a,c,e,f with a 5-CN substituent remained intact under the same conditions. This might be due to a poisoning of the catalyst, caused by the coordination of the cyano group to the palladium.

In order to avoid the critical deprotection in the last step of the synthesis, the preparation of the unprotected pyrimidines 11 was also examined in a reversed sequence, wherein the formamidine salt 2, obtained from 1 by hydrogenolytic O-debenzylation [17], was cyclized with the corresponding methylenemalic acid derivatives 3–7 (Table 1). The ring-closure of 2 with compounds 3–7 proceeded similarly to that of amidine salt 1, providing each target test compound 11a–f in moderate to good yields.

The cyclocondensations of amidine salts 1 and 2 with dialkyl benzylidenemalonates 8 and 9, under the same ring-closing conditions used for compounds 3–7, did not directly provide the expected pyrimidinone derivatives 10g,h and 11g,h (Table 1). Similarly to a literature example [20], compounds 8 and 9, when cyclized with 2, furnished 6-oxo-1,4,5,6-tetrahydropyrimidines 12 (Scheme 1). Our attempts to achieve the spontaneous oxidation of compounds 12g,h to get 10g,h by using prolonged reaction times or higher temperatures, were unsuccessful. Finally, the transformation of 12g,h into 10g,h was carried out by applying DDQ as an oxidant in an additional step. The removal of the O-benzyl protecting groups of 12g,h was then performed by hydrogenolysis over Pd(OH)2 to get the final products 11g,h in good yields.

#### Scheme 1. Synthesis of alkyl 2-[(β-D-glucopyranosyl)-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylates.

The formation of 2-C-glucopyranosyl-5-substituted-pyrimidines was also envisaged starting from the same carbohydrate precursors 1 and 2. To this end, NaOMe-mediated cyclisations of compounds 1 and 2 with vinamidinium salts 13–16 were accomplished to get the desired 2,5-disubstituted heterocycles 17 and 18, respectively, in good to high yields (Table 2). Compound 18a...
was prepared both by the ring-closure of 1 with 13, followed by a BCl₃-mediated O-debenzylation of the resulting pyrimidine 17a, and by a reversed debenzylation-cyclisation sequence 1→2→18a. In terms of the overall yields of 18a, the latter route proved to be more efficient (51% for 1→17a→18a vs. 80% for 1→2→18a). By applying this second synthetic pathway, high-yielding preparation of the test compounds 18b and 18c was also smoothly achieved (Table 2).

Table 2. Ring-closure of C-(β-D-glucopyranosyl)formamidines with vinamidinium salts.

| Reagent   | Product | Yield (%) |  |  |
|-----------|---------|-----------|  |  |
|           | 17      | from 17   |  |  |
| 13 H      | 1 ClO₄  | a H       | 60 | 85 | 81 |
| 14 Cl     | 1 PF₆   | b Cl      | 97 | ni | 88 |
| 15 Br     | 1 ClO₄  | c Br      | 90 | ni | 85 |
| 16 CH=NMMe⁺ | 2 ClO₄ | d CHO     | 86 | ni |  |

*ni: not investigated.

In addition, further transformations of compounds 17c and 17d were carried out to get additional 2-C-glucopyranosyl-5-substituted-pyrimidines (Scheme 2). A Pd(PPh₃)₂Cl₂-catalyzed cross-coupling of 5-bromopyrimidine 17c with phenylboronic acid furnished 5-phenylpyrimidine 17e in excellent yield, while the oxidation of 5-formylpyrimidine 17d with NIS in the presence of K₂CO₃ and MeOH resulted in methyl pyrimidine-5-carboxylate 17f in good yield. Finally, the cleavage of the O-benzyl protecting groups of 17e,f was performed with BCl₃ to obtain the test compounds 18e,f in high yields.
Scheme 2. Synthesis of further 2-(β-D-glucopyranosyl)-5-substituted-pyrimidines.

2.2. Enzyme Inhibition Studies

The new unprotected compounds 11 and 18 were tested as inhibitors of some glycoenzymes. Similarly to the previously tested 2-C-glucopyranosyl pyrimidines (I and II in Figure 1) [17], none of them exhibited inhibition against rabbit muscle glycogen phosphorylase b (rmGPb) and almond β-glucosidase.

While 2-(β-D-glucopyranosyl)-6-phenylpyrimidin-4(3H)-one 19 was earlier shown to be a submillimolar inhibitor of yeast α-glucosidase (IC50 = 0.7 mM) [17], the new analogs 11 had negligible effects against this enzyme.

Depending on the substitution pattern of the pyrimidine ring, varied inhibitory potencies of compounds 11 and 19 were observed towards bovine liver β-galactosidase (Table 3). The enzyme kinetic data of the comparable pairs 11a and 11e, 11c and 11f, and 11d and 11h clearly indicated the beneficial effect of the presence of a phenyl substituent at the C-6 position of the pyrimidine ring: while compounds 11a, 11c, and 11d did not inhibit the β-galactosidase, their phenyl-substituted counterparts 11e, 11f, and 11h, respectively, displayed a weak but noticeable inhibition in similar mM concentration ranges. The inhibitory activity of 11f-h in comparison to that of 19 showed that the introduction of a cyano group into the C-5 position of the heterocycle did not cause any significant effect on the potency (19 vs. 11f), but switching to the ester groups resulted in some strengthening of the inhibition (19 vs. 11g and 11h). A similar slight improvement was also observed in the pair 11a and 11b. Compound 11h, bearing both the phenyl and the ester substituent, proved to be the best inhibitor of the series, displaying submillimolar inhibitory effect against this β-galactosidase enzyme.

Among the 2-(β-D-glucopyranosyl)-5-substituted-pyrimidines, the unsubstituted 18a and the 5-halogen-substituted heterocycles 18b,c proved to be inactive, while pyrimidines, having the phenyl (18e) and the methyl ester (18f) group, showed weak inhibition against the β-galactosidase enzyme (Table 3). Although compounds 18e and 18f had no significant effects against this enzyme, their moderate activities indicated that the introduction of these substituents, not only at position 6 but also at 5 of the pyrimidine ring could also be advantageous.

Table 3. Inhibition of bovine liver β-galactosidase by the new 2-C-(β-D-glucopyranosyl)-pyrimidines.

| Compound | Inh. | Compound | Inh. |
|----------|------|----------|------|
| 11a      | NI at 4.1 mM | 11e      | 56% at 3.0 mM |
| 11b      | 40% at 3.6 mM | 11f      | 40% at 3.6 mM |
3. Experimental

3.1. Syntheses

3.1.1. General Methods

Optical rotations were measured on a Jasco P-2000 polarimeter (Jasco, Easton, MD, USA) at rt, and the data were calculated as an average of three parallel measurements. NMR spectra were recorded with Bruker DRX360 (360/90 MHz for $^1$H/$^1$C) and Bruker DRX400 (400/100 MHz for $^1$H/$^1$C) spectrometers. Chemical shifts are referenced to Me$_4$Si ($^1$H) or to the residual solvent signals ($^1$C). MS spectra were obtained by a Bruker Micro TOF-Q (ESI-MS) or a Bruker maXis II (ESI-HRMS) spectrometer. For TLC analysis, DC Alurolle Kieselgel 60 F$_{254}$ plates (Merck) were used and the spots were visualized under UV light and by gentle heating. For column chromatographic purification, Kieselgel 60 silica gel (Molar Chemicals, particle size 63–200 µm) was used. Anhydrous MeOH was dried by distillation over Mg turnings and iodine. Anhydrous EtOH was purchased from Molar Chemicals and used as received. 2-(Ethoxymethylene)malononitrile (3), ethyl 2-cyano-3-ethoxyacrylate (4), and diethyl 2-(ethoxymethylene)malonate (5) were commercially available chemicals (Merck). C-(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)formamidine hydrochloride (1) [18,19], C-(β-D-glucopyranosyl)formamidine hydrochloride (2) [17], 2-benzylidenemalononitrile (6) [21], 2-cyano-3-phenylacrylate (7) [22], dimethyl and diethyl benzylidemalonate (8 and 9 [22,23], respectively), 1,3-bis(dimethylamino)trimethinium perchlorate (13) [24], 2-chloro-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (14) [25], and 2-dimethylaminomethylene-1,3-bis(dimethyllimonio)propane diperchlorate (16) [26] were prepared according to published procedures.

3.1.2. General Procedure 1 for the Synthesis of 2-(β-D-Glucopyranosyl)-pyrimidines (10 or 11) by Cyclisation of C-β-D-Glucopyranosyl Formamidines (1 or 2) with Substituted Methylenealonic Acid Derivatives
To a solution of the corresponding C-(β-D-glucopyranosyl)formamidine hydrochloride (1 or 2) in dry MeOH (2 mL/100 mg amidine), ~1M solution of NaOMe in dry MeOH (3 equiv.) was added at 0 °C. After stirring the reaction mixture at this temperature for 10 min, the appropriate methylenemalonic acid derivative (2 equiv.) was added. The completion of the reaction was monitored by TLC (CHCl₃-MeOH = 9:1 and EtOAc-hexane = 1:1 in the case of O-perbenzylated derivatives and CHCl₃-MeOH = 7:3 in the case of unprotected derivatives). After the disappearance of the starting amidine (1 or 2), the reaction mixture was neutralized with glacial acid, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography.

3.1.3. General Procedure 2 for the Synthesis of Alkyl 2-(2′,3′,4′,6′-tetra-O-benzyl-β-D-glucopyranosyl)-4-phenyl-6-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylates (12) by Cyclisation of C-β-D-Glucopyranosyl Formamidine (1) with Benzylidenemalonate Derivatives

To a solution of amidine hydrochloride 1 (400 mg, 0.66 mmol) in dry MeOH or EtOH (2.5 mL/100 mg substrate), ~1M solution of sodium alkoxide in MeOH or EtOH (2 equiv.) was added and the mixture was stirred at rt for 10 min. To this mixture, the corresponding 2-benzylidenemalonate derivative (2 equiv.) was added and stirred at rt until the TLC (EtOAc-hexane = 1:2 and CHCl₃-MeOH = 9:1) showed the complete conversion of 1 (~6 h). The reaction mixture was then neutralized with glacial acid, concentrated under diminished pressure, and the residue was purified by column chromatography.

3.1.4. General Procedure 3 for the Oxidation of 1,4,5,6-Tetrahydropyrimidine Derivatives (12) by DDQ

A 1,4,5,6-tetrahydropyrimidine derivative (12) was dissolved in dry MeOH (2 mL/100 mg substrate), and DDQ (1 equiv.) was added. The reaction mixture was stirred at rt and monitored by TLC (EtOAc-hexane = 1:2). After the total consumption of the starting material (6 h), the solvent was removed in vacuo. The resulting oil was dissolved in EtOAc (30 mL) and extracted with 10% aq. solution of NaOH (5 × 10 mL). The organic phase was dried over MgSO₄, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography.

3.1.5. General Procedure 4 for the Synthesis of 2-(β-D-Glucopyranosyl)-pyrimidines (17 or 18) by Cyclisation of C-β-D-Glucopyranosyl Formamidine Hydrochlorides (1 or 2) and Vinamidinium Salts

To a solution of C-(β-D-glucopyranosyl)formamidine hydrochloride (1 or 2) in dry MeOH (2 mL/100 mg amidine), ~1M solution of NaOMe in dry MeOH (2.1 equiv.) was added. The reaction mixture was stirred at rt for 10 min, then the corresponding vinamidinium salt (1.1 equiv.) was added and the stirring was continued at rt. After completion of the reaction judged by TLC (CHCl₃-MeOH = 9:1 and EtOAc-hexane = 1:2 for benzylated compounds and CHCl₃-MeOH = 7:3 for unprotected derivatives), the mixture was neutralized with glacial acetic acid, then the solvent was removed under diminished pressure. The residue was purified by column chromatography.

3.1.6. Synthesis and Characterization of the New Compounds

4-Amino-2-(2′,3′,4′,6′-tetra-O-benzyl-β-D-glucopyranosyl)-pyrimidine-5-carbonitrile (10a). Prepared from compound 1 (400 mg, 0.66 mmol) and 2-(ethoxymethylene)malononitrile 3 (162 mg, 1.33 mmol) according to general procedure 1. Reaction time: 30 min. The title compound precipitated from the reaction mixture as a pale yellow amorphous solid. Yield: 325 mg (76%). R₆ = 0.55 (EtOAc-hexane = 1:1); [α]D = −1 (c 0.20, CH₂Cl₂); 1H NMR (400 MHz, CDCl₃) δ (ppm): 8.87 (2H, br s, NH₂), 8.33 (1H, s, H-6), 7.40–6.99 (20H, m, aromatics), 4.93, 4.89 (2 × 1H, 2d, J = 11.0 Hz in each, PhCH₂), 4.92, 4.69 (2 × 1H, 2d, J = 12.2 Hz in each, PhCH₂), 4.82, 4.74 (2 × 1H, 2d, J = 12.2 Hz in each, PhCH₂), 4.65, 4.22 (2 × 1H, 2d, J = 11.3 Hz in each, PhCH₂), 4.38 (1H, d, J = 9.5 Hz, H-1'), 4.38 (1H, d, J = 9.5 Hz, H-1'), 3.94 (1H, pt, J = 9.5, 9.3 Hz, H-2' or H-3' or H-4'), 3.85 (1H, pt, J = 9.4, 9.3 Hz, H-2' or H-3' or H-4'), 3.84 (1H, pt, J = 9.5, 9.3 Hz, H-2' or H-3' or H-4'), 3.79 (1H, dd, J = 11.9, 5.2 Hz, H-6'a), 3.64 (1H, dd, J = 11.9, 1.9 Hz, H-6'b), 3.52-3.49 (1H, m, H-5');
**Ethyl 4-amino-2-(2′,3′,4′,6′-tetra-O-benzyl-β-D-glucopyranosyl)-pyrimidine-5-carboxylate (10b)** and 2-(2′,3′,4′,6′-tetra-O-benzyl-β-D-glucopyranosyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (10c).

The title compounds were prepared from compound 1 (400 mg, 0.66 mmol) and ethyl 2-cyano-3-ethoxyacrylate 4 (224 mg, 1.33 mmol) according to general procedure 1. Reaction time: 1 h. Purified by column chromatography (EtOAc-hexane = 1:3) to yield 10b as the first and 10c as the second fraction. **10b**: Yield: 167 mg (37%), colourless syrup. Rf = 0.25 (EtOAc-hexane = 1:2); [α]D = +54 (c 0.20, CHCl3); 1H NMR (400 MHz, CDCl3) δ (ppm): 8.81 (1H, s, H-6), 7.84 (1H, br s, NH), 7.31–6.97 (20H, m, aromatics), 6.38 (1H, br s, NH2), 4.93, 4.89 (2 × 1H, 2d, J = 11.2 Hz in each, PhCH2), 4.84, 4.57 (2 × 1H, 2d, J = 10.7 Hz in each, PhCH2), 4.60, 4.27 (2 × 1H, 2d, J = 11.4 Hz in each, PhCH2), 4.60, 4.27 (2 × 1H, 2d, J = 12.2 Hz in each, PhCH2), 4.36 (2H, q, j = 7.2 Hz, CH2), 4.36 (1H, d, J = 9.6 Hz, H-1′), 4.03 (1H, pt, J = 9.6, 9.0 Hz, H-2′), 3.84 (1H, pt, J = 9.2, 9.0 Hz, H-3′), 3.76–3.37 (3H, m, H-4′, H-6′a, H-6′b), 3.65 (1H, ddd, J = 9.5, 4.5, 2.2 Hz, H-5′), 1.40 (3H, t, J = 7.2 Hz, CH2CH3); 13C NMR (100 MHz, CDCl3) δ (ppm): 168.9, 166.0, 162.8 (C-2, C-4, COOEt), 159.6 (C-6), 138.8, 138.2, 138.1, 128.5–127.5 (aromatics), 104.3 (C-5), 87.1, 82.9, 81.3, 79.8, 77.3 (C-1′–C-5′), 75.7, 75.2, 74.8, 73.5 (4 × PhCH2), 69.1 (C-6′), 61.3 (CH2CH3), 14.4 (CH3CH2). ESI-MS positive mode (m/z): Calcd for C54H49N4O7 [M + Na]+ 891.3. Found: 891.3.

**Ethyl 2-(2′,3′,4′,6′-tetra-O-benzyl-β-D-glucopyranosyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (10d).** Prepared from compound 1 (400 mg, 0.66 mmol) and diethyl 2-(ethoxymethylene)malonate 5 (265 µL, 1.33 mmol) according to general procedure 1. Reaction time: 1 h. Purified by column chromatography (EtOAc-hexane = 1:1) to give 367 mg (80%) colourless syrup. Rf = 0.25 (EtOAc-hexane = 1:2); [α]D = +54 (c 0.20, CHCl3); 1H NMR (400 MHz, CDCl3) δ (ppm): 8.81 (1H, s, H-6), 7.84 (1H, br s, NH), 7.31–6.97 (20H, m, aromatics), 6.38 (1H, br s, NH2), 4.93, 4.89 (2 × 1H, 2d, J = 11.2 Hz in each, PhCH2), 4.84, 4.57 (2 × 1H, 2d, J = 10.7 Hz in each, PhCH2), 4.60, 4.27 (2 × 1H, 2d, J = 11.4 Hz in each, PhCH2), 4.60, 4.27 (2 × 1H, 2d, J = 12.2 Hz in each, PhCH2), 4.36 (2H, q, j = 7.2 Hz, CH2), 4.36 (1H, d, J = 9.6 Hz, H-1′), 4.03 (1H, pt, J = 9.6, 9.0 Hz, H-2′), 3.84 (1H, pt, J = 9.2, 9.0 Hz, H-3′), 3.76–3.37 (3H, m, H-4′, H-6′a, H-6′b), 3.65 (1H, ddd, J = 9.5, 4.5, 2.2 Hz, H-5′), 1.40 (3H, t, J = 7.2 Hz, CH2CH3); 13C NMR (100 MHz, CDCl3) δ (ppm): 168.9, 166.0, 162.8 (C-2, C-4, COOEt), 159.6 (C-6), 138.8, 138.2, 138.1, 128.5–127.5 (aromatics), 104.3 (C-5), 87.1, 82.9, 81.3, 79.8, 77.3 (C-1′–C-5′), 75.7, 75.2, 74.8, 73.5 (4 × PhCH2), 69.1 (C-6′), 61.3 (CH2CH3), 14.4 (CH3CH2). ESI-MS positive mode (m/z): Calcd for C54H49N4O7 [M + Na]+ 891.3. Found: 891.3.
2-(2′,3′,4′,6′-Tetra-O-benzyl-β-D-glucopyranosyl)-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (10f). Prepared from compound 1 (400 mg, 0.66 mmol) and ethyl 2-cyano-3-phenylacrylate (7 (267 mg, 1.33 mmol) according to general procedure 1. Reaction time: 1 h. Purified by column chromatography (EtOAc-hexane = 2:3) to give 334 mg (70%) colourless syrup. Rf = 0.51 (EtOAc-hexane = 2:3) to give 334 mg (70%) colourless syrup. Rf = 0.51 (EtOAc-hexane = 2:3).

4-Amino-2-(β-D-glucopyranosyl)-pyrimidine-5-carboxylate (10g). Prepared from compound 12g (300 mg, 0.40 mmol) and DDQ (90 mg, 0.40 mmol) according to general procedure 3. Purified by column chromatography (EtOAc-hexane = 2:3) to give 157 mg (58%) pale yellow syrup. Rf = 0.48 (EtOAc-hexane = 1:1); [α]D = +11 (c 0.25, CHCl3); 1H NMR (400 MHz, CDCl3) δ (ppm): 8.07–7.02 (25H, m, aromatics), 4.98, 4.93 (2 × 1H, 2d, J = 11.2 Hz in each, PhCH3), 4.93, 4.72 (2 × 1H, 2d, J = 10.7 Hz in each, PhCH3), 4.77, 4.74 (2 × 1H, 2d, J = 11.3 Hz in each, PhCH3), 4.61, 4.53 (2 × 1H, 2d, J = 12.3 Hz in each, PhCH3), 4.52 (1H, d, J = 9.5 Hz, H-1′), 3.97–3.84 (6H, m, H-2′, H-3′ and/or H-4′, H-5′–H-6′). 13C NMR (90 MHz, CDCl3) δ (ppm): 166.0, 161.3 (2), 157.9 (C-2, C-4, C-6, COOMe), 138.3, 138.0, 137.9, 137.2, 136.8, 130.5, 128.5-127.8 (aromatics), 118.4 (C-5), 86.3, 79.2, 79.2, 78.8, 77.8 (C-1′–C-5′), 75.7, 75.3, 74.7, 73.4 (4 × PhCH3), 69.0 (C-6′), 52.6 (OCH3). ESI-MS positive mode (m/z): Calcd for C21H20N3O5+ [M + H]+ 720.3. Found: 720.6.

Ethyl 2-(2′,3′,4′,6′-tетра-O-бензил-β-D-глюкопиранозил)-4-фенил-6-оксо-1,6-диэпимеридин-5-карбонитрил (10h). Prepared from compound 12h (300 mg, 0.40 mmol) and DDQ (90 mg, 0.40 mmol) according to general procedure 3. Purified by column chromatography (EtOAc-hexane = 2:3) to give 159 mg (53%) pale yellow syrup. Rf = 0.50 (EtOAc-hexane = 1:1); [α]D = +62 (c 0.23, CHCl3); 1H NMR (400 MHz, CDCl3) δ (ppm): 12.67 (1H, br s, NH), 7.66–7.01 (25H, m, aromatics), 4.93, 4.91 (2 × 1H, 2d, J = 11.5 Hz, PhCH3), 4.88, 4.64 (2 × 1H, 2d, J = 10.8 Hz in each, PhCH3), 4.73, 4.47 (2 × 1H, 2d, J = 11.0 Hz, PhCH3), 4.58, 4.54 (2 × 1H, 2d, J = 12.1 Hz in each, PhCH3), 4.42 (1H, d, J = 9.4 Hz, H-1′), 3.94 (1H, pt, J = 9.2, 9.0 Hz, H-2′or H-3′or H-4′), 3.86–3.72 (5H, m, H-2′ and/or H-3′ and/or H-4′, H-5′–H-6′). 13C NMR (90 MHz, CDCl3) δ (ppm): 165.3, 161.4, 161.3, 157.9 (C-2, C-4, C-6, COOEt), 138.4, 138.1, 137.8, 137.2, 136.9, 130.3, 128.5-127.7 (aromatics), 118.7 (C-5), 86.4, 79.2 (2), 78.9, 77.8 (C-1′–C-5′), 75.7, 75.3, 74.7, 73.4 (4 × PhCH3), 69.0 (C-6′), 61.6 (CH2CH3), 13.8 (CH3CH2). ESI-MS positive mode (m/z): Calcd for C21H21N3O5+ [M + H]+ 733.3. Found: 733.6.

4-Amino-2-(β-D-glucopyranosyl)-pyrimidine-5-carboxylate (11a). Prepared from compound 2 (100 mg, 0.41 mmol) and 2-(ethoxymethylene)malononitrile (3 (101 mg, 0.82 mmol) according to general procedure 1. Reaction time: 30 min. Purified by column chromatography (CHCl3:MeOH = 5:1) to give 85 mg (83%) pale yellow syrup. Rf = 0.31 (CHCl3:MeOH = 3:1); [α]D = +42 (c 0.16, MeOH); 1H NMR (400 MHz, CDOD) δ (ppm): 8.56 (1H, s, H-6), 4.18 (1H, d, J = 9.5 Hz, H-1′), 3.85 (1H, dd, J = 12.2, 1.9 Hz, H-6′a), 3.70 (1H, dd, J = 12.2, 4.9 Hz, H-6′b), 3.67 (1H, pt, J = 9.5, 9.0 Hz, H-2′), 3.50 (1H, pt, J = 9.1, 9.0 Hz, H-3′), 3.44 (1H, pt, J = 9.4, 9.1 Hz, H-4′), 3.39 (1H, ddd, J = 9.4, 4.9, 1.9 Hz, H-5′); 13C NMR (100 MHz, CDOD) δ (ppm): 170.2, 164.4 (C-2, C-4), 161.8 (C-6), 115.4 (CN), 90.8 (C-5), 83.5, 82.3, 79.2, 74.4, 71.1 (C-1′–C-5′), 62.7 (C-6′). ESI-HRMS positive mode (m/z): calcd for C11H11N3O5 [M + H]+: 283.1037; C11H11N3O5 [M + Na]+: 305.0856. Found: [M + H]+: 283.1034; [M + Na]+: 305.0852.

Ethyl 4-amino-2-(β-D-glucopyranosyl)-pyrimidine-5-carboxylate (11b) and 2-(β-D-glucopyranosyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (11c). Method A: The Pd-catalyst (35 mg, 20% Pd(OH)2/C) was suspended in an anhydrous EtOAc-EtOH solvent mixture (10 mL in 1:5 ratio) under Ar and the suspension was saturated with H2 (3×). To this heterogeneous mixture, a solution of compound 10b (70 mg, 0.10 mmol) in EtOAc (1 mL) and one drop of cHCl were added. The reaction mixture was stirred under H2: at rt for two days, and the transformation was monitored by TLC (EtOAc-hexane
1.1 and CHCl3-MeOH 7:3). After complete conversion of the starting material, the mixture was neutralized with NaHCO3. The catalyst and insoluble inorganic salts were filtered off through a pad of Celite and washed three times with MeOH (3 × 3 mL). The resulting combined solution was concentrated under diminished pressure and the residue was purified by column chromatography (CHCl3-MeOH = 5:1). Yield of compound 11b: 17 mg (51%) colourless syrup. R = 0.55 (CHCl3-MeOH = 7:3); [α]D = –62 (c 0.15, MeOH); 1H NMR (400 MHz, D2O) δ (ppm): 8.82 (1H, s, H-6), 4.37 (2H, q, J = 7.1 Hz, CH2CH3), 4.28 (1H, d, J = 9.4 Hz, H-1), 3.93 (1H, dd, J = 12.2, 1.9 Hz, H-6′a), 3.81 (1H, dd, J = 12.2, 4.5 Hz, H-6′b), 3.73 (1H, pt, J = 9.4, 9.0 Hz, H-2), 3.69–3.54 (3H, m, H-3′, H-4′, H-5′), 1.38 (3H, t, J = 7.1 Hz, CH2CH3); 13C NMR (90 MHz, CD2OD) δ (ppm): 170.4, 166.9, 164.0, 159.7 (C-2, C-4, C-6, COOEt), 155.2 (C-1′), 84.0, 82.3, 79.3, 74.5, 71.2 (C-1′ – C-5′), 62.9 (C-6′), 62.4 (CH2CH3), 14.5 (CH3CH3). ESI-HRMS positive mode (m/z): calcd for C11H18N2O3+ [M + H]+ 331.1136; C11H19N2NaO3+ [M + Na]+ 353.0955. Found: [M + H]+ 331.1140; [M + Na]+ 353.0953.

Method B: Prepared from compound 11a (55 mg, 20%) as the second fraction. Compound 11c: colourless syrup. Rf = 0.39 (CHCl3-MeOH = 3:1); [α]D = +66 (c 0.16, MeOH); 1H NMR (400 MHz, CD2OD) δ (ppm): 8.33 (1H, s, H-4), 4.11 (1H, t, J = 9.4 Hz, H-1′), 3.88 (1H, dd, J = 12.0, 1.8 Hz, H-6′a), 3.71 (1H, dd, J = 12.0, 4.8 Hz, H-6′b), 3.58 (1H, pt, J = 9.3, 9.2 Hz, H-2′ or H-3′ or H-4′), 3.53–3.41 (3H, m, H-2′ and/or H-3′ and/or H-4′, H-5′); 13C NMR (100 MHz, CD2OD) δ (ppm): 173.1, 171.1 (C-2, C-6), 164.1 (C-4), 118.1 (C-5), 97.6 (C-5′), 81.8, 81.4, 79.1, 74.6, 71.0 (C-1′ – C-5′), 62.5 (C-6′). ESI-HRMS positive mode (m/z): Calcd. for C11H18N2O3+ [M + Na]+ 306.0697. Found: 306.0696.

Ethyl 2-(β-D-glucopyranosyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (11d). Method A: The Pd-catalyst (150 mg, 20% Pd(OH)2/C) was suspended in an anhydrous EtOAc-EtOH solvent mixture (30 mL in 1:5 ratio) under Ar. This degased suspension was saturated with H2 (3%). To this heterogenous mixture, a solution of compound 10a (335 mg, 0.48 mmol) in EtOAc (3 mL) and three drops of ccHCl were added. The reaction mixture was stirred under H2 at rt for two days, and the transformation was monitored by TLC (EtOAc-hexane 1:1 and CHCl3-MeOH 7:3). After the complete conversion of the starting material, the mixture was neutralized with NaHCO3. The catalyst and insoluble inorganic salts were filtered off through a pad of Celite and washed three times with MeOH (3 × 10 mL). The resulting solution was concentrated under reduced pressure and the residue was purified by column chromatography (CHCl3-MeOH = 3:1). Yield: 107 mg (67%), colourless syrup. Method B: Pre pared from compound 2 (100 mg, 0.41 mmol) and diethyl 2-(ethoxymethylene)malonate 5 (165 µL, 0.82 mmol) according to general procedure 1. Reaction time: 1 h. Purified by column chromatography (CHCl3-MeOH = 3:1) to give 70 mg (51%) colourless syrup. R = 0.39 (CHCl3-MeOH = 1:1); [α]D = +75 (c 0.15, MeOH); 1H NMR (360 MHz, D2O) δ (ppm): 8.70 (1H, s, H-4), 4.39–4.32 (3H, m, H-1′, CH2CH3), 3.94 (1H, dd, J = 12.2, 2.4 Hz, H-6′a), 3.82 (1H, dd, J = 12.2, 4.0 Hz, H-6′b), 3.72–3.60 (4H, m, H-2′ – H-5′), 1.36 (3H, t, J = 6.9 Hz, CH2CH3); 13C NMR (90 MHz, D2O) δ (ppm): 167.2, 166.7, 164.9, 157.3 (C-2, C-4, C-6, COOEt), 114.2 (C-5), 80.4, 79.7, 77.3, 73.0, 69.7 (C-1′ – C-5′), 62.8 (C-6′), 61.2 (CH2CH3), 14.0 (CH3CH2). ESI-HRMS positive mode (m/z): calcd for C11H18N2O3+ [M + H]+ 331.1136; C11H18N2NaO3+ [M + Na]+ 353.0955. Found: [M + H]+ 331.1140; [M + Na]+ 353.0953.

4-Amino-2-(β-D-glucopyranosyl)-6-phenyl-pirimidine-5-carbonitrile (11e). Prepared from compound 2 (50 mg, 0.21 mmol) and 2-benzylideneamanononitrile 6 (64 mg, 0.41 mmol) according to general procedure 1. Reaction time: 1 h. Purified by column chromatography (CHCl3-MeOH = 3:1) to give 63 mg (85%) pale yellow syrup. R = 0.49 (CHCl3-MeOH = 7:3); [α]D = +34 (c 0.17, MeOH); 1H NMR (400 MHz, CD2OD) δ (ppm): 7.89–7.87 (2H, d, J = 7.9 Hz, Ph), 7.57–7.50 (3H, m, Ph), 4.29 (1H, d, J = 9.6 Hz, H-1′), 3.86 (1H, dd, J = 12.1, 2.1 Hz, H-6′a), 3.81 (1H, pt, J = 9.5, 9.3 Hz, H-2′), 3.77 (1H, dd, J = 12.1, 4.7 Hz, H-6′b), 3.59–3.52 (2H, m, H-3′, H-4′), 3.45–3.42 (1H, m, H-5′); 13C NMR (100 MHz, CD2OD) δ (ppm): 170.4, 169.5, 166.2 (C-2, C-4, C-6), 137.5, 132.2, 129.9, 129.8, 129.6 (2) (Ph), 116.4 (CN), 90.8 (C-5), 87.8, 83.8, 82.2, 79.0, 70.9 (C-1′ – C-5′), 62.4 (C-6′). ESI-HRMS positive mode (m/z): Calcd for C11H18N2O3+ [M + H]+ 359.1350; C11H18N2NaO3+ [M + Na]+ 381.1169. Found: [M + H]+ 359.1350; [M + Na]+ 381.1169.
2-([β-D-Glucopyranosyl]-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate) (11f). Prepared from compound 2 (50 mg, 0.21 mmol) and ethyl 2-cyano-3-phenylacrylate 7 (83 mg, 0.41 mmol) according to general procedure 1. Reaction time: 1 h. Purified by column chromatography (CHCl3-MeOH = 7:3) to give 30 mg (41%) colourless syrup. \( \delta \) (ppm): 173.2, 171.1, 167.5 (C-2, C-4, C-6), 136.3, 131.7, 129.3 (2), 129.0 (2) (Ph), 118.7 (CN), 95.1 (C-5), 81.9, 80.4, 77.5, 73.3, 69.7 (C-1′), 3.91–3.78 (3H, m, H-3), 3.69–3.60 (3H, m, H-3′ – H-5′); \( \delta \) (ppm): 173.2, 171.1, 167.5 (C-2, C-4, C-6), 136.3, 131.7, 129.3 (2), 129.0 (2) (Ph), 118.7 (CN), 95.1 (C-5). ESI-HRMS positive mode (m/z): Calcd for C17H18N3O6+ [M + H]+ 360.1190; C17H17N3NaO6+ [M + Na]+ 382.1010. Found: [M + H]+ 360.1190; [M + Na]+ 382.1009.

Methyl 2-([β-D-glucopyranosyl]-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate) (11g). The Pd-catalyst (50 mg, 20% Pd(OH)2/C) was suspended in anhydrous EtOH (10 mL) under Ar. This degased suspension was saturatated with H2 (3×). To this heterogenous mixture, a solution of compound 1 (400 mg, 2.00 mmol) and dimethyl benzylidenemalonate 8 (292 mg, 1.33 mmol) according to general procedure 2. Purified by column chromatography (EtOAc-hexane = 2:3) to give 451 mg (90%) colourless syrup. \( \delta \) (ppm): 8.74, 8.67 (br s, 2 × NH), 7.33–7.10 (m, aromatics), 5.00 (d, \( J = 13.5 \) Hz, H-4 or H-5), 4.94 (d, \( J = 11.6 \) Hz, H-4 or H-5), 4.87–4.48 (m, PhCH), 4.10, 4.05 (2d, \( J = 9.1 \) Hz in each, 2 × H-1′), 3.79–3.55 (m, 2 × [H-2′ – H-6′a,b]), 3.61, 3.55 (2s, 2 × OMe), 3.49 (d, \( J = 11.5 \) Hz, H-4 or H-5), 3.22 (d, \( J = 13.8 \) Hz, H-4 or H-5); \( \delta \) (ppm): 168.3, 168.1, 166.2 (2 × [C-6, COOME]), 150.7, 150.5 (2 × C-2), 139.9 (2), 138.4, 138.2, 138.0, 137.9, 137.9, 137.8, 137.7 (2), 128.8–127.2 (aromatics), 86.3 (2), 79.2, 79.1, 79.1, 78.9, 78.7 (2), 77.4 (2) (2 × [C-1′ – C-5′]), 75.7 (2), 75.2
(2), 74.8 (2), 73.6, 73.6 (8 × PhCH₂), 68.8, 68.6 (2 × C-6'), 61.5, 61.4, 53.8, 53.7, 52.7, 52.7 (2 × C-4, C-5, OCH₃)]. ESI-HRMS positive mode (m/z): Calcd for C₉₅H₇₃N₂O₃²⁺ [M + H⁺] = 555.3. Found: 555.3.

Ethyl 2-(2′,3′,4′,6′-tetra-O-benzyl-β-D-glucopyranosyl)-4-phenyl-6-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylate (12h). Prepared from compound 2 (400 mg, 0.66 mmol) and diethyl benzylidinemalonate 9 (329 mg, 1.33 mmol) according to general procedure 2. Purified by column chromatography (EtOAc-hexane = 2:3) to give 413 mg (81%) colourless syrup. \( R_f = 0.46 \) (EtOAc-hexane = 2:3). 1H NMR (400 MHz, CDCl₃) δ (ppm): 7.15–7.05 (m, aromatics), 6.31 (2H, m, aromatics), 4.98 (2 × 1H, 2d, \( J = 11.2 \) Hz, PhCH₂), 4.85, 4.57 (2 × 1H, 2d, \( J = 10.8 \) Hz, PhCH₂), 4.50 (1H, d, \( J = 9.6 \) Hz, H-1'), 4.55, 4.50 (2 × 1H, 2d, \( J = 12.2 \) Hz, PhCH₂), 4.15 (1H, pt, \( J = 9.6, 9.2 \) Hz, H-2'), 3.90 (1H, pt, \( J = 9.2, 9.1 \) Hz, H-3'), 3.77–3.70 (4H, m, H-4′–H-6′a,b); 13C NMR (100 MHz, CDCl₃) δ (ppm): 166.5 (C-2), 157.3 (C-4, C-6), 138.8, 138.2, 138.1 (2), 128.5–127.5 (aromatics), 87.2, 83.2, 81.4, 79.9, 78.4 (C-1′–C-5′), 75.7, 75.2, 74.7, 73.5 (4 × PhCH₂), 69.3 (C-6′). ESI-MS positive mode (m/z): Calcd for C₄₆H₄₇N₂O₈²⁺ [M + H⁺] = 755.3. Found: 755.5.

2-Bromo-1,3-bis(dimethylamino)trimethinium perchlorate (15). 1,3-Bis(dimethylamino)trimethinium perchlorate 13 (5 g, 22.06 mmol) and NBS (3.93 g, 22.06 mmol) were stirred in dry CH₂Cl₂ at rt for 15 h. The solvent was then removed under diminished pressure and the residue was triturated with cold EtOH (15 mL) and the precipitate was filtered off. The obtained pale yellow solid (yield: 6.67 g, 99%) was used in the next step without further purification. 1H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.79–8.70 (m, aromatics), 4.99 (2H, s, PhCH₂), 4.81, 4.79 (2 × 1H, 2d, \( J = 11.6 \) Hz, PhCH₂), 3.85, 3.77 (4H, m, H-4′–H-6′a,b). ESI-MS positive mode (m/z): Calcd for C₃₈H₃₉N₂O₅⁺ [M + H⁺] = 603.3; Found: [M + H⁺] = 603.5.

(111 mg, 0.36 mmol) and 1,3-bis(dimethylamino)trimethinium perchlorate 13 (82 mg, 0.36 mmol) according to general procedure 4. Reaction time: 6 h. Purified by column chromatography (EtOAc-hexane = 1:2) to give 205 mg (97%) white solid. Mp: 68–70 °C; \( R_f = 0.40 \) (EtOAc-hexane = 1:3). 1H NMR (400 MHz, CDCl₃) δ (ppm): 8.68, 8.60 (br s, 2 × NH), 7.36–7.11 (m, aromatics), 4.99 (d, \( J = 13.3 \) Hz, H-4 or H-5), 4.92 (d, \( J = 11.8 \) Hz, H-4 or H-5), 4.08, 4.07 (2q, \( J = 7.1 \) Hz in each, 2 × CH₃CH₂), 4.05, 4.01 (2d, \( J = 9.1 \) Hz in each, 2 × H-1'), 3.79–3.53 (m, 2 × [H-2'–H-6']), 3.47 (d, \( J = 11.8 \) Hz, H-4 or H-5), 3.20 (d, \( J = 13.4 \) Hz, H-4 or H-5), 1.08, 1.06 (2t, \( J = 7.1 \) Hz in each, 2 × CH₃CH₂).
J = 9.6, 9.2 Hz, H-2'), 3.89 (1H, pt, J = 9.2, 9.1 Hz, H-3'), 3.75-3.67 (4H, m, H-4' – H-6'a,b); 13C NMR (100 MHz, CDCl3) δ (ppm): 164.3 (C-2), 157.7 (C-4, C-6), 138.6, 138.1, 138.0, 137.9, 128.5–127.5 (aromatics), 119.9 (C-5), 87.3, 82.3, 80.8, 79.9, 78.3 (C-1' – C-5'), 75.7, 75.2, 74.6, 73.5 (4 × PhCH3), 69.1 (C-6'); ESI-MS positive mode (m/z): Calcd for C39H39N2O6+[M + H]+ 681.1959; C39H38N2NaO6+[M + Na]+ 703.1778. Found: [M + H]+ 681.1965; [M + Na]+ 703.1782.

2-(2',3',4',6'-Tetra-O-benzyl-β-D-glucopyranosyl)-pyrimidine-5-carbaldehyde (17d). Prepared from amidine 1 (200 mg, 0.33 mmol) and 2-dimethylaminomethylene-1,3-bis(dimethylimino)propane dichloror 16 (139 mg, 0.36 mmol) according to general procedure 4. Reaction time: 4 h. Purified by column chromatography (EtOAc-hexane = 1:2) to give 180 mg (86%) white solid. Mp: 80–82 °C; Rf = 0.62 (EtOAc-hexane = 1:1); [α]D = +80 (c 0.21, CHCl3); 1H NMR (400 MHz, CDCl3) δ (ppm): 10.06 (1H, s, CHO), 9.01 (2H, s, H-4, H-6), 7.36–8.84 (20H, m, aromatics), 4.94 (2H, s, PhCH3), 4.86, 4.58 (2 × 1H, 2d, J = 10.7 Hz, PhCH3), 4.65, 4.25 (2 × 1H, 2d, J = 11.6 Hz, PhCH3), 4.63 (1H, d, J = 9.5 Hz, H-1'), 4.54, 4.49 (2 × 1H, 2d, J = 12.2 Hz, PhCH3), 4.12 (1H, pt, J = 9.5, 9.3 Hz, H-2'), 3.92 (1H, pt, J = 9.2, 9.1 Hz, H-3'), 3.77-3.69 (4H, m, H-4' – H-6'); 13C NMR (100 MHz, CDCl3) δ (ppm): 188.8 (CHO), 170.3 (C-2), 158.2 (C-4, C-6), 138.6, 138.1, 138.0, 137.9, 128.6–127.5 (aromatics), 127.7 (C-5), 87.3, 82.7, 81.0, 80.0, 78.3 (C-1' – C-5'), 75.8, 75.3, 74.7, 73.6 (4 × PhCH3), 69.2 (C-6'). ESI-MS positive mode (m/z): Calcd for C39H39N2O6+[M + H]+ 631.2803; C39H38N2NaO6+[M + Na]+ 653.2622. Found: [M + H]+ 631.2806; [M + Na]+ 653.2626.

2-(2',3',4',6'-Tetra-O-benzyl-β-D-glucopyranosyl)-5-phenylpyrimidine (17e). Compound 17c (380 mg, 0.56 mmol), phenylboronic acid (136 mg, 1.12 mmol, 2 equiv.), Pd(PPh3)4Cl2 (79 mg, 0.11 mmol, 0.2 equiv.), Cs2CO3 (363 mg, 1.12 mmol, 2 equiv.), and Bu4NF (1.12 mL, 1.12 mmol, 2 equiv.), 1M solution in dry THF were heated at 100 °C in dry 1,4-dioxane (10 mL). After 16 h, the solven was removed under diminished pressure and the residue was purified by column chromatography (EtOAc-hexane = 1:2). Yield: 340 mg (90%), white amorphous solid. Rf = 0.29 (EtOAc-hexane = 1:2); [α]D = +55 (c 0.27, CH2Cl2); 1H NMR (400 MHz, CDCl3) δ (ppm): 8.86 (2H, s, H-4, H-6), 7.56–6.87 (25H, m, aromatics), 4.97, 4.94 (2 × 1H, 2d, J = 11.1 Hz, PhCH3), 4.87, 4.59 (2 × 1H, 2d, J = 10.8 Hz, PhCH3), 4.65, 4.28 (2 × 1H, 2d, J = 11.4 Hz, PhCH3), 4.63 (1H, d, J = 9.6 Hz, H-1'), 4.56, 4.50 (2 × 1H, 2d, J = 12.2 Hz, PhCH3), 4.20 (1H, pt, J = 9.6, 9.3 Hz, H-2'), 3.93 (1H, pt, J = 9.3, 9.1 Hz, H-3'), 3.80–3.72 (4H, m, H-4' – H-6'a,b); 13C NMR (100 MHz, CDCl3) δ (ppm): 157.6 (C-4, C-6), 138.6, 138.1, 138.0, 137.9, 128.6–127.5 (aromatics), 127.7 (C-5), 87.3, 82.9, 81.2, 79.8, 78.4 (C-1' – C-5'), 75.7, 75.2, 74.7, 73.5 (4 × PhCH3), 69.2 (C-6'). ESI-MS positive mode (m/z): Calcd for C39H39N2O6+[M + H]+ 679.3. Found: [M + H]+ 679.6.

Methyl 2-(2',3',4',6'-tetra-O-benzyl-β-D-glucopyranosyl)-pyrimidine-5-carboxylate (17f). To a solution of compound 17d (100 mg, 0.16 mmol) in dry CH3CN (2 mL) NIS (107 mg, 0.48 mmol, 3 equiv.), K2CO3 (67 mg, 0.48 mmol, 3 equiv.), and MeOH (32 µL, 0.79 mmol, 5 equiv.) were added. The reaction mixture was stirred at rt until the TLC (EtOAc-hexane = 2:3) showed complete transformation of the starting material (5 h). The reaction was then quenched with 10% aq. solution of Na2SO4 (10 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (10 mL), dried over MgSO4, filtered, and the solvent was removed under diminished pressure. Column chromatographic purification of the residue (EtOAc-hexane = 1:2) gave 72 mg (69%) white amorphous solid. Rf = 0.33 (EtOAc-hexane = 1:2); [α]D = +53 (c 0.20, CH2Cl2); 1H NMR (400 MHz, CDCl3) δ (ppm): 9.14 (2H, s, H-4, H-6), 7.36–8.84 (20H, m, aromatics), 4.94 (2H, s, PhCH3), 4.86, 4.58 (2 × 1H, 2d, J = 10.8 Hz, PhCH3), 4.61, 4.21 (2 × 1H, 2d, J = 11.5 Hz, PhCH3), 4.61 (1H, d, J = 9.6 Hz, H-1'), 4.55, 4.49 (2 × 1H, 2d, J = 12.2 Hz, PhCH3), 4.11 (1H, pt, J = 9.6, 9.3 Hz, H-2'), 3.99 (3H, s, OCH3), 3.91 (1H, pt, J = 9.3, 9.1 Hz, H-3'), 3.77–3.69 (4H, m, H-4' – H-6'a,b); 13C NMR (100 MHz, CDCl3) δ (ppm): 169.4, 164.1 (COOMe, C-2), 158.2 (C-4, C-6), 138.6, 138.1, 138.0, 137.8, 128.5–127.5 (aromatics), 123.1 (C-5), 87.2, 82.7, 81.0, 79.9, 78.3 (C-1' – C-5'), 75.8, 75.2, 74.7, 73.5 (4 × PhCH3), 69.1 (C-6'). ESI-MS positive mode (m/z): Calcd for C40H38BrN2O7+[M + H]+ 697.2786; Found: [M + H]+ 697.2786.

2-(6-D-Glucopyranosyl)-pyrimidine (18a). Method A: Prepared from amidine 2 (100 mg, 0.41 mmol) and 1,3-bis(dimethylamino)trimethylinium perchlorate 13 (103 mg, 0.45 mmol) according to general procedure 4. Reaction time: 16 h. Purified by column chromatography (CHCl3-MeOH = 5:1) to give
81 mg (81%) colourless syrup. Method B: Compound 17a (200 mg, 0.33 mmol) was dissolved in anhydrous CHCl₃ (10 mL). The stirred reaction mixture was cooled to −78 °C and −1M solution of BCl₃ in CH₂Cl₂ (1.7 mL, 1.7 mmol, 5 equiv.) was added. The stirring was continued at this temperature and the reaction was monitored by TLC (EtOAc-hexane = 1:2 and CHCl₃-MeOH = 3:1). After the complete disappearance of the starting material (3 h), MeOH (15 mL) was added to the reaction mixture and was left to warm to rt. The solvents were removed under diminished pressure and the residue was purified by column chromatography (CHCl₃-MeOH = 5:1) to give 68 mg (85%) colourless syrup. Rf = 0.50 (CH₃Cl-MeOH = 3:1); δC (ppm): 31.5 (C-10); δH (ppm): 8.96 (2H, s, H-4, H-6), 4.41 (1H, d, J = 9.6 Hz, H-5'), 3.70 (1H, dd, J = 12.2, 4.6 Hz, H-6'b), 3.50–3.45 (2H, m, H-3' or H-4'), 7.43 (2H, t, J = 9.1 Hz, H-3' or H-4'), 7.37 (1H, d, J = 7.1 Hz, Ph), 7.34–7.29 (3H, m, Ph), 7.16–7.09 (3H, m, Ph), 7.09–6.88 (4H, m, Ph).

5-Chloro-2-(β-D-glucopyranosyl)-pyrimidine (18b). Prepared from amidine 2 (100 mg, 0.41 mmol) and 2-chloro-1,3-bis(dimethylamino)trimethinium hexafluorophosphate 14 (139 mg, 0.45 mmol) according to general procedure 4. Reaction time: 2 h. Purified by column chromatography (CHCl₃-MeOH = 9:1) to give 112 mg (85%) white solid. Mp: 224–226 °C; Rf = 0.25 (CH₃Cl-MeOH = 5:1); δC (ppm): 31.5 (C-10); δH (ppm): 8.96 (2H, s, H-4, H-6), 4.41 (1H, d, J = 9.6 Hz, H-5'), 3.70 (1H, dd, J = 12.2, 4.6 Hz, H-6'b), 3.50–3.45 (2H, m, H-3' or H-4'), 7.43 (2H, t, J = 9.1 Hz, H-3' or H-4'), 7.37 (1H, d, J = 7.1 Hz, H-5'), 3.50–3.45 (2H, m, H-3' or H-4', H-5'); ¹³C NMR (90 MHz, CD₃OD) δ (ppm): 166.2 (C-2), 159.4 (2) (C-4, C-6), 122.2 (C-5), 83.6, 82.3, 79.3, 74.8, 71.2 (C-1' – C-5'), 62.7 (C-6'). ESI-MS positive mode (m/z): C₁₀H₁₃BrN₂NaO₅⁺ [M + Na]⁺ 299.0405. Found: 299.0407.

5-Bromo-2-(β-D-glucopyranosyl)-pyrimidine (18c). Prepared from amidine 2 (100 mg, 0.41 mmol) and 2-bromo-1,3-bis(dimethylamino)trimethinium perchlorate 15 (138 mg, 0.45 mmol) according to general procedure 4. Reaction time: 2 h. Purified by column chromatography (CHCl₃-MeOH = 9:1) to give 112 mg (85%) white solid. Mp: 224–226 °C; Rf = 0.25 (CHCl₃-MeOH = 5:1); δC (ppm): 31.5 (C-10); δH (ppm): 8.96 (2H, s, H-4, H-6), 4.41 (1H, d, J = 9.6 Hz, H-5'), 3.70 (1H, dd, J = 12.2, 4.6 Hz, H-6'b), 3.50–3.45 (2H, m, H-3' or H-4'), 7.43 (2H, t, J = 9.1 Hz, H-3' or H-4'), 7.37 (1H, d, J = 7.1 Hz, H-5'), 3.50–3.45 (2H, m, H-3' or H-4', H-5'); ¹³C NMR (90 MHz, CD₃OD) δ (ppm): 166.0 (C-2), 159.2 (2) (C-4, C-6), 120.9 (C-5), 83.7, 82.6, 79.3, 74.7, 71.4 (C-1' – C-5'), 62.8 (C-6'). ESI-MS positive mode (m/z): C₁₀H₁₃BrN₂NaO₅⁺ [M + Na]⁺ 342.9900. Found: 342.9901.

2-(β-D-Glucopyranosyl)-5-phenylpyridazine (18e). Compound 17e (200 mg, 0.29 mmol) was dissolved in anhydrous CHCl₃ (10 mL). The stirred reaction mixture was cooled to −78 °C and a −1M solution of BCl₃ in CH₂Cl₂ (1.5 mL, 1.5 mmol, 5 equiv.) was added. The stirring was continued at this temperature and the reaction was monitored by TLC (EtOAc-hexane = 1:2 and CHCl₃-MeOH = 3:1). After the complete disappearance of the starting material (2 h), MeOH (10 mL) was added to the reaction mixture and was left to warm to rt. The solvents were removed under diminished pressure and the residue was purified by column chromatography (CHCl₃-MeOH = 9:1) to give 87 mg (85%) colourless syrup. Rf = 0.50 (CHCl₃-MeOH = 3:1); δC (ppm): 31.5 (C-10); δH (ppm): 8.96 (2H, s, H-4, H-6), 7.72 (2H, d, J = 7.1 Hz, Ph), 7.56–7.46 (3H, m, Ph), 4.49 (1H, d, J = 9.5 Hz, H-1'), 3.90 (1H, dd, J = 12.1, 1.7 Hz, H-6'a), 3.81 (1H, pt, J = 9.5, 9.1 Hz, H-2'), 3.74 (1H, dd, J = 12.1, 4.8 Hz, H-6'b), 3.59 (1H, pt, J = 9.1, 9.0 Hz, H-3' or H-4'), 3.53 (1H, pt, J = 9.2, 9.0 Hz, H-3' or H-4'), 3.53–3.51 (1H, m, H-5'); ¹³C NMR (90 MHz, CD₃OD) δ (ppm): 165.5 (C-2), 156.3 (2) (C-4, C-6), 135.1, 134.9 (Ph, C-5), 130.6 (2), 130.3, 128.1 (2) (Ph), 83.6, 82.5, 79.4, 74.9, 71.3 (C-1' – C-5'), 62.9 (C-6'). ESI-MS positive mode (m/z): C₉H₈N₂NaO₅⁺ [M + Na]⁺ 341.1108. Found: 341.1108.

Methyl 2-(β-D-glucopyranosyl)-pyrimidine-5-carboxylate (18f). Compound 17f (200 mg, 0.30 mmol) was dissolved in anhydrous CHCl₃ (10 mL). The stirred reaction mixture was cooled to −78 °C and a −1M solution of BCl₃ in CH₂Cl₂ (1.5 mL, 1.51 mmol, 5 equiv.) was added. The stirring was continued at this temperature and the reaction was monitored by TLC (EtOAc-hexane = 1:2 and CHCl₃-MeOH = 3:1). After complete disappearance of the starting material (2 h), MeOH (15 mL) was added to the
reaction mixture and was left to warm to rt. The solvents were removed under diminished pressure and the residue was purified by column chromatography (CHCl₃-MeOH = 9:1) to give 74 mg (81%) colourless syrup. Rf = 0.31 (CH₃Cl-MeOH = 5:1); [α]D = +51 (c 0.22, H₂O); ¹H NMR (360 MHz, CD₃OD) δ (ppm): 9.29 (2H, s, H-4, H-6), 4.52 (1H, d, J = 9.6 Hz, H-1'), 3.99 (3H, s, OCH₃), 3.88 (1H, dd, J = 12.2, 4.6 Hz, H-6'), 3.78 (1H, dd, J = 12.2, 4.6 Hz, H-6b), 3.62–3.47 (3H, m, H-3', H-4', H-5'); ¹³C NMR (90 MHz, CD₃OD) δ (ppm): 171.0 (C=O), 165.1 (C-2), 159.3 (2) (C-4, C-6), 124.8 (C-5), 83.8, 82.5, 79.3, 74.7, 71.2 (C-1' – C-5'), 62.8 (C-6'), 53.3 (OCH₃). ESI-MS positive mode (m/z): C₁₂H₁₆N₂NaO₇+ [M + Na]+ 323.0850. Found: 323.0851.

3.2. Enzyme Assays

The inhibition of rmGPb by the test compounds was investigated with a maximal inhibitory concentration of 625 µM by applying a general protocol described earlier [17,27]. In the glycosidase assays, the inhibition experiments were made under the same conditions, except for buffer composition, substrate and enzyme concentration, which were as follows:

- β-Glucosidase from almonds (Sigma-Aldrich Kft., Budapest, Hungary): 2.5 mM PNP-β-Glc substrate in citrate-phosphate buffer pH 5.2 using 0.25 mg/mL of enzyme.
- α-Glucosidase from Saccharomyces cerevisiae (Sigma-Aldrich Kft., Budapest, Hungary): 0.5 mM PNP-α-Glc in glycerophosphate buffer pH 6.9 using 0.02 mg/mL of enzyme.
- Bovine liver β-galactosidase (Sigma-Aldrich Kft., Budapest, Hungary): 1 mM PNP-β-Gal in citrate-phosphate buffer pH 7.3 using 0.12 mg/mL of enzyme.

A 10 µL aliquot for each of the different inhibitor stock solutions was mixed with 370 µL of the buffer and 20 µL of the enzyme stock solution in a plastic UV cuvette. After equilibration at 37 °C for 5 min, a 100 µL aliquot of the substrate stock solution was added. The resulting solutions were thoroughly mixed, and the change in absorbance was followed at 400 nm over 240 s in 2 s intervals using the Parallel Kinetics Analysis program of a JASCO V550 (JASCO Tokyo, Japan) spectrophotometer. Progress curves were plotted and fitted to a straight line. ΔA/min values, proportional to initial rate, were considered to be enzyme activities. In a control experiment, the aliquot of the inhibitor solution was replaced by the same amount of buffer. The initial rate data for the enzymatic substrate hydrolysis in the presence and absence of inhibitor were transferred into percentages of overall inhibition and plotted against the inhibitor concentration in logarithmic scale for IC₅₀ determination.

4. Conclusion

New representatives of 2-C-glycopyranosyl pyrimidines, such as 2-C-(β-D-glucopyranosyl)-5,6-disubstituted-pyrimidin-4(3H)-ones, 4-amino-2-C-(β-D-glucopyranosyl)-5,6-disubstituted-pyrimidines, and 2-C-(β-D-glucopyranosyl)-5-substituted-pyrimidines were synthesized by ring-closures of O-perbenzylated and O-unprotected C-(β-D-glucopyranosyl)formamidine hydrochlorides with methylenemalonic acid derivatives or vinamidinium salts. The inhibitory activities of the resulting 5-mono- and 4,5,6-trisubstituted pyrimidines were investigated against some glycoenzymes. While none of the new compounds proved to be effective against glycogen phosphorylase and α- and β-glucosidase enzymes, some aryl and/or ester substituted derivatives displayed modest inhibitory potency against bovine liver β-galactosidase.

Author Contributions: E.S. synthesized the compounds, G.G. performed the kinetic measurements of the compounds against glycosidase enzymes. L.S. and É.B. conceived the research and wrote the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Research, Development and Innovation Office of Hungary (Grant FK125067) and the EU co-financed by the European Regional Development Fund under Projects GINOP-2.3.2-15-2016-00008 and GINOP-2.3.3-15-2016-00004. T. Doca and Á. Sipos are thanked for the kinetic assay of the new compounds against rmGPb.

Conflicts of Interest: The authors declare no conflict of interest.
References
1. Bokor, É.; Kun, S.; Goyard, D.; Totó, M.; Praly, J.P.; Vidal, S.; Somsák, L. C-Glycopyranosyl Arenes and Hetarenes: Synthetic Methods and Bioactivity Focused on Antidiabetic Potential. Chem. Rev. 2017, 117, 1687–1764.
2. Compain, P. Glycomimetics: Design, Synthesis, and Therapeutic Applications. Molecules 2018, 23, 1658.
3. Tamburri, A.; Colombo, C.; Bernardi, A. Design and synthesis of glycomimetics: Recent advances. Med. Res. Rev. 2019, 1–37.
4. Ernst, B.; Magnani, J.L. From carbohydrate leads to glycomimetic drugs. Nat. Rev. Drug Discov. 2009, 8, 661–677.
5. Goekjian, P.; Haudrechy, A.; Menhour, B.; Coiffier, C., C-Furanosides: Synthesis and Stereochemistry. 1st ed.; Academic Press: 2017.
6. Shaban, M.A.E.; Nasr, A.Y., The Chemistry of C-Nucleosides and Their Analogues. Part 1. C-Nucleosides of Hetero Monocyclic Bases. In Adv. Heterocycl. Chem., Katritzky, A.R., Ed. Academic Press, San Diego, 1997, 68, 223–432.
7. Wu, Q.; Simons, C. Synthetic Methodologies for C-Nucleosides. Synthesis 2004, 1533–1553.
8. Hocek, M.; Štambaský, J.; Kočovský, P. C-Nucleosides: Synthetic Strategies and Biological Applications. Chem. Rev. 2009, 109, 6729–6764.
9. Bouteireira, O.; Matheu, M.I.; Diaz, Y.; Castillón, S. Synthesis of C-Nucleosides. In Chemical Synthesis of Nucleoside Analogues; Merino, P., Ed. John Wiley & Sons, Inc., Hoboken, New Jersey, 2013; pp. 263–316.
10. Riley, T.A.; Hennen, W.J.; Dalley, N.K.; Wilson, B.E.; Robins, R.K.; Larson, S.B. Synthesis of 2-[β-D-ribofuranosyl]pyrimidines, A new class of C-nucleosides. J. Heterocycl. Chem. 1987, 24, 955–964.
11. Iaroshenko, V.O.; Dudkin, S.; Sosnovskikh, V.Y.; Villinger, A.; Langer, P. (β-D-Ribofuranosyl)formamidine in the Design and Synthesis of 2-(β-D-Ribofuranosyl)pyrimidines, Including RF-Containing Derivatives. Eur. J. Org. Chem. 2013, 3166–3173.
12. Togo, H.; Ishigami, S.; Fuji, M.; Ikuma, T.; Yokoyama, M. Synthesis of C-nucleosides via radical coupling reaction. J. Chem. Soc. Perkin Trans. 1 1994, 2931-2942.
13. Hoffmann, M.G.; Schmidt, R.R. O-Glycosylimidate, 19. Reaktionen von Glycosyl-trichloracetimidaten mit silylierten C-Nucleophilen. Liebig’s Ann. Chem. 1985, 2403-2419.
14. Löpfe, M.; Siegel, J.S. Diastereoselective Synthesis of 2’,3’-Dideoxy-β-C-Glucopyranosides as Intermediates for the Synthesis of 2’,3’-Dideoxy-β-D-Glycopyranosyl-C-Nucleosides. Nucleos. Nucleot. Nucl. 2007, 26, 1029–1035.
15. Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. Three-Component Biginelli Cyclocondensation Reaction Using C-Glycosylated Substrates. Preparation of a Collection of Dihydropyrimidinone Glycoconjugates and the Synthesis of C-Glycosylated Monastrol Analogues. J. Org. Chem. 2002, 67, 6979–6994.
16. Dondoni, A.; Massi, A. Design and Synthesis of New Classes of Heterocyclic C-Glycoconjugates and Carbon-Linked Sugar and Heterocyclic Amino Acids by Asymmetric Multicomponent Reactions (AMCRs). Accounts Chem. Res. 2006, 39, 451–463.
17. Szennyes, E.; Bokor, Éva; Langer, P.; Gyémánt, G.; Docsa, T.; Sipos, Ádám; Somsák, L. The first general synthesis of 2-C-[β-D-glucopyranosyl]pyrimidines and their evaluation as inhibitors of some glycoenzymes. New J. Chem. 2018, 42, 17439–17446.
18. Szennyes, E.; Bokor, Éva; Batt, A.; Docsa, T.; Gergely, P.; Somsák, L. Improved preparation of 4(S)-aryl-2-(β-D-glucopyranosyl)imidazoles, the most efficient glucose analogue inhibitors of glycosgen phosphorylase. RSC Adv. 2016, 6, 94787–94794.
19. Szennyes, E.; Bokor, É.; Kiss, A.; Somsák, L.; Pascal, Y.; Preparation of 2,6-anhydro-3,4,5,7-tetra-O-benzyl-D-glycoer-D-gulo-heptonimidamide. In Carbohydrate Chemistry: Proven Synthetic Methods, Vogel, C.; Murphy, P. V., Eds. CRC Press: Boca Raton, 2017; Vol. 4, pp 323-332.
20. Lorente, A.; Fuentes, L.; Soto, J.L.; Navio, J.L.G. Synthesis of 6-Aryl-5-isopropoxycarbonyl-4-thioxo-3,4-dihydropyrimidines from 3-Substituted Alkyl 2-Cyano-3-thiocarboxamidoprenoates. Synthesis 1985, 86–89.
21. Beukers, M.W.; Chang, L.C.W.; Künzel, J.K.V.F.D.; Mulder-Krieger, T.; Spanjersberg, R.F.; Brussee, J.; Ijzerman, A.P. New, Non-Adenosine, High-Potency Agonists for the Human Adenosine A2a Receptor with an Improved Selectivity Profile Compared to the Reference AgonistN-Ethylcarboxamidoadenosine. J. Med. Chem. 2004, 47, 3707–3709.
22. Meskini, I.; Daoudi, M.; Kerbal, A.; Bennani, B.; Sheikh, J.; Parvez, A.; Toupet, L.; Ben Hadda, T. Synthesis, characterization and coordination chemistry of substituted β-amino dicarbonyls. *J. Saudi Chem. Soc.* **2012**, *16*, 161–173.

23. Montoya-Balbás, I.J.; Valentín-Guevara, B.; López-Mendoza, E.; Linzaga-Elizalde, I.; Ordóñez, M.; Román-Bravo, P. Efficient Synthesis of β-Aryl-γ-lactams and Their Resolution with (S)-Naproxen: Preparation of (R)- and (S)-Baclofen. *Molecules* **2015**, *20*, 22028–22043.

24. Arnold, Z.; Dvořák, D.; Havranek, M. Convenient Preparation of 1,3-Bis(dimethylamino)trimethinium Perchlorate, Tetrafluoroborate and Hexafluorophosphate. *Collect. Czechoslov. Chem. Commun.* **1996**, *61*, 1637–1641.

25. Davies, I. W.; Marcoux, J. F.; Wu, J.; Palucki, M.; Corley, E. G.; Robbins, M. A.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. J., An efficient preparation of vinamidinium hexafluorophosphate salts. *J. Org. Chem.* **2000**, *65*, 4571–4574.

26. Arnold, Z. Note on the formylation of chloro- and bromoacetic acid. *Collect. Czechoslov. Chem. Commun.* **1965**, *30*, 2125–2127.

27. Oikonomakos, N.G.; Skamnaki, V.T.; Ősz, E.; Szilágyi, L.; Somsák, L.; Docsa, T.; Tóth, B.; Gergely, P. Kinetic and Crystallographic Studies of Glucopyranosylidene Spirothiohydantoin Binding to Glycogen Phosphorylase b. *Bioorgan. Med. Chem.* **2002**, *10*, 261–268.

**Sample Availability:** Samples of the compounds are not available from the authors.