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Article

# Design, Synthesis and Antifibrotic Activities of Carbohydrate-Modified 1-(Substituted aryl)-5-trifluoromethyl-2(1*H*) Pyridones

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**Abstract:** Pirfenidone, a pyridone compound, is an effective and novel antifibrotic agent. In this article, we describe the design, synthesis and activity evaluation of novel antifibrotic agents, 1-(substituted aryl)-5-trifluoromethyl-2(1*H*) pyridones modified with carbohydrate. Most of the title compounds exhibited comparable or better inhibitory activity than fluorofenidone. Notably, compound **19a** demonstrated the highest cell-based inhibitory activity against NIH 3T3 (IC<sub>50</sub> = 0.17 mM).

Keywords: antifibrotic; pirfenidone; fluorofenidone; carbohydrate modified; glucose

# 1. Introduction

Fibrosis of organs and tissues (e.g., heart, lungs, liver, kidneys, blood vessel and skin) is an important pathological change associated with many diseases that are major causes of human morbidity and mortality [1,2]. Generally, fibrosis can occur as a consequence of different pathological

conditions, such as tissue damage, inflammatory diseases, foreign implants, and tumors. It is clear that fibrosis of different organs and tissues possesses the same feature of fibroblast accumulation and excess deposition of extracellular matrix (ECM), which leads to distorted organ architecture and function [3,4]. There are various cytokines, chemokines, and growth factors involved in the development of fibrosis [5]. In spite of the increased knowledge about the pathogenesis of fibrosis and the different mediators involved, there is still no effective treatment for fibrosis.

Pirfenidone (5-methyl-1-phenyl-2(1*H*)-pyridone, Figure 1, compound **1a**), is an effective and novel antifibrotic agent that is potentially effective for the treatment of idiopathic pulmonary fibrosis (IPF) [6] that was launched in Japan in 2008. Pirfenidone can inhibit fibroblast proliferation and collagen synthesis, and it ameliorates bleomycin-induced and cyclophosphamide-induced lung fibrosis [7,8]. In order to improve the antifibrotic activity of pirfenidone, a series of pirfenidone derivatives (Figure 1) were synthesized [9–12]. Fluorofenidone (Figure 1, compound **1b**), an analogue of pirfenidone, shows equivalent antifibrotic activity, lower toxicity and longer half-life than the parent compound pirfenidone. However, the activities of pirfenidone and fluorofenidone are relatively weak; their effective doses are 500 mg/kg for the treatment of renal fibrosis in rats and the regular dose of pirfenidone for Japanese patients with IPF is 400–600 mg three-times daily [6,13]. The metabolized products have no *in vivo* activity, which could be the cause of high effective doses of pirfenidone and fluorofenidone. Replacement of the methyl group with trifluoromethyl (Figure 1) could protect the derivative from metabolism, but trifluoromethyl substitution increases lipid solubility and toxicity. Therefore, it is necessary to prepare more effective antifibrotic agents with novel chemical structures and improved water solubility.





The aim of this study was to prepare antifibrotic compounds with higher water solubility. Because carbohydrates are a kind of polyhydroxy compounds with no toxicity and high water solubility, attachment of a carbohydrate moiety should increase hydrophilicity [14]. The modification with carbohydrate also influences the pharmacokinetic properties of the modified compounds. Recent advancements in molecular glycobiology have facilitated the development of effective glycodrugs [15]. A series of *N*-substituted 1-(4-amino-2-chlorophenyl)-5-trifluoromethyl-2(1*H*) pyridones were previously synthesized and tested for NIH 3T3 inhibitory activity [10]. Therefore, we selected amines **15–19** (Table 1, R = H) as parent compounds for modification with monosaccharides. Herein, we report the design, synthesis and biological evaluation of carbohydrate-modified 1-(substituted aryl)-5-trifluoromethyl-2(1*H*) pyridones. The structures of the final target compounds are shown in Table 1. We explored the SAR using methyl 6-deoxy- $\alpha$ -D-glucopyranoside, methyl 6-deoxy- $\alpha$ -D-mannopyranoside and methyl 6-deoxy- $\beta$ -D-galactofuranoside.

|          | $F_3C$<br>NO<br>$(CH_2)_n$                    | CI<br>N                 | F <sub>3</sub> C<br>NO | F <sub>3</sub> C<br>NO |                         |
|----------|---|-------------------------|------------------------|------------------------|-------------------------|
|          | HN<br>R                                       | HN<br>R<br>R            | HN                     | R<br>H                 |                         |
|          | <b>15,15a-c</b> n =0<br><b>18,18a-c</b> n = 1 | 16, 16a-c               | 17,17 a-c              | <b>19,19a-c</b> n = 1  |                         |
| Compound | R   | IC <sub>50</sub> (mM) * | Compound               | R                      | IC <sub>50</sub> (mM) * |
| 1b       |   | 4.18                    | 18                     | Н                      | 1.31                    |
| 15a      | HO HO OCH3                                    | 3.93                    | 18a                    | HON HO OCH3            | 2.47                    |
| 15b      | HOT OCH3                                      | 5.68                    | 18b                    | нос осн осн            | 13.17                   |
| 15c      |   | 8.40                    | 18c                    |                        | 3.30                    |
| 16       | Н   | 0.46                    | 19                     | Н                      | 1.71                    |
| 16a      | HO OCH3                                       | N.D. <sup>a</sup>       | 19a                    | HO HO OCH3             | 0.17                    |
| 16b      | HOTO  | 1.13                    | 19b                    | HOTO                   | 0.79                    |
| 16c      | OCH3<br>OCH3<br>OH OH                         | N.D. <sup>a</sup>       | 19c                    |                        | 0.84                    |
| 17a      | HOTHO OCH3                                    | 2.63                    |                        |                        |                         |
| 17b      | HO<br>HO<br>OCH <sub>3</sub>                  | 5.81                    |                        |                        |                         |
| 17c      |   | 0.42                    |                        |                        |                         |

Table 1. NIH 3T3 inhibitory activity.

\* p < 0.05; <sup>a</sup> N.D.: not determined.

# 2. Results and Discussion

The preparation of methyl 2,3,4-tri-*O*-acetyl-6-aldehydo- $\alpha$ -D-gluco-hexodialdo-1,5-pyranoside (**8**) and methyl 2,3,4-tri-*O*-acetyl-6-aldehydo- $\alpha$ -D-manno-hexodialdo-1,5-pyranoside (**12**) is described in Scheme 1. Methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl- $\alpha$ -D-glucopyranoside (**6**) was prepared directly from methyl  $\alpha$ -D-glucopyranoside in two steps. Removal of trityl protection was accomplished by treatment with boron trifluoride etherate in methanol and methylene chloride to produce compound **7** [16]. Subsequently selective oxidation of a primary hydroxyl group to an aldehydo group was performed at room temperature with a mild oxidation reagent, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and [bis(acetoxy)iodo]benzene (BAIB) [17]. Using the same method, compound **12** was obtained from

methyl  $\alpha$ -D-mannopyranoside 9. Galactose aldehyde can be prepared with a isopropylidene moiety as a protective group (Scheme 1). Isopropylidenation of D-galactose with sulfuric acid-copper sulfate as catalyst in acetone produced 1,2;3,4-di-*O*-isopropylidene-D-galactose (13) in 58.3% yield [18]. The conversion of compound 13 to 14 was performed with the same method used in the conversion of compound 7 to 8. The structure of compounds 7–8 and 11–14 were in accordance with their reported spectroscopic data [19–21].





*Reagents and conditions*: (a) Ph<sub>3</sub>CCl, DMAP, pyridine, 60 °C, 5 h; (b) Ac<sub>2</sub>O, rt, 2 h; (c) BF<sub>3</sub>-Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h; (d) TEMPO, BAIB, CH<sub>2</sub>Cl<sub>2</sub>, rt, overnight.

The synthesis of **15a-19a** and **15b-19b** is shown in Scheme 2. Nucleophilic addition of the aldehyde **8** or **12** with amine **15–19** [10] in methanol and acetic acid followed by dehydration produced the corresponding imines, which were further reduced with sodium cyanoborohydride to give the corresponding secondary amines [22]. Amines were converted to the desired compounds **15a-19a** and **15b–19b** by treatment with sodium methoxide in methanol. The synthesis of **15c–19c** is also described in Scheme 2. Using the same method [22], secondary amines **14a–e** were prepared. Treatment of **14a–e** with a solution of 0.5 M HCl/CH<sub>3</sub>OH under room temperature, caused removal of the isopropylidene groups and the formation of methyl  $\beta$ -D-galactofuranosides **15c–19c** as the main product. Under these conditions, deprotection of **14a** also gave a minor amount of the corresponding galactopyranoside (<1%).

Scheme 2. Synthesis of compounds 15a-19a, 15b-19b and 15c-19c.



*Reagents and conditions:* (a) HOAc, CH<sub>3</sub>OH, 0.5 h, then NaCNBH<sub>3</sub>, 2 h; (b) 0.05 M NaOCH<sub>3</sub>/CH<sub>3</sub>OH, rt, 1 h; (c) HOAc, CH<sub>3</sub>OH, 0.5h, then NaCNBH<sub>3</sub>, 2h; (d) 0.5 M HCl/CH<sub>3</sub>OH, rt, 12 h.

#### Biological Assay

A cell-based fibrosis inhibition assay was performed to evaluate the inhibitory effects of the prepared compounds on NIH 3T3 cells. NIH 3T3 (mouse embryonic lung fibroblast, State Key Laboratory of Genetics) cells were seeded on 96-well plates (Costar) in DMEM containing 10% NBS  $(3 \times 10^4 \text{ cell per well in 100 } \mu\text{L} \text{ medium})$  in humidified air with 5% CO<sub>2</sub> at 37 °C. Different concentrations of test compounds and fluorofenidone were added to the medium, and DMSO was used as a solvent for the test compounds and fluorofenidone, which were applied at a final concentration of 0.1% (v/v) in cell culture medium. Cells were then incubated for 48 hours, followed by detecting with MTT spectrophotometry. Briefly, 5 mg/mL MTT (100  $\mu$ L) was added to each well, and incubated for 4 hours at 37 °C. All liquid in each well was then discarded and DMSO (150  $\mu$ L) was added. The OD at 570 nm was detected by spectrometry. IC<sub>50</sub> was determined by nonlinear regression analysis using GraphPad PRISM.

Of the aryl amines connected with a carbohydrate that were tested, compound **19a** exhibited the highest inhibitory activity against NIH 3T3 (IC<sub>50</sub> = 0.17 mM) among the five aryl amines modified with glucose. When the carbohydrate moiety was mannose, **19b** appeared to have the highest inhibitory activity (IC<sub>50</sub> = 0.79 mM). When the carbohydrate moiety was galactose, **17c** demonstrated the highest inhibitory activity (IC<sub>50</sub> = 0.42 mM), while **19c** showed two-fold lower inhibitory activity (IC<sub>50</sub> = 0.84 mM) than **17c**. Thus, among the five aryl amines that were modified with carbohydrate, **19** yielded more active compounds than the other aryl amines.

The same aryl amine-type compounds were also explored. Compound **15a** demonstrated better inhibitory activity than **15b** and **15c** ( $IC_{50} = 3.93 \text{ mM}$  for **15a**,  $IC_{50} = 5.68 \text{ mM}$  for **15b**,  $IC_{50} = 8.40 \text{ mM}$  for **15c**); compound **17c** showed the highest inhibitory activity among compounds **17a–c** ( $IC_{50} = 2.63 \text{ mM}$  for **17a**,  $IC_{50} = 5.81 \text{ mM}$  for **17b**,  $IC_{50} = 0.42 \text{ mM}$  for **17c**); compound **18a** appeared to have significantly higher activity than **18b** and slightly better activity than **18c** in NIH 3T3 inhibition ( $IC_{50} = 2.47 \text{ mM}$  for **18a**,  $IC_{50} = 13.17 \text{ mM}$  for **18b**,  $IC_{50} = 3.30 \text{ mM}$  for **19a**,  $IC_{50} = 0.79 \text{ mM}$  for **19b**,  $IC_{50} = 0.84 \text{ mM}$  for **19c**). These results indicate that among the three carbohydrates used for the modification of pirfenidone analogues, glucose appeared to be a better candidate (e.g., **19a**,  $IC_{50} = 0.17 \text{ mM}$ ), although some compounds that were modified with galactose also had high inhibitory activity (e.g., **17c**,  $IC_{50} = 0.42 \text{ mM}$ ).

Compounds 17, 18, and 19 differ in the NHR (R= various carbohydrate moieties) positions. When NHR was modified at the *ortho* position, the antifibrotic activities of all three compounds were increased, especially compound 19a which showed ten-fold higher activity compared with compound 19 (R = H); when NHR was modified at the *para* position, the antifibrotic activities were decreased; when NHR was modified at the *meta* position, compound 17c showed better antifibrotic activities compared with 17a and 17b. Among these compounds, compound 19a, that is NHR modified with glucose at the *ortho* position, exhibited the highest antifibrotic activity.

When a CH<sub>2</sub> group was used to link the substituted phenyl ring with 5-trifluoromethyl-2(1H)-pyridone (Table 1, compounds **18a–c** and **19a–c**), some of the resulting products showed obviously higher NIH 3T3 inhibitory activities (Table 1, compound **19a–c**), perhaps due to the increased flexibility between two substituted aryl rings.

Some modifications of pirfenidone analogues with different monosaccharides appeared to increase the inhibitory activity. For example, compounds **19a–c**, which were prepared by modification of pirfenidone analogue **19** with a carbohydrate ring, showed a significant increase of inhibitory activity in NIH 3T3 cells. Compound **19a** demonstrated ten-fold higher activity compared with pirfenidone analogue **19**, but modifications of **16** and **18** with carbohydrates led to decreases in inhibitory activities against NIH 3T3 cells.

## 3. Experimental

## 3.1. General

Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. Solvents were purified following standard literature procedures. Analytical TLC was performed on silica gel60  $F_{254}$  precoated on glass plates, with detection by fluorescence and/or by staining with 5% concentrated sulphuric acid in EtOH. <sup>1</sup>H- (400 MHz) and <sup>13</sup>C-NMR spectra (100 MHz) were recorded on a Bruker DRX-400 spectrometer at 25 °C. Chemical shifts ( $\delta$ ) for <sup>1</sup>H and <sup>13</sup>C spectra are expressed in ppm relative to internal Me<sub>4</sub>Si as standard. Signals were abbreviated as s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Sugar signals were numbered as customary. ESI mass spectra and high resolution mass spectrometry (HRMS) were recorded using an Agilent Technologies 1100 Series instrument (ESI ionization). Optical rotations were measured in a 1.00 dm tube with an Optical Activity AA-10R polarimeter in methanol or chloroform.

#### 3.2. General Procedure for the Synthesis of Compounds 14a-e

Amine (compounds 15–19, 0.5 mmol) was added to a solution of compounds 14 (155 mg, 0.6 mmol) in dry methanol (2 mL) and acetic acid (1.5 mL) under stirring and under a nitrogen atmosphere at room temperature. After 10 min NaCNBH<sub>3</sub> (40 mg, 0.6 mmol) was added. The solution was stirred at room temperature for 30 min. After completion of the reaction (TLC 3:1 petroleum ether b.p. 60-90 °C-EtOAc), the methanol was evaporated under reduced pressure, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and washed with saturated NaHCO<sub>3</sub> (3 × 5 mL) and with water (5 mL). The organic phase was dried over sodium sulphate and the solvent was evaporated under reduced pressure to give a crude mass which was purified by flash chromatography (4:1 petroleum ether b.p. 60–90 °C-EtOAc).

1,2;3,4-di-O-Isopropylidene-6-deoxy-6-(4-(5-trifluoromethyl-2(1H)-pyridone-1-yl)-anilino)-α-Dgalactopyranose (14a). Compound 15 (127 mg, 0.5 mmol) was used to prepare compound 14a (205 mg, 82.3%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –75 (c 0.10, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.72 (s, 1H), 7.46 (dd,  $J_1 = 2.8$  Hz,  $J_2 = 9.6$  Hz, 1H), 7.15–7.13 (m, 2H), 6.73–6.68 (m, 3H), 5.56 (d, J = 5.2 Hz, 1H, H-1), 4.64 (dd,  $J_1 = 2.4$  Hz,  $J_2 = 8.0$  Hz, 1H, H-3), 4.34 (dd,  $J_1 = 2.4$  Hz,  $J_2 = 5.2$  Hz, 1H, H-2), 4.26 (dd,  $J_1 = 2.0$  Hz,  $J_2 = 8.0$  Hz, 1H, H-4), 4.04–4.00 (m, 1H, H-5), 3.40–3.37 (m, 2H, H-6), 1.48 (s, 3H, CH<sub>3</sub>), 1.44 (s, 3H, CH<sub>3</sub>), 1.37 (s, 3H, CH<sub>3</sub>), 1.33 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR(CDCl<sub>3</sub>): δ 162.1 (C=O), 148.7, 138.3, 138.2, 135.0, 129.7, 122.0, 113.2, 109.5, 109.1, 108.7, 96.4 (C-1), 71.6, 70.8, 70.6 and 65.7 (C-2, C-3, C-4, C-5), 43.9 (C-6), 26.0 (CH<sub>3</sub>), 26.0 (CH<sub>3</sub>), 24.9 (CH<sub>3</sub>), 24.4 (CH<sub>3</sub>); ESI-MS: Calcd for  $C_{24}H_{27}N_2O_6F_3$ : 497.2[M+H]<sup>+</sup>, found: 497.2[M+H]<sup>+</sup>.

1,2;3,4-di-O-Isopropylidene-6-deoxy-6-(3-chloro-4-(5-trifluoromethyl-2(1H)-pyridone-1-yl)-anilino)-  $\alpha$ -D-galactopyranose (14b). Compound 16 (145 mg, 0.5 mmol) was used to prepare compound 14b (195 mg, 73.6%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –59 (c 0.10, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.58 (s, 1H), 7.51 (dd,  $J_1 = 2.8$  Hz,  $J_2 = 9.6$  Hz, 1H), 7.10 (dd,  $J_1 = 1.6$  Hz,  $J_2 = 8.8$  Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 6.71 (d, J = 2.8 Hz, 1H), 6.63–6.60 (m, 1H), 5.56 (d, J = 5.2 Hz, 1H, H-1), 4.64 (dd,  $J_1 = 2.4$  Hz,  $J_2 = 8.0$  Hz, 1H, H-3), 4.35 (dd,  $J_1 = 2.4$  Hz,  $J_2 = 5.2$  Hz, 1H, H-2), 4.26 (dd,  $J_1 = 2.0$  Hz,  $J_2 = 8.0$  Hz, 1H, H-4), 4.02–3.99 (m, 1H, H-5), 3.38–3.35 (m, 2H, H-6), 1.48 (s, 3H, CH<sub>3</sub>), 1.47 (s, 3H, CH<sub>3</sub>), 1.37 (s, 3H, CH<sub>3</sub>), 1.34 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta$  161.7 (C=O), 150.0, 138.7, 135.5, 132.0, 129.2, 126.5, 122.3, 113.3, 112.2, 112.1, 109.6, 108.8, 96.4 (C-1), 71.6, 70.8, 70.6 and 65.6 (C-2, C-3, C-4, C-5), 43.8 (C-6), 26.0 (CH<sub>3</sub>), 24.9 (CH<sub>3</sub>), 24.4 (CH<sub>3</sub>); ESI-MS: Calcd for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>Cl: 531.2 [M+H]<sup>+</sup>, found: 531.1 [M+H]<sup>+</sup>.

1,2;3,4-di-O-Isopropylidene-6-deoxy-6-(3-(5-trifluoromethyl-2(1H)-pyridone-1-yl-methylene)-anilino) -α-D-galactopyranose (14c). Compound 17 (135 mg, 0.5 mmol) was used to prepare compound 14c (192 mg, 75.3%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –47 (c 0.10, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.63 (s, 1H), 7.41 (d, J = 1.6 Hz, 1H), 7.18–7.14 (m, 1H), 6.67–6.59 (m, 4H), 5.54 (d, J = 4.8 Hz, 1H, H-1), 5.04 (m, 2H, CH<sub>2</sub>), 4.62 (dd,  $J_1 = 1.6$  Hz,  $J_2 = 8.0$  Hz, 1H, H-3), 4.33 (t, J = 2.4 Hz, 1H, H-2), 4.25 (d, J = 7.6 Hz, 1H, H-4), 3.98 (d, J = 4.8 Hz, 1H, H-5), 3.40–3.29 (m, 2H, H-6), 1.47 (s, 3H, CH<sub>3</sub>), 1.37 (s, 3H, CH<sub>3</sub>), 1.36 (s, 3H, CH<sub>3</sub>), 1.31 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 161.9 (C=O), 148.8, 136.7, 136.1, 134.8, 130.0, 121.5, 117.3, 113.1, 109.5, 108.7, 96.4 (C-1), 71.7, 70.8, 70.6 and 65.7 (C-2, C-3, C-4, C-5), 52.3 (CH<sub>2</sub>), 43.9 (C-6), 26.0 (CH<sub>3</sub>), 25.8 (CH<sub>3</sub>), 24.9 (CH<sub>3</sub>), 24.4 (CH<sub>3</sub>); ESI-MS: Calcd for C<sub>25</sub>H<sub>29</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 511.2 [M+H]<sup>+</sup>, found: 511.2 [M+H]<sup>+</sup>.

*1,2;3,4-di-O-Isopropylidene-6-*deoxy-*6-(4-(5-trifluoromethyl-2(1*H)*-pyridone-1-yl-methylene)-anilino)* -*α-D-galactopyranose* (**14d**). Compound **18** (135 mg, 0.5 mmol) was used to prepare compound **14d** (207 mg, 81.2%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –68 (c 0.10, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.60 (s, 1H), 7.39 (dd,  $J_1 = 2.0$  Hz,  $J_2 = 9.6$  Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.65–6.62 (m, 3H), 5.54 (d, J = 4.8 Hz, 1H, H-1), 5.00 (s, 2H, CH<sub>2</sub>), 4.62 (dd,  $J_1 = 2.0$  Hz,  $J_2 = 8.0$  Hz, 1H, H-3), 4.33–4.31 (m, 1H, H-2), 4.25–4.23 (m, 1H, H-4), 3.99 (t, J = 6.0 Hz, 1H, H-5), 3.41–3.30 (m, 2H, H-6), 1.47 (s, 3H, CH<sub>3</sub>), 1.36 (s, 3H, CH<sub>3</sub>), 1.33 (s, 3H, CH<sub>3</sub>), 1.30 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta$  162.0 (C=O), 148.4, 136.4, 136.3, 134.7, 134.6, 130.1, 123.5, 121.4, 113.6, 109.5, 108.7, 96.4 (C-1), 71.7, 70.8, 70.6 and 65.6 (C-2, C-3, C-4, C-5), 52.1 (CH<sub>2</sub>), 43.9 (C-6), 26.0 (CH<sub>3</sub>), 25.7 (CH<sub>3</sub>), 24.9 (CH<sub>3</sub>), 24.4 (CH<sub>3</sub>); ESI-MS: Calcd for C<sub>25</sub>H<sub>29</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 511.2 [M+H]<sup>+</sup>, found: 511.2 [M+H]<sup>+</sup>.

1,2;3,4-di-O-Isopropylidene-6-deoxy-6-(2-(5-trifluoromethyl-2(1H)-pyridone-1-yl-methylene)anilino)-α-D-galactopyranose (14e). Compound 19 (135 mg, 0.5 mmol) was used to prepare compound 14e (210 mg, 82.4%) as a colorless syrup;  $[\alpha]^{25}{}_{D}$  –62 (c 0.10, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.68 (s, 1H), 7.42 (dd,  $J_1$  = 2.0 Hz,  $J_2$  = 9.6 Hz, 1H), 7.25 (m, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.72–6.64 (m, 3H), 5.44 (d, J = 5.2 Hz, 1H, H-1), 5.20–4.95 (m, 2H, CH<sub>2</sub>), 4.57 (dd,  $J_1$  = 2.0 Hz,  $J_2$  = 8.0 Hz, 1H H-3), 4.27 (dd,  $J_1$  = 2.0 Hz,  $J_2$  = 5.2 Hz, 1H H-2), 4.21 (d, J = 8.8 Hz, 1H, H-4), 3.94 (t, J = 6.4 Hz, 1H, H-5), 3.50–3.43 (m, 1H, H-6), 3.36–3.31 (m, 1H, H-6), 1.47 (s, 3H, CH<sub>3</sub>), 1.34 (s, 3H, CH<sub>3</sub>), 1.26 (d, 6H, 2xCH<sub>3</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta$  162.4 (C=O), 146.6, 136.1, 136.1, 135.0, 131.3, 130.5, 121.3, 119.3, 116.9, 111.6, 110.3, 109.3, 108.5, 96.4 (C-1), 71.4, 70.8, 70.6 and 65.1 (C-2, C-3, C-4, C-5), 49.1 (CH<sub>2</sub>), 43.6 (C-6), 26.0 (CH<sub>3</sub>), 25.6 (CH<sub>3</sub>), 24.9 (CH<sub>3</sub>), 24.4 (CH<sub>3</sub>); ESI-MS: Calcd for C<sub>25</sub>H<sub>29</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 511.2 [M+H]<sup>+</sup>, found: 511.2 [M+H]<sup>+</sup>.

## 3.3. General Procedure for the Synthesis of Compounds 15a-19a and 15b-19b

Amine (compound **15–19**, 0.5 mmol) was added to a solution of compounds **8** or **12** (0.6 mmol) in dry methanol (2 ml) and acetic acid (1.5 mL) under stirring and under nitrogen atmosphere at room temperature. After 10 min NaCNBH<sub>3</sub> (40 mg, 0.6 mmol) was added. The solution was stirred at room temperature for 30 min. After completion of the reaction (TLC 3:1 petroleum ether b.p. 60–90 °C-EtOAc), the methanol was evaporated under reduced pressure, the reaction mixture was diluted with  $CH_2Cl_2$  (5 mL) and washed with saturated NaHCO<sub>3</sub> (3 × 5 mL) and with water (5 mL). The organic phase was dried over sodium sulphate and the solvent was evaporated under reduced pressure to give a crude mass which was dissolved in 0.05 M NaOMe/MeOH (5 mL) and stirred at ambient temperature for 30 min. The stirring reaction mixture was neutralized with prewashed Amberlite IR 120-H<sup>+</sup>. The resin was filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (7:1 CHCl<sub>3</sub>-MeOH).

*Methyl* 6-*deoxy*-6-(4-(5-*trifluoromethyl*-2(1H)-*pyridone*-1-*yl*)-*anilino*)- $\alpha$ -*D*-*glucopyranoside* (15a). Compound 15 (127 mg, 0.5 mmol) and 8 (190 mg, 0.6 mmol) were used to prepare compound 15a (143 mg, 66.5%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –63 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-*d*<sub>4</sub>)  $\delta$  7.97 (s, 1H), 7.66 (dd,  $J_1 = 2.4$  Hz,  $J_2 = 9.6$  Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 9.2 Hz, 1H), 4.62 (d, J = 3.6 Hz, 1H, H-1), 3.71–3.63 (m, 1H), 3.59–3.55 (m, 2H), 3.38–3.35 (m, 1H), 3.28 (s, 3H), 3.22–3.17 (m, 2H); <sup>13</sup>C-NMR (MeOH-*d*<sub>4</sub>)  $\delta$  164.5 (C=O), 151.0, 140.6, 140.5, 137.3, 130.3, 128.1, 122.2, 113.6, 101.2 (C-1), 75.1, 73.6, 73.5 and 71.4 (C-2, C-3, C-4, C-5), 55.5 (OCH<sub>3</sub>), 45.7 (C-6); HRMS: Calcd for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub> [M+H]<sup>+</sup> 431.1431, found 431.1425.

*Methyl* 6-*deoxy*-6-(3-*chloro*-4-(5-*trifluoromethyl*-2(1H)-*pyridone*-1-*yl*)-*anilino*)- $\alpha$ -*D*-glucopyranoside (16a). Compound 16 (145 mg, 0.5 mmol) and 8 (190 mg, 0.6 mmol) were used to prepare compound 16 (152 mg, 65.5%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –34 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  7.92 (s, 1H), 7.70 (dd,  $J_1$  = 2.8 Hz,  $J_2$  = 9.6 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 6.84 (m, 1H), 6.68 (m, 2H), 4.62 (d, J = 3.6 Hz, 1H, H-1), 3.63–3.60 (m, 1H), 3.59–3.51 (m, 2H), 3.38–3.34 (m, 1H), 3.29 (s, 3H, OCH<sub>3</sub>), 3.26–3.17 (m, 3H); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  164.1 (C=O), 152.5, 141.2, 137.8, 132.7, 130.2, 126.7, 122.5, 113.8, 112.8, 101.2 (C-1), 75.1, 73.6, 73.3 and 71.6 (C-2, C-3, C-4, C-5), 55.6 (OCH<sub>3</sub>), 45.5 (C-6); HRMS: Calcd for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>Cl: 465.1041 [M+H]<sup>+</sup>, found: 465.1038 [M+H]<sup>+</sup>.

*Methyl 6-deoxy-6-(3-(5-trifluoromethyl-2(1*H)*-pyridone-1-yl-methylene)-anilino)-* $\alpha$ *-D-glucopyranoside* (17a). Compound 17 (135 mg, 0.5 mmol) and 8 (190 mg, 0.6 mmol) were used to prepare compound 17a (150 mg, 67.6%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –45 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  8.06 (s, 1H), 7.55 (dd,  $J_1 = 2.4$  Hz,  $J_2 = 9.6$  Hz, 1H), 7.02 (t, J = 8.0 Hz, 1H), 6.61–6.58 (m, 3H), 6.49 (d, J = 7.6 Hz, 1H), 5.03 (s, 2H, CH<sub>2</sub>), 4.57 (d, J = 2.8 Hz, 1H, H-1), 3.62–3.48 (m, 3H), 3.35–3.12 (m,

1H), 3.16 (s, 3H, OCH<sub>3</sub>), 3.19–3.06 (m, 2H); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  161.2 (C=O), 147.8, 136.6, 136.6, 135.0, 134.1, 127.8, 123.3, 120.6, 118.9, 114.6, 111.3, 111.0, 108.7, 108.4, 98.2 (C-1), 72.2, 70.7, 70.7 and 68.19 (C-2, C-3, C-4, C-5), 52.5 (OCH<sub>3</sub>), 50.9 (CH<sub>2</sub>), 43.0 (C-6); HRMS: Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 445.1587 [M+H]<sup>+</sup>, found: 445.1583 [M+H]<sup>+</sup>.

*Methyl 6-deoxy-6-(4-(5-trifluoromethyl-2(1H)-pyridone-1-yl-methylene)-anilino)-* $\alpha$ -*D-glucopyranoside* (**18a**). Compound **18** (135 mg, 0.5 mmol) and **8** (190 mg, 0.6 mmol) were used to prepare compound **18a** (155 mg, 69.8%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –54 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  8.03 (s, 1H), 7.54 (dd,  $J_1 = 2.8$  Hz,  $J_2 = 9.6$  Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 4.4 Hz, 2H), 6.56 (d, J = 9.6 Hz, 1H), 4.98 (s, 2H, CH<sub>2</sub>), 4.57 (d, J = 3.6 Hz, 1H, H-1), 3.63–3.58 (m, 1H), 3.55–3.49 (m, 2H), 3.34–3.31 (m, 1H), 3.24–3.23 (m, 1H), 3.18 (s, 3H, OCH<sub>3</sub>), 3.15–3.06 (m, 2H); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  162.8 (C=O), 148.9, 137.7, 137.7, 135.5, 129.3, 123.5, 120.3, 113.1, 99.8 (C-1), 73.7, 72.2, 72.2 and 69.6 (C-2, C-3, C-4, C-5), 54.0 (OCH<sub>3</sub>), 52.1 (CH<sub>2</sub>), 44.5 (C-6); HRMS: Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 467.1400 [M+Na]<sup>+</sup>, found: 465.1391 [M+Na]<sup>+</sup>.

*Methyl 6-deoxy-6-(2-(5-trifluoromethyl-2(1*H)*-pyridone-1-yl-methylene)-anilino)-* $\alpha$ *-D-glucopyranoside* (19a). Compound 19 (135 mg, 0.5 mmol) and 8 (190 mg, 0.6 mmol) were used to prepare compound 19a (147 mg, 66.2%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –57 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  7.90 (s, 1H), 7.55 (dd,  $J_1 = 1.6$  Hz,  $J_2 = 7.6$  Hz, 1H), 7.15 (m, 2H), 6.70 (d, J = 8.0 Hz, 1H), 6.61 (m, 2H), 5.06 (m, 2H, CH<sub>2</sub>), 4.51 (d, J = 3.6 Hz, 1H, H-1), 3.67–3.59 (m, 1H), 3.52–3.47 (m, 2H), 3.37–3.31 (m, 1H), 3.22 (s, 1H), 3.16–3.10 (m, 2H), 3.02 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  162.9 (C=O), 146.6, 137.0, 137.0, 135.6, 131.0, 130.0, 127.3, 120.3, 119.5, 116.6, 111.1, 110.6, 99.8 (C-1), 73.7, 72.2, 72.1 and 69.0 (C-2, C-3, C-4, C-5), 54.0 (OCH<sub>3</sub>), 48.2 (CH<sub>2</sub>), 44.2 (C-6); HRMS: Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 445.1587 [M+H]<sup>+</sup>, found: 445.1586 [M+H]<sup>+</sup>.

*Methyl* 6-*deoxy*-6-(4-(5-*trifluoromethyl*-2(1H)-*pyridone*-1-*yl*)-*anilino*)- $\alpha$ -*D*-*mannopyranoside* (15b). Compound 15 (127 mg, 0.5 mmol) and 12 (190 mg, 0.6 mmol) were used to prepare compound 15b (140 mg, 65.1%) as a colorless syrup;  $[\alpha]^{25}_{D}$  +82 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  7.98 (s, 1H), 7.67 (dd,  $J_1 = 2.4$  Hz,  $J_2 = 9.6$  Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 9.2 Hz, 1H), 4.61 (d, J = 1.2 Hz, 1H, H-1), 3.76 (s, 1H), 3.64–3.59 (m, 3H), 3.54–3.51 (m, 1H), 3.32–3.28 (m, 1H), 3.26 (s, 3H, OCH<sub>3</sub>), <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  164.5 (C=O), 151.0, 140.6, 140.5, 140.5, 137.3, 130.2, 128.1, 126.2, 123.6, 122.2, 113.0, 111.5, 111.1, 102.8(C-1), 72.6, 72.1, 72.1 and 69.9 (C-2, C-3, C-4, C-5), 55.2 (OCH<sub>3</sub>), 45.5 (C-6); HRMS: Calcd for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 431.1431 [M+H]<sup>+</sup>, found: 431.1425 [M+H]<sup>+</sup>.

*Methyl* 6-*deoxy*-6-(3-*chloro*-4-(5-*trifluoromethyl*-2(1H)-*pyridone*-1-*yl*)-*anilino*)- $\alpha$ -*D*-*mannopyranoside* (**16b**). Compound **16** (145 mg, 0.5 mmol) and **12** (190 mg, 0.6 mmol) were used to prepare compound **16b** (145 mg, 62.5%) as a colorless syrup;  $[\alpha]^{25}_{D}$ -59 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  7.93 (s, 1H), 7.71 (dd,  $J_1$  = 2.4 Hz,  $J_2$  = 9.6 Hz, 1H), 7.09 (d, J = 2.2 Hz, 2H), 6.84 (dd,  $J_1$  = 0.4 Hz,  $J_2$  = 1.6 Hz, 1H), 6.71–6.66 (m, 2H), 4.60 (d, J = 1.6 Hz, 1H, H-1), 3.76 (s, 1H), 3.64–3.57 (m, 3H), 3.52–3.48 (m, 1H), 3.30–3.26 (m, 2H), 3.28 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  162.7 (C=O), 151.1, 139.8, 139.7, 136.4, 131.3, 128.8, 125.3, 124.7, 122.1, 121.1, 112.3, 111.4, 111.4, 110.2, 109.9, 101.4 (C-1),

71.2, 70.9, 70.7 and 68.4 (C-2, C-3, C-4, C-5), 53.9 (OCH<sub>3</sub>), 43.8 (C-6); HRMS: Calcd for  $C_{19}H_{21}N_2O_6F_3Cl$ : 465.1041 [M+H]<sup>+</sup>, found: 465.1039 [M+H]<sup>+</sup>.

*Methyl 6-deoxy-6-(3-(5-trifluoromethyl-2(1*H)*-pyridone-1-yl-methylene)-anilino)-α-D-mannopyranoside* (17b). Compound 17 (135 mg, 0.5 mmol) and 12 (190 mg, 0.6 mmol) were used to prepare compound 17b (154 mg, 69.4%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –83 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  8.08 (s, 1H), 7.60 (dd,  $J_1 = 2.8$  Hz,  $J_2 = 9.6$  Hz, 1H), 7.06 (dd,  $J_1 = 7.6$  Hz,  $J_2 = 8.0$  Hz, 1H), 6.63–6.60 (m, 3H), 6.52 (d, J = 7.2 Hz, 1H), 5.07 (s, 2H, CH<sub>2</sub>), 4.57 (d, J = 1.6 Hz, 1H, H-1), 3.74 (t, 1H), 3.62–3.56 (m, 3H), 3.49–3.46 (m, 1H), 3.27–3.25 (m, 1H), 3.17 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  162.7 (C=O), 149.3, 138.1, 136.5, 135.7, 129.3, 124.8, 120.4, 116.0, 112.7, 112.3, 110.2, 109.9, 101.3 (C-1), 71.2, 70.7, 70.3 and 68.6 (C-2, C-3, C-4, C-5), 53.7 (OCH<sub>3</sub>), 52.4 (CH<sub>2</sub>), 44.2 (C-6); HRMS: Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 445.1587 [M+H]<sup>+</sup>, found: 445.1585 [M+H]<sup>+</sup>.

*Methyl 6-deoxy-6-(4-(5-trifluoromethyl-2(1*H)*-pyridone-1-yl-methylene)-anilino)-α-D-mannopyranoside* (18b). Compound 18 (135 mg, 0.5 mmol) and 12 (190 mg, 0.6 mmol) were used to prepare compound 18b (150 mg, 67.6%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –67 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  8.06 (s, 1H), 7.58 (dd,  $J_1 = 2.8$  Hz,  $J_2 = 2.4$  Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 9.6 Hz, 1H), 5.01 (s, 2H, CH<sub>2</sub>), 4.57 (d, J = 1.6 Hz, 1H, H-1), 3.73 (t, 1H), 3.61–3.55 (m, 3H), 3.51–3.46 (m, 1H), 3.27–3.25 (m, 3H), 3.19 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  164.2 (C=O), 150.4, 139.1, 136.9,130.7, 126.2, 124.9, 123.5, 121.7, 114.4, 111.6, 111.2, 102.7 (C-1), 72.6, 72.1, 71.8 and 70.1 (C-2, C-3, C-4, C-5), 55.1 (OCH<sub>3</sub>), 53.5 (CH<sub>2</sub>), 45.7 (C-6); HRMS: Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 445.1587 [M+H]<sup>+</sup>, found: 445.1589 [M+H]<sup>+</sup>.

*Methyl 6-deoxy-6-(2-(5-trifluoromethyl-2(1*H)*-pyridone-1-yl-methylene)-anilino)-α-D-mannopyranoside* (19b). Compound 19 (135 mg, 0.5 mmol) and 12 (190 mg, 0.6 mmol) were used to prepare compound 19b (151 mg, 68.0%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –72 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  7.95 (s, 1H), 7.58 (d, J = 9.6 Hz 1H), 7.23–7.17 (m, 2H), 6.72–6.70 (m, 2H), 6.65 (t, J = 7.6 Hz, 1H), 5.19–5.09 (m, 2H, CH<sub>2</sub>), 4.62 (s, 1H, H-1), 3.75 (s, 1H), 3.69–3.60 (m, 3H), 3.46–3.42 (m, 1H), 3.34–3.27 (m, 2H), 3.14 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  163.0 (C=O), 146.7, 137.1, 137.0, 136.9, 135.7, 130.9, 130.1, 124.6, 121.9, 120.2, 119.5, 116.5, 110.9, 110.9, 110.6, 101.5(C-1), 71.3, 71.0, 70.0 and 68.5 (C-2, C-3, C-4, C-5), 53.8 (OCH<sub>3</sub>), 43.8 (C-6); HRMS: Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 445.1587 [M+H]<sup>+</sup>, found: 445.1581 [M+H]<sup>+</sup>.

#### 3.4. General Procedure for the Synthesis of Compounds 15c–19c

Compound **14a–e** (0.2 mmol) was added to a solution of 0.5 M HCl/MeOH (5 mL) under stirring and under nitrogen atmosphere at room temperature. The progress of reaction was monitored by TLC (6:1CHCl<sub>3</sub>-MeOH). After completion of the reaction the solvent was evaporated under reduced pressure, the residue was purified by flash chromatography (7:1CHCl<sub>3</sub>-MeOH).

*Methyl* 6-deoxy-6-(4-(5-trifluoromethyl-2(1H)-pyridone-1-yl)-anilino)- $\beta$ -D-galactofuranoside (15c). Compound 14a (100 mg, 0.2 mmol) was used to prepare compound 15c (45 mg, 52.3%) as a colorless syrup;  $[\alpha]^{25}_{D}$  –48 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  7.93 (s, 1H), 7.62 (dd,  $J_1 = 2.8$  Hz,  $J_2 = 9.6$  Hz, 1H), 7.02 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 9.6 Hz, 1H), 4.69 (s, 1H, H-1), 3.85–3.77 (m, 4H), 3.34–3.13 (m, 5H); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  163.3 (C=O), 149.7, 139.4, 136.1, 129.0, 127.0, 121.0, 114.8, 112.4, 110.3, 109.9, 109.3 (C-1), 83.9, 82.0, 77.6 and 68.8 (C-2, C-3, C-4, C-5), 54.3 (OCH<sub>3</sub>), 46.3 (C-6); HRMS: Calcd for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 431.1424 [M+H]<sup>+</sup>, found: 431.1420 [M+H]<sup>+</sup>.

*Methyl* 6-deoxy-6-(3-chloro-4-(5-trifluoromethyl-2(1H)-pyridone-1-yl)-anilino)- $\beta$ -D-galactofuranoside (**16c**). Compound **14b** (106 mg, 0.2 mmol) was used to prepare compound **16c** (42 mg, 45.2%) as a yellow syrup;  $[\alpha]^{25}_{D}$  –64 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  7.95 (s, 1H), 7.69 (dd,  $J_1$  = 2.8 Hz,  $J_2$  = 9.6 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.79 (t, J = 2.4 Hz, 1H), 6.66–6.63 (m, 2H), 4.73 (d, J = 1.6 Hz, 1H, H-1), 3.96–3.95 (m, 1H), 3.87–3.85 (m, 2H), 3.83–3.78 (m, 1H), 3.38–3.35 (m, 1H), 3.32 (s, 3H, OCH<sub>3</sub>), 3.25–3.23 (m, 1H), 3.22–3.16 (m, 1H); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  162.7 (C=O), 150.9, 139.7, 136.4, 131.3, 128.9, 125.2, 112.0, 111.2, 109.1, 83.6, 81.7, 77.3 and 68.5 (C-2, C-3, C-4, C-5), 54.0 (OCH<sub>3</sub>), 45.8 (C-6); HRMS: Calcd for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>Cl: 465.1035 [M+H]<sup>+</sup>, found: 465.1038 [M+H]<sup>+</sup>.

*Methyl 6-deoxy-6-(3-(5-trifluoromethyl-2(1*H)*-pyridone-1-yl-methylene)-anilino)-β-D-galactofuranoside* (17c). Compound 14c (100 mg, 0.2 mmol) was used to prepare compound 17c (52 mg, 58.4%) as a yellow syrup;  $[\alpha]^{25}_{D}$  –34 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  8.07 (s, 1H), 7.58 (dd,  $J_1$  = 2.8 Hz,  $J_2$  = 9.6 Hz, 1H), 7.05–7.01 (m, 1H), 6.60–6.55 (m, 3H), 6.48 (d, J = 7.6 Hz, 1H), 5.04 (s, 2H, CH<sub>2</sub>), 4.71 (d, J = 1.2 Hz, 1H, H-1), 3.95–3.93 (m, 1H), 3.87–3.83 (m, 2H), 3.80–3.79 (m, 1H), 3.30 (s, 3H, OCH<sub>3</sub>), 3.24 (m, 1H), 3.15–3.10 (m, 1H); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  164.1(C=O), 150.7, 139.5, 138.0, 137.1, 130.7, 121.8, 117.2, 113.6, 113.4, 111.7, 110.5, 85.3, 83.2, 78.9 and 70.0 (C-2, C-3, C-4, C-5), 55.3 (OCH<sub>3</sub>), 53.8 (CH<sub>2</sub>), 47.7 (C-6); HRMS: Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 445.1581 [M+H]<sup>+</sup>, found: 445.1587 [M+H]<sup>+</sup>.

*Methyl 6-deoxy-6-(4-(5-trifluoromethyl-2(1*H)*-pyridone-1-yl-methylene)-anilino)-β-D-galactofuranoside* (**18c**). Compound **14d** (100 mg, 0.2 mmol) was used to prepare compound **18c** (47 mg, 52.8%) as a yellow syrup;  $[\alpha]^{25}_{D}$  –75 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  8.06 (s, 1H), 7.56 (dd,  $J_1$  = 2.8 Hz,  $J_2$  = 9.6 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 6.61–6.54 (m, 3H), 4.98 (s, 2H, CH<sub>2</sub>), 4.70 (d, J = 2.0 Hz, 1H, H-1), 3.94–3.91 (m, 1H), 3.85–3.82 (m, 2H), 3.80–3.76 (m, 1H), 3.29 (s, 3H, OCH<sub>3</sub>), 3.25–3.23 (m, 3H), 3.16–3.11 (m, 1H); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  162.8 (C=O), 148.9, 137.8, 135.5, 129.4, 123.4, 120.3, 112.6, 109.1, 83.7, 81.9, 77.4 and 68.6 (C-2, C-3, C-4, C-5), 54.0 (OCH<sub>3</sub>), 52.1 (CH<sub>2</sub>), 46.2 (C-6); HRMS: Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>F<sub>3</sub>: 467.1400 [M+Na]<sup>+</sup>, found: 465.1380 [M+Na]<sup>+</sup>.

*Methyl 6-deoxy-6-(2-(5-trifluoromethyl-2(1H)-pyridone-1-yl-methylene)-anilino)-β-D-galactofuranoside* (**19c**). Compound **14e** (100 mg, 0.2 mmol) was used to prepare compound **19c** (49 mg, 55.1%) as a yellow syrup;  $[\alpha]^{25}_{D}$  –72 (c 0.10, MeOH); <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>):  $\delta$  7.97 (s, 1H), 7.57 (dd,  $J_1$  = 2.8 Hz,  $J_2$  = 7.2 Hz, 1H), 7.16–7.10 (m, 2H), 6.68 (d, J = 8.0 Hz, 1H), 6.63–6.59 (m, 2H), 5.09 (s, 2H, CH<sub>2</sub>), 4.73 (s, 1H, H-1), 3.97–3.96 (m, 1H), 3.88–3.84 (m, 3H), 3.36–3.17 (m, 5H); <sup>13</sup>C-NMR (MeOH-d<sub>4</sub>):  $\delta$  163.0 (C=O), 146.5, 137.3, 137.2, 135.7, 130.4, 129.9, 120.3, 119.5, 116.5, 110.8, 109.1, 84.0, 81.8, 77.5 and 68.5 (C-2, C-3, C-4, C-5), 54.0 (OCH<sub>3</sub>), 48.5 (CH<sub>2</sub>), 46.2 (C-6); HRMS: Calcd for  $C_{20}H_{23}N_2O_6F_3$ : 445.1581 [M+H]<sup>+</sup>, found: 445.1583 [M+H]<sup>+</sup>.

## 4. Conclusions

In conclusion, we report the design, synthesis and biological evaluation of some carbohydratemodified 1-(substituted aryl)-5-trifluoromethyl-2(1*H*) pyridones. Our studies suggest that some modifications of pirfenidone analogues with carbohydrates appear to increase the inhibitory activity against NIH 3T3 cell proliferation. Among the compounds tested, compound **19a**, which was synthesized by modification of pirfenidone analogue **19** with glucose, demonstrated the highest cell-based inhibitory activity (IC<sub>50</sub> = 0.17 mM).

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Sample Availability: Samples of the compounds are available from the authors.

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