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One pot protecting group free synthesis of multifunctional biphenyl methyl-C-β-d-glycosides in aqueous medium

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Abstract

One pot reaction of the butenonyl-*C*-glycosides with malononitrile in the presence of K_2CO_3 in water under mild reaction conditions led to the formation of small library of multifunctional biphenyl methyl-*C*-glycosides in good yields has been reported. The reaction is equally applicable with the substrates having different glycosyl pyranoses and aromatic rings with different substituents.

***Keywords*:** Biphenyl methyl-*C*-glycosides, Butenoyl-*C*-glycosides, K_2CO_3, Knoevenagel, Michael, Malononitrile.

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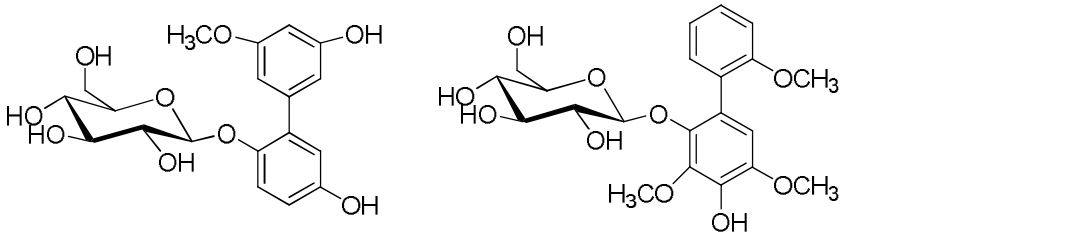
Introduction

C-Glycosides have received increasing interest in medicinal chemistry as carbohydrate biomimetics.[1-3] As compared to *O*-glycoside linkage in glycosides the *C*-glycosidic linkage offers stability to glycosidic bonds towards acidic or enzymatic hydrolysis and therefore these compounds are comparatively more stable. *C*-Glycosides of synthetic and natural origins have been reported to have a vast array of biological activities. Further, these glycosides may exist in two anomeric forms the α-glycosides and *β*-glycosides and in general the latter ones have been studied in great detail for different biological activties. Among the naturally occurring *C*-aryl glycosides with *β*-glycosidic linkages several *C*-glycosyl falvonoids and antibiotics of gilvocarcin family, the pluramycins and others are associated with interesting biological activities.[4-6] In most of the naturally occurring *C*-glycosides having a hexa pyranoid unit the thermodynamically more favorable *β*-configuration predominates. These compounds are of interest as anti-tumor, [7-9] antibiotics,[10-12] or anti-inflammatory agents. [13,14] Several pharmacologically important biphenyl glycosides have been isolated from various parts of the plants and two of the representatives[15,16] (**A** and **B**) are shown in Fig 1a. These phenolic C-glycosides have shown significant antioxidant activity.[17] More recently several of aryl-*β*-*C*-glycosides (Fig 1b) [18,19] have been synthesised as potent inhibitors SGLT2. The latter is an important target to develop new generation of antidiabetic drugs and many such aryl-*β*-C-glycosides are clinical candidate for the treatment of diabetes. [20]

The methods adopted for the synthesis of aryl- *β*-*C*-glycosides involve the use of BuLi and sophisticated reaction conditions. Therefore, we were interested to prepare aryl-*β*-*C*-methyl glycoside analogs of SGLT2 inhibitors where the oxygen atom in glycosides is replaced by a methylene group using a straight forward and economical method. Biphenyl system has been developed from substituted enones and malononitrile using various potentially hazardous bases and organic solvents.[21-23] Solvent free approach to synthesise polysubstituted benzene from enones and malononitrile under basic conditions has also been reported.[24] Methods reported so far, for the synthesis of biphenyl suffers from some drawbacks, higher cost of reagents, non eco friendly catalysts, harsh refluxing conditions, unwanted side products etc.[25-27] However, very recent report[28] on use of ionic liquid in such reactions to get biphenyl derivatives encouraged us to see the reactions of butenonyl-*C*-glycosides in water under the influence of different bases.



A, From leaves of *Eriobotrya japonica* **B,** From fruits of *Pyracantha fortuneana*

Figure 1a. Naturally occurring biphenyl glycosides

R=H, R'=-Et, Dapagliflozin
R=-COOEt, R'=-CH_3,Sergliflozin
R=CH_3, R'=Et, LX-4211

Figure 1b: SGLT2 inhibitors in clinical trial for diabetes and our proposed molecules

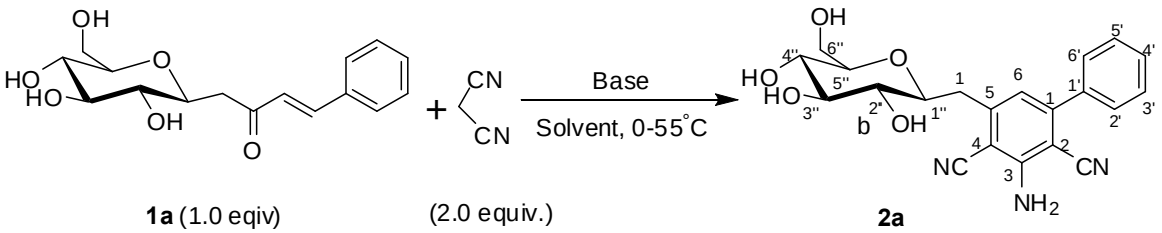
Moreover, application of protecting groups/modification of the free OH in sugars is most often a key requirement in carbohydrate chemistry. Any protocol which avoids the protection/de-protection of the functional groups and water or no water as reaction medium[29] in organic synthesis obviously eliminates the cost and makes the process simple. In the present communication, we have prepared biphenyl methyl-*C*-glycosides by K_2CO_3 catalysed reaction of butenonyl-*C*-glycosides and malononitrile in water. Method developed by us is devoid of any protection or deprotection step and quite economical and eco freindly and no sophisticated reaction conditions are required.

Results and discussion

The starting butenonyl-*C*-glycosides (**1a-1o**) could be accessed from abundantly available D-glucose following our recently reported and literature methods.[30-33] The biphenyl methyl β-*C*-

glucopyranosides were obtained by reaction of butenoyl-*C*-glucopyranisdes with malononitrile in presence of a base as catalyst.

To optimize the reaction conditions, the reaction of one equivalent of *(E)*-1-(*β*-D-glucopyranosylmethyl)-4-phenyl-but-3-en-2-one (**1a**) with malononitrile (2.0 eq.) in different organic solvents under the influence of various bases at different temperatures, was carried out to give 3-amino-5-[(*β*-D-glucopyranosyl) methyl]biphenyl-2,4-dicarbonitrile (**2a**) (Scheme 1) and the results are shown in Table 1. The reaction of (**1a**) with malononitrile in the presence of different bases at ambient temperature although resulted into the required biphenyl glycosides but the yield was very poor. However, elevation of reaction temperature to 50-55 °C resulted in better yield of the product.



Scheme 1: Reaction of *(E)*-1-(*β*-D-glucopyranosylmethyl)-4-phenyl-but-3-en-2-one (**1a**) with malononitrile under different reaction conditions.

Table 1 Optimization of reaction conditions for the synthesis biphenylmethyl- *β*-D-glycoside

Entry	Catalyst (1.0 equivalent)	Solvent	Reaction time (h)	Isolated yield (%)
1	Pyrrolidine	Water	28	30
2	Triethylamine	Water	30	18
3	DBU	-do-	29	5
4	K_2CO_3	do-	24	78
5	K_2CO_3	DMSO	27	5
6	K_2CO_3	DCM	32	4
7	K_2CO_3	THF	24	40
8	NaOEt	C_2H_5OH	26	2
9	Li_2CO_3	Water	34	25
10	Na_2CO_3	C_2H_5OH	24	28

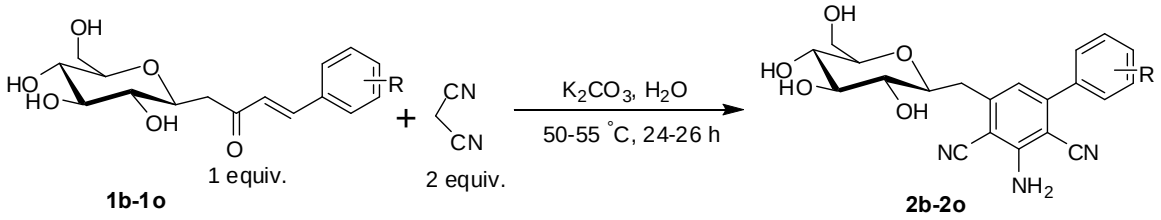
11	Cs_2CO_3	Water	26	50
12	$CaCO_3$	Water	25	41
13	KOH	Water	27	10
14	NaOH	Water	25	25
15	LiOH	Water	29	35
16	K_2CO_3	C_2H_5OH	28	40
17	K_2CO_3	Glycerol	30	15

We have used secondary (pyrrolidine) and tertiary amines (Et_3N and DBU) as catalyst in the above reaction. The secondary amine (Entry 1, Table 1) is better than the tertiary amines. However, the yield was not satisfactory. Keeping in the mind, the basicity of inorganic bases, we used a series of inorganic bases. Out of alkali metal hydroxides, sodium hydroxide was comparatively better (Entry 14, Table 1) than potassium or lithium hydroxides. Among the metal carbonates used as basic catalyst both potassium and sodium carbonates catalyse the reaction satisfactorily but K_2CO_3 in water (Entry 4, Table 1) proved better. The calcium carbonate resulted in poor yield of the required product. The above reaction under the influence of sodium ethoxide in ethanol was also screened but several products were observed on TLC indicating alkoxide is not a suitable catalyst for this reaction. Moreover, screening of different solvents for the above reaction revealed that polar protic solvents were always better than polar aprotic and non polar solvents. Reaction was unsuccessful at 0°C while it was sluggish at ambient temperature. Among various permutations and combinations of solvents and bases used, one equivalent of potassium carbonate as base, water as solvent and reaction temperature of 50-55 °C was found to be the most optimal reaction conditions to give the desired compound **2a** in 78 % yield (Entry 4, Table 1).

The structure of (**2a**) was established on the basis of its spectroscopic data and microanalysis. The IR spectrum of compound **2a** exhibited absorption bands at 3224 cm^{-1} and 2216 cm^{-1} indicating the presence of OH and CN groups. ESMS of the compound display *m/z* = 396 $[M+H]^+$ peak corresponding to its molecular formula. In the ^1H NMR spectrum, compound **2a**, exhibited the aromatic protons as two multiplets each integrating two and three protons respectively in the range of δ 7.61-7.57 and δ 7.52-7.49. The exchangeable NH_2 protons were visible as broad singlet at δ 6.56, while the aromatic H-4 was seen as singlet at δ 6.86. The hydroxyl protons of glucopyranose unit at C-2′′, C-3′′and C-4′′ were obsreved as a three distinct doublets at δ 5.15 (J = 5.52 Hz), δ 4.92 (J = 4.65 Hz) and δ 4.87 (J = 4.47 Hz) respectively, while the OH proton at C-6′′appeared as triplet at δ 4.21(J = 5.58 Hz). One of the two methylene protons (H-6a′′) was observed as dd (J_1 = 5.94, J_2 = 11.19 Hz) at δ 3.63 while the other (H-6b′′) was visible along with one of the sugar ring proton as multiplet in the range of δ 3.40-3.34. Other three glycosyl ring protons were observed as three sets of multiplets at δ 3.28-3.27 (CH), 3.21-3.14 (m, 1H, H-1′′), and 3.06-3.04(m, 1H, CH) respectively. The two protons of the methylene linker between biphenyl and sugar moeity were observed as multiplet

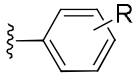
at δ 3.01-2.93 and a dd at δ 2.79 (J_1 = 8.91, J_2 = 14.8 Hz) respectively. ^{13}C NMR spectrum of compound signals at δ 153.8 accounted the aromatic quaternary carbon while the signals for two C≡N carbons were observed at δ 116.6 and 116.0. The carbons of phenyl ring were seen in the range of δ 149.7-93.3. The C-1′′ appeared at δ 80.9, while C-2′′, C-3′′, C-4′′, and C-5′′ carbons were visible at δ 78.8, δ 78.4, δ 74.0, and δ 70.8 respectively. The two methylene carbons OCH_2 and CH_2 were observed at δ 61.9 and δ 37.3.

Based on the above optimized reaction conditions, the scope of various *(E)*-1-(*β*-D-glucopyranosyl)-4-(aryl)-but-3-en-2-ones (**1b-1o**) as substrates having different susbtitutents in the phenyl ring was investigated to get the respective biphenyl methyl-C-*β*-D-glucospyranosides (Scheme 2). The results are depicted in Table 2.



Scheme 2 Preparation of different biphenyl methyl-*β*-D-glucopyranosides (**2b-2o**)

Table 2 Syntheses of biphenylmethyl- *C*-β-D-glucopyranosides (**2b-2o**)

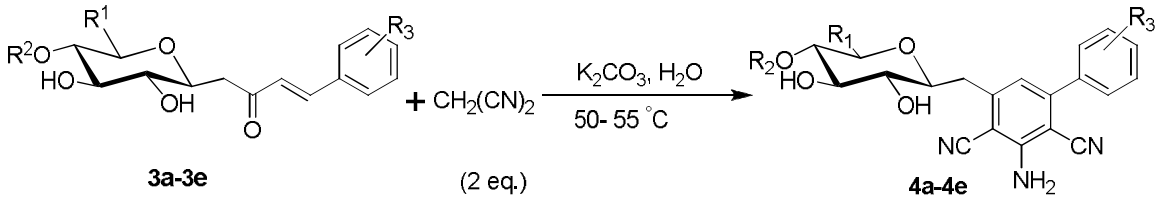
Entry	Substrate	Product		Reaction time (h)	Isolated yield[a] (%)
1	**1b**	**2b**	4-Br-phenyl	25	60
2	**1c**	**2c**	4-benzyloxyphenyl	26	48
3	**1d**	**2d**	4-methoxyphenyl	24	68
4	**1e**	**2e**	3,4-dimethoxyphenyl	24	70
5	**1f**	**2f**	4-chlorophenyl	25	64
6	**1g**	**2g**	4-fluorophenyl	24	69
7	**1h**	**2h**	2-napthyl	26	70
8	**1i**	**2i**	4-hydroxyphenyl	25	52
9	**1j**	**2j**	4-(NMe_2)phenyl	25	58
10	**1k**	**2k**	2-thiophenyl	24	55
11	**1l**	**2l**	3-nitrophenyl	24	66

12	**1m**	**2m**	3-pyridyl	26	50
13	**1n**	**2n**	2-chlorophenyl	25	60
14	**1o**	**2o**	3,4-methylenedioxyphenyl	26	70

[a]isolated yields are based on the butenonyl glycosides substrates

It is clear from Table 2, that yield of the biphenylmethyl-*C*-β-D-glucopyranosides in the above reaction with butenonyl glycosides bearing 2- or 4-halo and methoxy substituent's in the aromatic moiety (Entry 1, 3, 5, 6, 13, Table 2) is better than with the glycosyl substrates having the 4-substituent as hydroxyl, *N*,*N*-dimethylamine and benzyloxy. The electron withdrawing group (-NO_2) at phenyl ring also favours the reaction as the yield of resulting product is good (entry 11, table 2). Even di substitution and substitution with bulky naphthyl group in aromatic ring of glucosyl butanone offers comparable yields. However, when the aromatic ring in the substrate was replaced by a heteroaromatic ring, thiophenyle and pyridyl ring (entries 10 and 12 Table 2) the yield of the resulting product is reduced. Thus the method is of general use to prepare biphenyl methyl-*C*-glcyosides with any sort of aromatic ring.

We have extended this work to see the scope of this reaction with butenonyl glycopyranoses with xylopyranose and a disachharide cellobiose sugar. Thus the reaction 1-(*β*-D-xylopyranosyl)-4-(aryl)-but-3-en-2-ones (**3a**-**3d**) and a disaccharide (cellobiose) derived butenonyl-*C*- glycoside (**3e**) with malononitrile separately under the above optimal reaction conditions resulted respective biphenyl methyl-*C*-*β*-D-xylopyranosides (**4a**-**4d**) and biphenyl methyl-*C*-*β*-D-cellobioside (**4e**) in good yields (Scheme 3). As shown in scheme 3 the biphenyl methyl *β*-D-xylopyranosides (**4a**-**4d**) were obtained comparatively in better yields as compared to the above biphenyl methyl *β*-D-glucopyranosides.



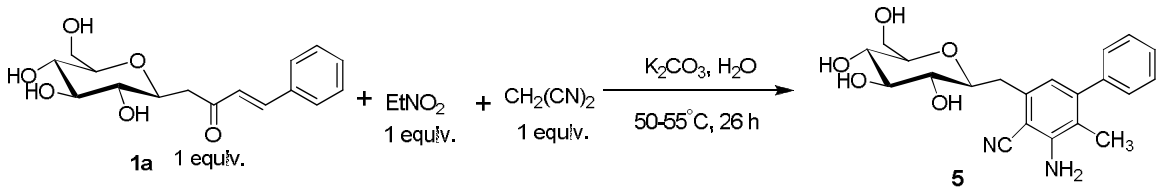
3a, 4a: $R_1 = R_2 = R_3 = H$,
3b, 4b: $R_1 = R_2 = H$, R_3 = 4-Cl,
3c, 4c: $R_1 = R_2 = H$, R_3 = 3-NO_2
3d, 4d: $R_1 = R_2 = H$, R_3 = 4-OCH_3,
3e, 4e: $R_1 = CH_2OH$, R_2 = *β*-D-glucopyranos-1-yl, $R_3 = H$

Compounds	Yield (%)
4a	76
4b	73
4c	73
4d	75
4e	61

Scheme 3: Syntheses of 3-amino-5-[(*β*-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitriles (**4a**-**4d**) and 3-amino-5-[(*β*-D-cellobiosyl)methyl]biphenyl-2,4-dicarbonitrile (**4e**)

To enhance the scope of this reaction to get biphenyl methyl-*C*-glycosides with different substitutents in the aromatic ring and to gain an insight into the reaction mechanism the above

glucopyranosyl butanone **1a** was reacted with nitroethane (1.0 equiv) and malononitrile (1.0 equiv.) instead of two equvalent of malanotnitrile alone as above. The reaction led to the formation of 3-amino-2-methyl-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-4-carbonitrile (**5**) as product in good yield.



Scheme4: Synthesis of 3-amino-2-methyl-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-4-carbonitrile (**5**)

Structures of all the biphenyl methyl-*C*- glycosides were established on the basis of their spectroscopic data and microanalyses. The stereochemistry and structures of these compounds were further confirmed by X-ray crystallographic data and ortep diagram of one such a prototype, compound **4a** (Fig 2).

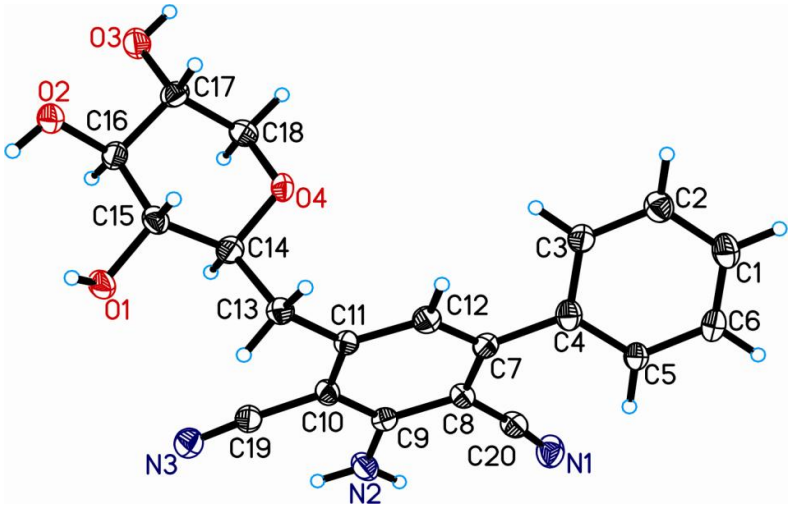


Figure 2 X-ray structure of 3-amino-5-[(*β*-D-xylopyranosyl)methyl] biphenyl-2,4-dicarbonitrile (**4a**)

Although the mechanistic details of the reaction are not well established yet a most plausible reaction mechanism may be advanced for the formation of biphenyl methyl-C- glycosides. The proposed mechanism is similar to that recently reported for the preparation of biphenyls using ionic liquids[36] and depicted in Fig 3. The most probable mechanism as depicted in Fig 3 involves initially a Michael addition of malononitrile to the double bond of glycosyl butanone (**I**) resulting in an adduct (**II**). The latter on a Knovenagel reaction with antoher molecule of malanonitrile in presence of base (B) gives the intermediate **III**. The base abstracts a proton from **III** to generate a carbanion, which makes a nucleophilic attack on to one of nitriles to give cyaloaddition product (**IV**). The base catalysed elimination of HCN gave an intermediate imine (**V**), which on aerial oxidation afforded the biphenyl methyl glycosides (**VI**).

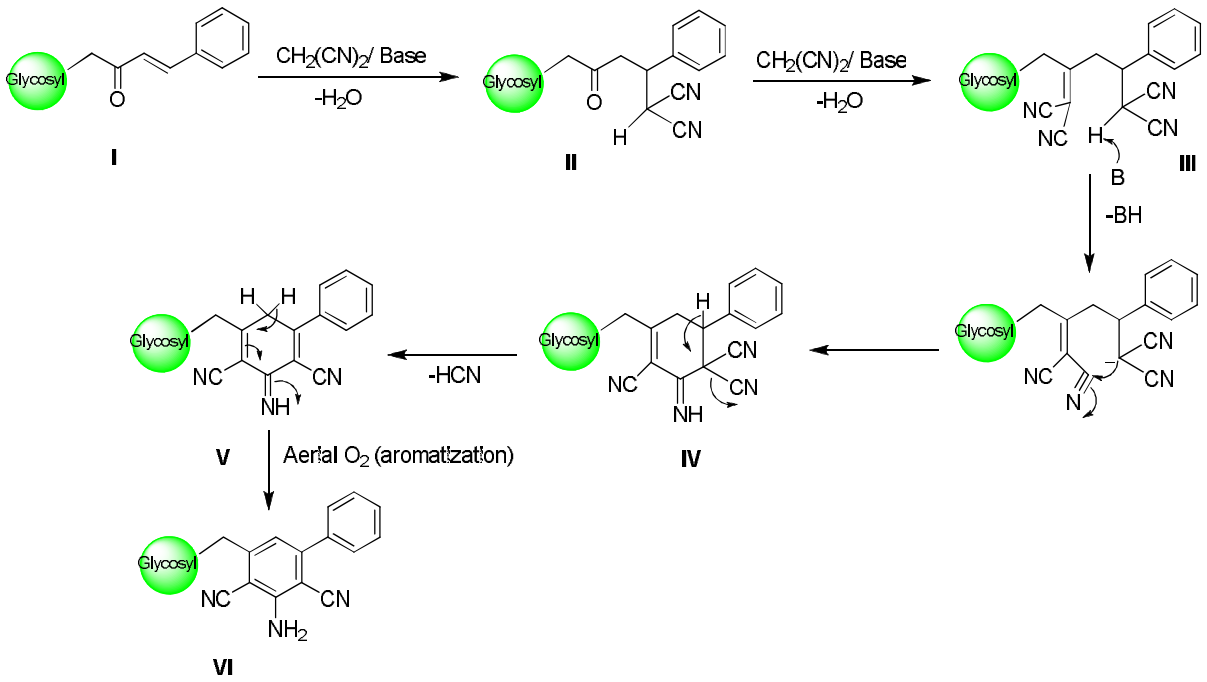


Figure 3 Reaction mechanism proposed for the formation of biphenyl glycosides

Conclusions

In summary, a facile and eco friendly efficient one-pot protection free aqueous synthesis of biphenyl methyl-*C*-glycosides has been developed *via* sequential Michael addition, Knoevenagel condensation and intramolecular nucleophilic cyclization reactions of (*E*)-1-(*β*-D-glucopyranosyl)-4-(aryl)but-3-en-2-ones with malononitrile, in presence of potassium carbonate as a catalyst. The method is applicable for the synthesis of multifunctional biphenyl methyl C-glycosides having potential application in organic and medicinal chemistry. Valuable features of this protocol including one pot, simple procedure, mild conditions, and good yields make it an efficient and promising synthetic strategy to buildup biphenyl methyl-*C*-glycosides. The latter have tremendous potential for creating molecular diversity of immense value due to presence of different functional groups.

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Experimental section:

General method

Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 F_{254}, with detection by UV light, spraying a 20% $KMnO_4$ aq solution and/or spraying a 4% H_2SO_4 ethanolic solution. Column chromatography was performed on silica gel (60-120 mesh E. Merck). IR spectra were recorded as thin films or in KBr soln with a Perkin Elmer Spectrum RX-1 (4000-450 cm^{-1}) spectrophotometer. The ^1H

(200 MHz and 300 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker DRX-300 in DMSO. Chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as internal reference, unless otherwise stated; s (singlet), d (doublet), t (triplet), m (multiplet), dd (double doublet), ddd (doublet of double of doublet), bs (broad singlet); *J* in hertz. ESI mass spectra were performed using Quattro II (Micromass). Optical rotations were measured in a 1.0 dm tube with a Rudolph Autopol III polarimeter in DMSO. Elemental analysis was carried out with the help of German made Vario-EL (III). All spectroscopic data including elemental analysis were carried out in SAIF (sophisticated analytical instrumental facility), CDRI, and Lucknow.

General procedure for the preparation of compounds (2a-2o, 4a-4e)

To a stirred solution of *(E)*1-(*β*-D-glucopyranosyl)-4-(aryl)but-3-en-2-one (3.24 mmol) or *(E)*1-(*β*-D-xylopyranosyl)-4-(aryl)but-3-en-2-one (3.59 mmol) or *(E)*1-(*β*-D-cellobiosyl)-4-(phenyl)but-3-en-2-one (2.55 mmol) and malononitrile (6.49 or 7.19 or 5.10 mmol) in water, potassium carbonate (3.24 or 3.59 or 2.55 mmol) was added at room temperature and reaction temperature was brought to 50-55 ˚C. After completion of the reaction, the reaction mixture was extracted by ethyl acetate/water. The organic layer was dried over sodium sulphate (Na_2SO_4) and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (60-120 mesh) using methanol: chloroform as eluant to give corresponding 3-amino-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**2a-2o**) or 3-amino-5-[(*β*-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**4a-4d**) or 3-amino-5-[(*β*-D-cellobiosyl)methyl]biphenyl-2,4-dicarbonitrile (**4e**) as a solid product.

General procedure for the preparation of compounds (5)

To a stirred solution of *(E)*1-(*β*-D-glucopyranosyl)-4-(aryl)but-3-en-2-one (3.24 mmol) and nitroethane (3.12mmol) in water, potassium carbonate (12.19 mmol) was added at room temperature and reaction was shifted at 50-55˚C for 4-5 hour (till disappearance of starting material). Malononitrile (6.49 mmol) was added and reaction was stirred for 26hour at same temperature. After completion of the reaction, the reaction mixture was extracted by ethyl acetate/water. The organic layer was dried over sodium sulphate (Na_2SO_4) and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (60-120 mesh) using methanol: chloroform as eluant to give corresponding 3-Amino, 2-methyl, 5-[(β-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile **(5)** as a solid.

3-Amino-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2a): It was obtained by the reaction of compound **1a** (1.0g, 3.24 mmol), malononitrile (0.42 g, 6.49 mmol) and potassium carbonate (0.44 g, 3.24 mmol), in water as white solid (1.00g, yield 78%), Analysis Found: C, 63.75; H, 5.31; N, 10.60; for $C_{21}H_{21}N_3O_5$ requires: C, 63.79; H, 5.35; N, 10.63; M.p. 228-231°C; R_f 0.5 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -105.63 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3224 (OH), 2216 (C≡N), 1644, 1577, 1428; ^1H NMR (300 MHz, DMSO); δ = 7.61-7.57 (2H, m, ArH), 7.52-7.49 (3H, m, ArH), 6.86 (1H, s, ArH), 6.56 (2H, s, $ArNH_2$), 5.15 (1H, d, *J* = 5.5 Hz, OH), 4.92 (1H, d, *J* = 4.6 Hz, OH), 4.87 (1H, d, *J* = 4.4 Hz, OH), 4.21 (1H, t, *J* = 5.5 Hz, OH), 3.63 (1H, dd, J_1 = 5.9, J_2= 11.1Hz, H-6´´a), 3.40-3.34 (2H, m, CH, H-6´´b), 3.28-3.27 (1H, m, CH), 3.21-3.14 (1H, m, H-1´´), 3.06-3.04 (2H, m, CH), 3.01-2.93 (1H, m, H-1b), 2.79 (1H, dd, J_1 = 8.9, J_2= 14.7 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.8 (Ar-C), 149.7 (Ar-C), 149.3 (Ar-C), 138.1 (Ar-C), 129.7 (Ar-CH), 129.0 (Ar-CH), 128.9 (Ar-CH), 119.7 (Ar-CH), 116.1 (C≡N), 116.1 (C≡N), 96.8 (Ar-C), 93.2 (Ar-C), 80.9 (CH), 78.8 (Ar-C), 78.4 (CH), 74.0 (CH), 70.8 (CH), 61.9 (OCH_2), 37.2 (CH_2); ESMS *m/z* 396 $(M+H)^+$.

3-Amino-4′-bromo-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2b): It was obtained by the reaction of compound **1b** (1.2 g, 3.10 mmol), malononitrile (0.40 g, 6.20 mmol) and potassium carbonate (0.80 g, 7.14 mmol), in water as white solid (0.84 g, yield 58%), Analysis Found: C, 53.21; H, 4.18; Br, 16.80; N, 8.81. for $C_{21}H_{20}BrN_3O_5$ requires: C, 53.18; H, 4.25; Br, 16.85; N, 8.86; M.p. 119-122 °C; R_f 0.45 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -18.51 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3352 (OH), 2217 (C≡N), 1638, 1578, 1437; ^{1}H NMR (300 MHz, DMSO) δ = 7.71 (2H, d, *J* = 8.4 Hz, ArH), 7.56 (2H, d, *J* = 8.4 Hz, ArH), 6.87 (1H, s, ArH), 6.66 (2H, s, $ArNH_2$), 5.16 (1H, d, *J* = 5.1 Hz, OH), 4.91 (1H, bs, OH), 4.87 (1H, bs, OH), 4.22 (1H, bs, OH), 3.65 (1H, dd, J_1 = 3.6, J_2 = 11.2 Hz, H-6′′a), 3.39-3.27 (3H, m, 2xCH, H-6′′b), 3.17 (1H, bs, H-1′′), 3.05 (2H, m, CH), 3.00 (1H, dd, J_1 = 5.1, J_2 = 8.7 Hz, H-1b), 2.78 (1H, dd, J_1 = 8.8, J_2 = 14.7 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.8 (Ar-C), 150,0 (Ar-C), 148.1 (Ar-C), 137.3 (Ar-C), 132.0 (Ar-CH), 131.1 (Ar-CH), 123.3 (Ar-C), 119.5 (Ar-CH), 116.5 (C≡N), 115.9 (C≡N), 97.0 (Ar-C), 93.0 (Ar-C), 81.0 (CH), 78.7 (CH), 78.4 (CH), 74.0 (CH), 70.9 (CH), 61,8 (OCH_2), 37.2 (CH_2); ESMS *m/z* = 476 $(M+H)^+$.

3-Amino-4′-(benzyloxy)-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2c): It was obtained by the reaction of compound **1c** (1.0 g, 2.41 mmol), malononitrile (0.31 g, 4.83 mmol) and potassium carbonate (0.33 g, 2.41 mmol), in water as yellow solid (0.58 g, yield 48%), Analysis Found: C, 67.12; H, 5.48; N, 8.31 for $C_{28}H_{27}N_3O_6$ requires: C, 67.05; H, 5.43; N, 8.38; M.p. 138-141°C; R_f 0.45 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -13.53 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3393 (OH), 2263 (C≡N), 1627, 1246, 1095; ^{1}H NMR (300 MHz, DMSO) δ =7.66-7.54 (1H, m, ArH), 7.49 -7.47 (2H, m, ArH), 7.44-7.33 (7H, m, ArH), 7.15-7.12 (2H, d, *J* = 8.6 Hz, ArH), 6.84 (1H, s, ArH), 6.50 (1H, s, ArH), 5.18 (2H, s, OCH_2), 5.14 (1H, s, OH), 4.91-4.86 (2H, m, OH), 4.21 (1H, t, *J* = 5.2 Hz, OH), 3.64-3.57 (3H, m, 2xCH, H-6′′a), 3.32-3.26 (3H, m, 2xCH, H-6′′b), 3.17-3.16 (1H, m, H-1′′), 3.05-3.00 (2H, m, CH), 2.99-2.90 (1H, m, H-1b), 2.76 (1H, dd, J_1 = 9.0, J_2 = 14.7 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 164.5 (Ar-C), 159.7 (Ar-C), 153.9 (Ar-C), 149.5 (Ar-C), 149.0 (Ar-C), 137.3 (Ar-C), 130.5 (Ar-CH), 128.9 (Ar-CH), 128.4 (Ar-CH), 128.2 (Ar-CH), 116.9 (C≡N), 116.7 (C≡N), 115.3 (Ar-CH), 96.2 (Ar-C), 93.0 (Ar-C), 80.9 (CH), 78.8 (CH), 78.4 (CH), 74.0 (CH), 70.9 (CH), 69.8 (OCH_2), 61.8 (OCH_2), 25.8 (CH_2); ESMS *m/z* = 521 $(M+7)^+$.

3-Amino-4′-methoxy-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2d): It was obtained by the reaction of compound **1d** (1.0g, 2.90 mmol), malononitrile (0.39 g, 5.91 mmol) and potassium carbonate (0.40 g, 2.95 mmol), in water as Light yellow solid (0.84g, yield 67%), Analysis Found: C, 62.20; H, 5.41; N, 9.82 for $C_{22}H_{23}N_3O_6$ requires: C, 62.11; H, 5.45; N, 9.88; M.p. 181-184°C; R_f 0.55 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -55.48 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3411 (OH), 2219 (C≡N), 1648, 1520, 1216; ^{1}H NMR (300 MHz, DMSO) δ = 7.41 (1H, d, *J* = 7.8 Hz, ArH), 7,15-7.03 (3H, m, ArH), 6.85 (1H, s, ArH), 6.62 (2H, s, $ArNH_2$), 5.23 (1H, d, *J* = 5.4 Hz, OH), 5.01 (1H, d, *J* = 4.7 Hz, OH), 4.94 (1H, s, OH), 4.28 (1H, t, *J* = 5.5 Hz, OH), 3.80 (3H, s, OCH_3), 3.62 (1H, dd, J_1 = 4.4, J_2 = 10.8 Hz, H-6′′a), 3.43-3.26 (3H, m, 2xCH, H-6′′b), 3.16-3.12 (1H, m, H-1′′), 3.04-2.91 (3H, m, 2xCH, H-1b), 2.76 (1H, dd, J_1 = 9.0, J_2 = 14.6 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 159.6 (Ar-C), 153.8 (Ar-C), 149.7 (Ar-C), 149.2 (Ar-C), 139.5 (Ar-C), 130.2 (Ar-CH), 121.2 (Ar-CH), 119.7 (Ar-CH), 116.6 (C≡N), 116.0 (C≡N), 115.5 (Ar-CH), 114.3 (Ar-CH), 96.8 (Ar-C), 93.2 (Ar-C), 80.9 (CH), 78.8 (CH), 78.4 (CH), 74.0 (CH), 70.8 (CH), 61.9 (OCH_2), 55.7 (OCH_3), 37.3 (CH_2); ESMS *m/z* = 426 $(M+H)^+$.

3-Amino-3′,4′-dimethoxy-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2e): It was obtained by the reaction of compound **1e** (1.0g, 2.71 mmol), malononitrile (0.35 g, 5.41 mmol) and potassium carbonate (0.37g, 2.71 mmol), in water as Light yellow solid (0.76g, yield 70%), Analysis Found: C, 60.60; H, 5.49; N, 9.18 for $C_{23}H_{25}N_3O_7$ requires: C, 60.65; H, 5.53; N, 9.23; M.p. 135-138°C; R_f 0.55 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -57.0 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3350 (OH), 2216 (C≡N), 1638, 1581, 1518; ^{1}H NMR (300 MHz, DMSO) δ = 7.17 (3H, m, ArH), 6.88 (1H, s, ArH), 6.48 (2H, s, $ArNH_2$), 5.14 (1H, bs, OH), 4.88 (2H, bs, OH), 4.20 (1H, bs, OH), 4.26 (1H, t, *J* = 5.3Hz, OH), 3.82 (6H, bs, 2xOCH_3), 3.64-3.57 (1H, m, H-6′′a), 3.40-3.34 (3H, m, 2xCH, H-6′′b), 3.18-3.15 (1H, m, H-1′′), 3.07-3.05 (2H, m, CH), 3.00-2.94 (1H, m, H-1b), 2.77 (1H, dd, J_1 = 8.9, J_2 = 14.7 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.9 (Ar-C), 150.2 (Ar-C), 149.5 (Ar-C), 149.3 (Ar-C), 148.9 (Ar-C), 130.4 (Ar-CH), 121.7 (Ar-CH), 119.5 (Ar-CH), 117.0 (C≡N), 116.1 (C≡N), 112.5 (Ar-CH), 112.1 (Ar-CH), 96.1 (Ar-C), 93.2 (Ar-C), 80.9 (CH), 79.6 (Ar-C), 78.8 (CH), 78.4 (CH), 74.1 (CH), 70.9 (CH), 61.9 (OCH_2), 56.0 (OCH_3), 37.2 (CH_2); ESMS *m/z* 472 $(M+H)^+$.

3-Amino-4′-chloro-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2f): It was obtained by the reaction of compound **2f** (1.1g, 3.21 mmol), malononitrile (0.42 g, 6.40 mmol) and potassium carbonate (0.44 g, 3.21 mmol), in water as white solid (0.87g, yield 64%), Analysis Found: C, 58.71; H, 4.61; Cl, 8.21; N, 9.72 for $C_{21}H_{20}ClN_3O_5$ requires: C, 58.68; H, 4.69; Cl, 8.25; N, 9.78; M.p. 130-132°C; R_f 0.52 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -136.99 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3224 (OH), 2216 (C≡N), 1644, 1577, 1428; ^{1}H NMR (300 MHz, CD_3OD); δ =7.60-7.47 (4H, m, ArH), 6.91 (1H, s, ArH), 3.81 (1H, dd, J_1 = 3.51, J_2= 17.5 Hz, H-6′′a), 3.64 (1H, dd, J_1 = 7.98, J_2= 17.7 Hz, H-6′′b) 3.52-3.43 (2H, m, CH), 3.39-3.34 (1H, m, H-1′′), 3.31-3.26 (1H, m, CH), 3.22-3.09 (2H, m, CH, H-1b), 2.96 (1H, dd, J_1 = 13.53, J_2= 21.9 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 154.9 (Ar-C), 150.5 (Ar-C), 149.8 (Ar-C), 138.0 (Ar-C), 136.5 (Ar-C), 131.4 (Ar-CH), 129.9 (Ar-CH), 117.0 (C≡N), 116.7 (C≡N), 98.4 (Ar-C), 94.7 (Ar-C), 81.5 (CH), 80.4 (CH), 79.7 (CH), 75.2 (CH), 71.9 (CH), 63.1 (OCH_2), 38.3 (CH_2); ESMS *m/z* 430.2 $(M+H)^+$.

3-Amino-4′-fluoro-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2g): It was obtained by the reaction of compound **1g** (1.0g, 3.00 mmol), malononitrile (0.40 g, 6.13 mmol) and potassium carbonate (0.42 g, 3.06 mmol), in water as yellow solid (0.73g, yield 69%), Analysis Found: C, 61.11; H, 4.91; N, 10.21 for $C_{21}H_{20}FN_3O_5$ requires: C, 61.01; H, 4.88; N, 10.16; M.p. 168-171 °C; R_f 0.58 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -71.69.(c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3344 (OH), 2218 (C≡N), 1646, 1579, 1236; ^{1}H NMR (300 MHz, DMSO) δ = 7.67 (2H, m, ArH), 7.36 (2H, m, ArH), 6.86 (1H, s, ArH), 6.58 (2H, s, $ArNH_2$), 5.15 (1H, d, *J* = 5.4 Hz, OH), 4.92-4.90 (1H, d, *J* = 4.6 Hz, OH), 4.87-4.85 (1H, d, *J* = 4.2 Hz, OH), 4.22 (1H, t, *J* = 5.4 Hz, OH), 3.65 (1H, dd, J_1 = 5.3, J_2= 11.3 Hz, H-6′′a), 3.39-3.27 (3H, m, 2_XCH, H-6′′b), 3.18-3.13 (m, 1H, H-1′′), 3.06 (m, 2H, CH), 3.00 (dd, J_1 = 5.5, J_2= 8.8 Hz, 1H, H-1b), 2.78 (dd, J_1 = 8.8, J_2= 14.7 Hz, 1H, H-1a); ^{13} C NMR (50 MHz, DMSO) δ = 153.8(Ar-C), 150,0 (Ar-C), 148.1 (Ar-C), 137.3 (Ar-C),132.0 (Ar-CH), 131.1 (Ar-CH), 123.3 (Ar-C), 119.5 (Ar-CH), 116.5 (C≡N), 115.9 (C≡N), 97.0 (Ar-C), 93.0 (Ar-C), 81.0 (CH), 78.7 (CH), 78.4 (CH), 74.0 (CH), 70.9 (CH), 61,8 (OCH_2), 37.2 (CH_2); ESMS *m/z* = 437 $(M+Na+H)^+$.

2-Amino-4′-(naphthalen-2-yl)-6-[(*β*-D-glucopyranosyl)methyl]isophthalonitrile (2h): It was obtained by the reaction of compound **1h** (1.1g, 3.07 mmol), malononitrile (0.40 g, 6.14 mmol) and potassium carbonate (0.42 g, 3.07 mmol), in water as yellow solid (0.94g, yield 70%), Analysis Found: C, 67.50; H, 5.12; N, 9.38 for $C_{25}H_{23}N_3O_5$ requires: C, 67.41; H, 5.20; N, 9.43;

R_f 0.6 (20% MeOH:$CHCl_3$); M.p. 230-233°C; $[\alpha]_D^{25}$ -51.99 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3351(OH), 2216 (C≡N), 1637, 1579, 1288; ^{1}H NMR (300 MHz, DMSO) δ = 8.18 (1H, s, ArH), 8.05 -8.01 (3H, m, ArH), 7.74 (1H, d, *J* = 8.2 Hz, ArH), 7.61 (2H, m, ArH), 7.00 (1H, s, ArH) 6.67 (2H, s, $ArNH_2$), 5.23 (1H, d, *J* = 5.2 Hz, OH), 4.99 (1H, d, *J* = 4.2 Hz, OH), 4.94 (1H, bs, OH), 4.33 (1H, bs, OH), 3.67-3.65 (1H, m, H-6´´a), 3.37-3.31 (3H, m, 2xCH, H-6´´b), 3.18 (1H, m, H-1´´), 3.07-3.02 (2H, m, CH), 2.99-2.97 (1H, m, H-1b), 2.80 (1H, dd, J_1 = 8.6, J_2= 14.2 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.9 (Ar-C), 149.8 (Ar-C), 149.3 (Ar-C),135.6 (Ar-C), 133.3 (Ar-C),133.0 (Ar-C), 128.9 (Ar-CH), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.5 (Ar-CH) 127.1 (Ar-CH),126.5 (Ar-CH), 120.0 (Ar-CH), 116.7 (C≡N), 116.0 (C≡N), 96.7 (Ar-C), 93.4 (Ar-C), 81 0 (CH), 78.8 (CH), 78.4 (CH), 74.0 (CH), 70.9 (CH), 61.9 (OCH_2), 37.2 (CH_2); ESMS *m/z* = 466 $(M+21)^+$.

3-Amino-4´-hydroxy-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2i): It was obtained by the reaction of compound **1i** (1.0g, 3.00 mmol), malononitrile (0.40 g, 6.10 mmol) and potassium carbonate (0.42 g, 3.01 mmol), in water as yellow solid (0.58g, yield 52%), Analysis Found: C, 61.31; H, 5.14; N, 10.21; for $C_{21}H_{21}N_3O_6$ requires: C, 61.40; H, 5.19; N, 10.18; M.p. 242-245°C; R_f 0.48 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -22.75 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3361 (OH), 2213 (C≡N), 1648, 1582, 1229; ^{1}H NMR (300 MHz, DMSO) δ = 9.98 (1H, s, Ar*OH*), 7.46 (1H, d, *J* = 8.4 Hz, ArH), 6.88-6.82 (3H, m, ArH), 6.49 (2H, s, $ArNH_2$), 5.19 (1H, d, *J* = 5.4 Hz, OH), 4.98 (1H, d, *J* = 4.4 Hz, OH), 4.92 (1H, bs, OH), 4.26 (1H, t, *J* = 5.3Hz, OH), 3.65 (1H, dd, J_1 = 4.9, J_2= 11.0 Hz, H-6´´a), 3.41-3.25 (3H, m, 2xCH, H-6´´b), 3.17-3.16 (1H, m, H-1´´), 3.05 (2H, bs, CH), 2.99-2.92 (1H, m, H-1b), 2.76 (1H, dd, J_1 = 8.9, J_2 = 14.6 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 159.0 (Ar-C), 153.9 (Ar-C), 149.5 (Ar-C), 130.5 (Ar-CH), 128.7 (Ar-CH), 119.7 (Ar-CH), 117.0 (C≡N), 116.0 (C≡N), 115.8 (Ar-CH), 95.9 (Ar-C), 92.9 (Ar-C), 80.9 (CH), 78.9 (CH), 78.4 (CH), 74.0 (CH), 70.9 (CH), 61.9 (OCH_2), 37.2 (CH_2); ESMS *m/z* = 412 $(M+H)^+$.

3-Amino-4´-(dimethylamino)-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2j): It was obtained by the reaction of compound **1j** (1.2g, 3.41 mmol), malononitrile (0.45 g, 6.81 mmol) and potassium carbonate (0.47 g, 3.41 mmol), in water as yellow solid (0.83g, yield 58%), Analysis Found: C, 63.12; H, 6.01; N, 12.69 for $C_{23}H_{26}N_4O_5$ requires: C, 63.00; H, 5.98; N, 12.78; M.p. 230-233°C; R_f 0.45 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -26.93 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3449 (OH), 2563, 1777, 1626; ^{1}H NMR (300 MHz, DMSO); δ =7.49 (2H, d, *J* = 8.7Hz, ArH), 6.83 (3H, m, ArH), 6.43 (2H, s, $ArNH_2$), 5.17 (1H, d, *J* = 5.4Hz, OH), 4.95 (1H, d, *J* = 4.6Hz, OH), 4.89 (1H, bs, OH), 4.25 (1H, t, *J* = 5.5Hz, OH), 3.65 (1H, dd, J_1 = 5.0, J_2= 11.2 Hz, H-6´´a), 3.36-3.24 (3H, m, 2xCH, H-6´´b), 3.17-3.15 (1H, m, H-1´´), 3.05 (2H, bs, CH), 2.97-2.85 (7H, m, 2xNC*H*$_3$, H-1b), 2.74 (1H, dd, J_1 = 8.9, J_2 = 14.8 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 154.0 (Ar-C), 151.1 (Ar-C), 149.6 (Ar-C),149.1 (Ar-C), 129.9 (Ar-CH), 125.3 (Ar-CH), 119.1 (Ar-CH), 117.2 (C≡N), 116.3 (C≡N), 112.5 (Ar-CH), 95.2 (Ar-C), 92.4 (Ar-C), 80.8 (CH), 78.8 (Ar-C), 78.4 (CH), 74.0 (CH), 70.8 (CH), 61.8 (OCH_2), 37.1 (CH_2); ESMS *m/z* 439 $(M+H)^+$.

2-Amino-4´-(thiophen-2-yl)-6-[(*β*-D-glucopyranosyl)methyl]isophthalonitrile (2k): It was obtained by the reaction of compound **1k** (1.2g, 3.81 mmol), malononitrile (0.50 g, 7.64 mmol) and potassium carbonate (0.52 g, 3.82 mmol), in water as light yellow solid (0.83g, yield 55%), Analysis Found C, 56.85; H, 4.77; N, 10.47 for $C_{19}H_{19}N_3O_5S$ requires: 56.79; H, 4.56; N, 10.36; M.p. 209-212 °C; R_f 0.52 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -79.22 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3457 (OH), 2214 (C≡N), 1635, 1580, 1290; ^{1}H NMR (300 MHz, DMSO) δ = 7.82-

7.80 (1H, m, ArH), 7,69-7.68 (1H, m, ArH), 7.24-7.21 (1H, m, ArH), 6.99 (1H, s, ArH), 6.66 (2H, s, $ArNH_2$), 5.21 (1H, d, J = 5.5 Hz, OH), 5.00 (1H, d, J = 4.5 Hz, OH), 4.93 (1H, d, J = 4.0 Hz, OH), 4.26 (1H, t, J = 5.5 Hz, OH), 3.64 (1H, dd, J_1 = 5.2, J_2 = 10.9 Hz, H-6´´a), 3. 39-3.25 (3H, m, 2xCH, H-6´´b), 3.17-3.12 (1H, m, H-1´´), 3.09-3.07 (2H, m, CH), 2.99 (1H, m, H-1b), 2.77 (1H, dd, J_1 = 8.9, J_2= 14.8 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 154.2 (Ar-C), 150.0 (Ar-C), 141.1 (Ar-C), 139.1 (Ar-C), 129.8 (Ar-CH), 129.3 (Ar-CH), 128.8 (Ar-CH), 118.8 (Ar-CH), 116.8 (C≡N), 115.9 (C≡N), 96.6 (Ar-C), 91.5 (Ar-C), 80.9 (CH), 78.8 (CH), 78.4 (CH), 73.9 (CH), 70.7 (CH), 61.7 (OCH_2), 37.3 (CH_2); ESMS m/z = 426 $(M+H)^+$.

3-Amino-3´-nitro-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2l): It was obtained by the reaction of compound **1l** (1.1g, 3.10 mmol), malononitrile (0.41 g, 6.20 mmol) and potassium carbonate (0.43 g, 3.10 mmol), in water as yellow solid (0.91g, yield 66%), Analysis Found: C, 57.31; H, 4.64; N, 12.79 for $C_{21}H_{20}N_4O_7$ requires: C, 57.27; H, 4.58; N, 12.72; M.p. 137-140 °C; R_f 0.6 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -119.3 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3353 (OH), 2219 (C≡N), 1644, 1531, 1349; ^{1}H NMR (300 MHz, DMSO) δ = 8.39-8.30 (m, 2H, ArH), 8.08 -8.05 (1H, d, J = 7.8 Hz, ArH), 7.84 (1H, t, J = 7.9 Hz, ArH), 6.96 (1H, s, ArH), 6.73 (2H, s, $ArNH_2$), 5.18 (1H, d, J = 5.4 Hz, OH), 4.94 (1H, d, J = 4.6 Hz, OH), 4.89 (1H, d, J = 3.9 Hz, OH), 4.20 (1H, t, J = 5.5 Hz, OH), 3.64 (1H, dd, J_1 = 5.2, J_2 = 11.2 Hz, H-6´´a), 3.41-3.29 (3H, m, 2xCH, H-6´´b), 3.17-3.14 (1H, m, H-1´´), 3.06-3.00 (2H, m, CH), 2.98-2.93 (1H, m, H-1b), 2.80 (1H, dd, J_1 = 8.9, J_2 = 14.7 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.8 (Ar-C), 150.3(Ar-C), 148.2(Ar-C), 146.8 (Ar-C), 139.5 (Ar-C), 135.7 (Ar-CH), 130.8 (Ar-CH), 124.4 (Ar-CH), 123.6 (Ar-CH), 119.7 (Ar-CH), 116.3 (C≡N), 115.7 (C≡N), 97.7 (Ar-C), 93.2 (Ar-C), 80.9 (CH), 78.7 (CH), 78.4 (CH), 74.1 (CH), 70.9 (CH), 61.8 (OCH_2), 37.2 (CH_2); ESMS m/z = 460 $(M+H)^+$.

2-Amino-4´-(pyridin-3-yl)-6-[(*β*-D-glucopyranosyl)methyl] isophthalonitrile (2m): It was obtained by the reaction of compound **1m** (1.1g, 3.55 mmol), malononitrile (0.47 g, 7.11 mmol) and potassium carbonate (0.49 g, 3.55 mmol), in water as white solid (0.66g, yield 50%), Analysis Found: C, 60.69; H, 5.15; N, 14.21 for $C_{20}H_{20}N_4O_5$ requires: C, 60.60; H, 5.09; N, 14.13; m.p. 209-211 °C; R_f 0.48 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -69.44 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3369 (OH), 2210 (C≡N), 1629, 1581, 1473; ^{1}H NMR (300 MHz, DMSO); δ =8.77-8.77 (1H, m, ArH), 8.69-8.67 (1H, m, ArH), 8.04 (1H, d, J = 6.0Hz, ArH), 7.56-7.52 (1H, m, ArH), 6.91 (1H, s, ArH), 6.74 (2H, s, $ArNH_2$), 5.23 (1H, d, J = 5.4Hz, OH), 5.00 (1H, d, J = 4.5Hz, OH), 4.94 (1H, d, J = 4.2Hz, OH), 4.30 (1H, t, J = 5.4Hz, OH), 3.60-3.58 (1H, m, H-6´´a), 3.39-3.28 (3H, m, 2xCH, H-6´´b), 3.17-3.15 (1H, m, H-1´´), 3.00-2.94 (3H, m, 2xCH, H-1b), 2.75-2.73 (1H, m, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.8 (Ar-C), 150.5 (Ar-C), 150.2 (Ar-C), 149.2 (Ar-C), 146.0 (Ar-C), 136.7 (Ar-CH), 134.0 (Ar-CH), 131.4(Ar-CH), 124.0 (Ar-CH), 119.7 (Ar-CH), 116.5 (C≡N), 115.8 (C≡N), 97.4 (Ar-C), 93.3 (Ar-C), 80.9 (CH), 80.4(CH), 79.3(CH), 78.9 (CH), 74.0 (CH) 70.9 (CH), 61.8 (OCH_2), 37.3 (CH_2); ESMS m/z 397.3 $(M+H)^+$.

3-Amino-2´-chloro-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (2n): It was obtained by the reaction of compound **1n** (1.2g, 3.50 mmol), malononitrile (0.46 g, 7.01 mmol) and potassium carbonate (0.48 g, 3.50 mmol), in water as White solid (0.75g, yield 60%), Analysis Found: C, 58.62; H, 4.63; Cl, 8.21; N, 9.70 for $C_{21}H_{20}ClN_3O_5$ requires: C, 58.68; H, 4.69; Cl, 8.25; N, 9.78; O, 18.61; M.p. 120-123°C; R_f 0.55 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -93.07 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3424 (OH), 2217 (C≡N), 1630, 1218; ^{1}H NMR (300 MHz, DMSO); δ =7.62 (1H, d, J = 6.6Hz, ArH), 7.46-7.43 (3H, m, ArH), 6.74 (1H, s, ArH), 6.64

(2H, s, $ArNH_2$), 5.12 (1H, d, *J* = 3.99Hz, OH), 4.91 (1H, bs, OH), 4.84 (1H, bs, OH), 4.41 (1H, bs, OH), 3.56-3.16 (6H, m, 4xCH, H-6´´a &H-6´´b), 3.16-2.97 (3H, m, CH, H-1´´, H-1b), 2.79-2.77 (1H, m, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.1 (Ar-C), 149.8 (Ar-C), 137.2 (Ar-C), 131.9 (Ar-CH), 131.1 (Ar-CH), 130.0 (Ar-CH), 127.8 (Ar-CH), 115.7 (C≡N), 97.5 (Ar-C), 95.0 (Ar-C), 80.8 (CH), 78.7 (CH), 78.4 (CH), 73.9 (CH), 70.7 (CH), 61.7 (OCH_2), 37.3 (CH_2);ESMS *m/z* 418 $(M+H)^+$;

2-Amino-4´-(benzo[d][1,3]dioxol-5-yl)-6-[(*β*-D-glucocopyranosyl)methyl] isophthalonitrile (2o): It was obtained by the reaction of compound **1o** (1.1g, 3.12 mmol), malononitrile (0.41 g, 6.24 mmol) and potassium carbonate (0.43 g, 3.12 mmol), in water as yellow solid (0.96g, yield 70%), Analysis Found: C, 60.19; H, 4.89; N, 9.50 for $C_{22}H_{21}N_3O_7$ requires: C, 60.13; H, 4.82; N, 9.56; m.p. 164-167 °C; R_f 0.52 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -80.96 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3360 (OH), 2211 (C≡N), 1649, 1569, 1246; ^{1}H NMR (300 MHz, DMSO) δ = 7.17 (1H, s, ArH), 7.11-7.01 (2H, m, ArH), 6.81 (1H, s, ArH), 6.56 (2H, s, $ArNH_2$), 6.10 (2H, bs, CH_2), 5.19 (1H, d, *J* = 5.4 Hz, OH), 4.97 (1H, d, *J* = 4.4 Hz, OH), 4.91 (1H, bs, OH), 4.25 (1H, t, *J* = 5.3 Hz, OH), 3.64-3.58 (1H, dd, J_1 = 4.8, J_2= 11.2 Hz, H-6´´a), 3.37-3.25 (3H, m, 2xCH, H-6´´b), 3.17-3.15 (1H, m, H-1´´), 3.05 (2H, m, CH), 2.99-2.94 (1H, m, H-1b), 2.80 (1H, dd, J_1 = 8.8, J_2= 14.7 Hz, H-1a) ^{13}C NMR (50 MHz, DMSO) δ = 158.6 (Ar-C), 154.3 (Ar-C), 153.7 (Ar-C), 153.4 (Ar-C), 152.7 (Ar-C), 136.7 (Ar-C), 128.0 (Ar-CH), 128.5 (Ar-CH), 124.4 (Ar-CH), 121.5 (Ar-CH), 120.8 (C≡N), 114.1 (Ar-CH), 113.6 (Ar-CH), 106.7 (CH_2), 101.1 (Ar-C), 98.0 (Ar-C), 85.7 (CH), 84.4 (Ar-C), 83.5 (CH), 83.2 (CH), 78.8 (CH), 75.5 (CH) 66.6 (OCH_2), 42.0 (CH_2); ESMS *m/z* = 461 $(M+22)^+$.

3-Amino-5-[(*β*-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (4a): It was obtained by the reaction of compound **3a** (1.0g, 3.59 mmol), malononitrile (0.47 g, 7.19 mmol) and potassium carbonate (0.49 g, 3.59 mmol), in water as white solid (1.01g, yield 74%), Analysis Found C, 65.74; H, 5.24; N, 11.50 for $C_{20}H_{19}N_3O_4$ requires: C, 65.79; H, 5.31; N, 11.46. M.p. 175-178 °C; R_f 0.54 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -96.61 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3339 (OH), 2205 (C≡N), 1720, 1620, 1576; ^{1}H NMR (300 MHz, DMSO); δ =7.56-7.49 (5H, m, ArH), 6.72 (1H, s, ArH), 6.65 (2H, s, $ArNH_2$), 5.26 (1H, d, *J* = 5.5Hz, OH), 5.04 (1H, d, *J* = 4.6Hz, OH), 4.98 (1H, d, *J* = 4.8Hz, OH), 3.66 (1H, dd, J_1 = 5.1, J_2 = 10.8 Hz, H-5´´a), 3.40-3.21 (3H, m, 2xCH, H-5´´b), 3.14-3.06 (1H, m, H-1´´), 2.99-2.87 (2H, m, CH, H-1b), 2.75 (1H, dd, J_1 = 8.9, J_2 = 13.9 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.9 (Ar-C), 149.9 (Ar-C), 149.4 (Ar-C), 138.1 (Ar-C), 129.7 (Ar-CH), 129.1(Ar-CH), 128.9 (Ar-CH), 119.5 (Ar-CH), 116.6 (C≡N), 115.9 (C≡N), 97.1 (Ar-C), 93.3 (Ar-C), 80.4 (CH), 78.5 (CH), 74.2 (CH), 70.3 (CH), 60.3 (CH_2), 37.2 (CH_2); ESMS *m/z* 543 $(M+H)^+$.

3-Amino-4´-chloro-5-[(*β*-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (4b) It was obtained by the reaction of compound **3b** (1.0g, 3.20 mmol), malononitrile (0.42 g, 6.41 mmol) and potassium carbonate (0.44 g, 3.20 mmol), in water as white solid (0.96g, yield 73%), Analysis Found: C, 60.13; H, 4.64; Cl, 8.89; N, 10.51 for $C_{20}H_{18}ClN_3O_4$ requires: C, 60.08; H, 4.54; Cl, 8.87; N, 10.70; M.p. 202-205 °C; R_f 0.52 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -80.62 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3351 (OH), 2216 (C≡N), 1649, 1579, 1287; ^{1}H NMR (300 MHz, DMSO); δ =7.58 (1H, bs, ArH), 6.72 (1H, s, ArH), 6.62 (2H, s, $ArNH_2$), 5.20 (1H, d, *J* = 5.3Hz, OH), 4.96 (1H, d, *J* = 4.3Hz, OH), 4.91 (1H, d, *J* = 4.8Hz, OH), 3.66 (1H, dd, J_1 = 5.2, J_2 = 10.8 Hz, H-5´´a), 3.35-3.28 (2H, m, CH, H-5´´b), 3.26-3.25 (1H, m, CH), 3.14-3.07 (1H, m, H-1´´), 3.00-2.88 (2H, m, CH, H-1b), 2.76 (1H, dd, J_1 = 8.7, J_2= 13.6 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.8 (Ar-C), 150.0 (Ar-C), 148.1 (Ar-C), 146.9 (Ar-C), 138.8 (Ar-C), 134.7

(Ar-CH), 130.8 (Ar-CH), 129.1 (Ar-CH), 119.3 (Ar-CH), 116.4 (C≡N) 115.8 (C≡N), 97.4 (Ar-C), 93.2 (Ar-C), 80.3 (CH), 79.6 (CH), 78.5 (CH), 74.2 (CH), 70.2 (OCH_2), 37.8 (CH_2); ESMS *m/z* 496 $(M+H)^+$.

3-Amino-3′-nitro-5-[(*β*-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (4c) It was obtained by the reaction of compound **3c** (1.0g, 3.09 mmol), malononitrile (0.40 g, 6.19 mmol) and potassium carbonate (0.42 g, 3.09 mmol), in water as white solid (0.89g, yield 73%), Analysis Found: C, 58.57; H, 4.49; N, 13.71 for $C_{20}H_{18}N_4O_6$ requires: C, 58.53; H, 4.42; N, 13.65; M.p. 219-222 °C; R_f 0.56 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -72.72 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3376 (OH), 2217 (C≡N), 1812, 1587, 1217; ^{1}H NMR (300 MHz, DMSO); δ =8.37-8.33 (1H, m, ArH), 8.06 (1H, d, *J* = 7.6Hz, ArH), 7.85 (1H, t, *J* = 7.8Hz, ArH), 6.83 (1H, s, ArH), 6.71 (2H, s, $ArNH_2$), 5.21 (1H, d, *J* = 5.3Hz, OH), 4.96 (1H, d, *J* = 4.2Hz, OH), 4.91 (1H, d, *J* = 4.7Hz, OH), 3.66 (1H, dd, J_1 = 5.1, J_2= 10.8 Hz, H-5′′a), 3.39-3.24 (2H, m, CH, H-5′′b), 3.17-3.00 (2H, m, CH, H-1′′), 2.97-2.89 (2H, m, CH, H-1b), 2.78 (1H, dd, J_1 = 9.1, J_2= 13.8 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.8 (Ar-C), 150.4 (Ar-C), 148.2 (Ar-C), 146.9 (Ar-C), 139.4 (Ar-C), 135.6 (Ar-CH), 130.8 (Ar-CH), 124.4 (Ar-CH), 123.7 (Ar-CH), 119.4 (Ar-CH), 116.3 (C≡N) 115.7 (C≡N), 98.0 (Ar-C), 93.3(Ar-C), 80.2 (CH), 79.6 (CH), 78.5 (CH), 74.3 (CH), 70.2 (OCH_2), 37.9 (CH_2); ESMS *m/z* 551 $(M+H)^+$.

3-Amino-4′-methoxy-5-[(*β*-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (4d) It was obtained by the reaction of compound **3d** (1.1g, 3.57 mmol), malononitrile (0.47 g, 7.14 mmol) and potassium carbonate (0.49 g, 3.57 mmol), in water as white solid (0.98g, yield 75%), Analysis Found: C, 63.79; H, 5.35; N, 10.63 for $C_{21}H_{21}N_3O_5$ requires C, 63.68; H, 5.29; N, 10.53. M.p. 190-193°C; R_f 0.55 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -96.54 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3362 (OH), 2215 (C≡N), 1650, 1580, 1293; ^{1}H NMR (300 MHz, DMSO); δ =7.53 (2H, d, *J* = 8.6Hz, ArH), 7.08 (2H, d, *J* = 8.6Hz, ArH), 6.70 (1H, s, ArH), 6.52 (2H, s, $ArNH_2$), 5.19 (1H, d, *J* = 5.4Hz, OH), 4.95 (1H, d, *J* = 4.5Hz, OH), 4.91 (1H, d, *J* = 4.8Hz, OH), 3.82 (3H, s, OCH_3), 3.66 (1H, dd, J_1 = 5.1, J_2= 10.8 Hz, H-5′′a), 3.35-3.24 (3H, m, 2xCH, H-5′′b), 3.14-3.07 (1H, m, H-1′′), 2.99-2.87 (2H, m, CH, H-1b), 2.74 (1H, dd, J_1 = 8.9, J_2= 13.8 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 160.6 (Ar-C), 153.9 (Ar-C), 149.6 (Ar-C), 149.1 (Ar-C), 130.3 (Ar-CH), 130.2 (Ar-CH), 119.3 (Ar-CH), 116.8 (C≡N) 114.5 (C≡N), 96.5 (Ar-C), 93.1 (Ar-C), 80.3 (CH), 78.5 (CH), 74.2 (CH), 70.2 (OCH_2), 55.8 (OCH_3), 37.7 (CH_2); ESMS *m/z* 456 $(M+H)^+$.

3-Amino-5-[(*β*-D-cellobiosyl)methyl]biphenyl-2,4-dicarbonitrile (4e) It was obtained by the reaction of compound **3e** (1.2g, 2.55 mmol), malononitrile (0.33g, 5.10 mmol) and potassium carbonate (0.35g, 2.55 mmol), in water as white solid (0.71g, yield 61%), Analysis Found: C, 58.31; H, 5.72; N, 7.49 for $C_{27}H_{31}N_3O_{10}$ requires : C, 58.16; H, 5.60; N, 7.54; M.p. 236-239°C; R_f 0.4 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -44.42 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3424(OH), 2217 (C≡N), 1630, 1218; ^{1}H NMR (300 MHz, DMSO); δ =7.59-7.57 (2H, m, ArH), 7.51-7.49 (3H, m, ArH), 6.84 (1H, s, ArH), 6.61 (2H, s, $ArNH_2$), 5.40 (1H, d, *J* = 5.4Hz, OH), 5.27 (1H, d, *J* = 4.7Hz, OH), 5.05-5.04 (1H, d, *J* = 4.7Hz, OH), 5.03-5.01 (1H, d, *J* = 5.3Hz, OH), 4.73 (1H, bs, OH), 4.63 (1H, t, *J* = 5.1Hz, OH), 4.38(1H, t, *J* = 5.7Hz, OH), 4.27 (1H, d, *J* = 7.7Hz, H-1′′′), 3.70-3.67 (2H, m, H-6a & H-6′′a), 3.56-3.51(1H, m, H-6′′b), 3.42-3.38 (1H, m, H-6′′′b), 3.32-3.28 (5H, m, CH), 3.23.-3.12 (3H, m, CH), 3.08-2.98 (3H, m, 2xCH, H-1b), 2.78 (1H, dd, J_1 = 8.9, J_2= 14.7 Hz, H-1a); ^{13}C NMR (50 MHz, DMSO) δ = 153.8 (Ar-C), 149.5 (Ar-C), 149.3 (Ar-C), 138.1 (Ar-C), 129.7 (Ar-CH), 129.0 (Ar-CH), 128.9 (Ar-CH), 119.7 (Ar-CH), 116.6 (C≡N), 115.7 (C≡N), 103.6 (CH), 96.8 (Ar-C), 93.3 (Ar-C), 81.4 (CH), 79.6 (CH),78.8

(CH),78.4 (CH), 78.7 (CH), 78.4 (CH), 75.1 (CH), 73.7 (CH), 70.4 (CH), 61.4 (OCH_2), 37.1 (CH_2); ESMS *m/z* 577 $(M+H)^+$.

3-amino-2-methyl-5-[(*β*-D-glucopyranosyl)methyl]biphenyl-4-carbonitrile(5) It was obtained by the reaction of compound **2a** (1.0g, 3.24 mmol), with nitroethane (0.23ml, 3.12 mmol) in the presence of potassium carbonate (0.44 g, 3.24 mmol), followed by addition of malononitrile (0.21 g, 3.24 mmol) in water as yellow solid (0.84g, yield 65%), Analysis Found: C, 65.72; H, 6.34; N, 7.31; O, 20.87 for $C_{21}H_{21}N_3O_5$ requires: C, 65.61; H, 6.29; N, 7.29; O, 20.81; M.p. 210-213°C; R_f 0.61 (20% MeOH:$CHCl_3$); $[\alpha]_D^{25}$ -30.63 (c 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3283 (OH), 2954, 2368 (C≡N), 1665, 1457; ^1H NMR (300 MHz, $CDCl_3$+DMSO); δ =7.55-7.53 (1H, m, ArH), 7.46-7.45 (1H, m, ArH), 7.40-7.30 (2H, m, ArH), 7.26-7.23 (1H, m, ArH), 6.55 (1H, s, ArH), 6.24 (1H, s, $ArNH_2$), 4.87 (1H, d, *J* = 4.5Hz, OH), 4.78-4.69 (3H, m, OH), 3.78 (1H, m, H-6´´a), 3.61-3.54 (2H, m, CH, H-6´´b), 3.47-3.45 (1H, m, CH), 3.38-3.28 (2H, m, CH, H-1´´), 3.14-3.02 (2H, m, CH, H-1b), 2.79-2.64 (1H, m, H-1a), 1.98 (3H, s, CH_3); ^{13}C NMR (50 MHz, DMSO) δ = 150.0 (Ar-C), 146.0 (Ar-C), 141.5 (Ar-C), 139.6 (Ar-C), 138.1 (Ar-C), 129.3 (Ar-CH), 129.1(Ar-CH), 128.7 (Ar-CH), 128.2 (Ar-CH), 127.3 (Ar-CH), 120.2 (Ar-C), 119.7 (Ar-CH), 117.5 (C≡N), 95.7 (Ar-C), 80.3 (CH), 79.6 (Ar-C), 78.5 (CH), 73.6 (CH), 70.8 (CH), 62.1 (OCH_2), 36.5 (CH_2), 14.7(CH_3); ESMS *m/z* 383 $(M+H)^+$.

The crystal data of (4a), $C_{20}H_{19}N_3O_4$, *M* = 411.45, Monoclinic, $P2_1$, *a* = 11.358(4)Å,*b* = 7.015(3) Å, *c* = 12.389(5)Å, α = 90.00°, *β* = 105.219(6)°, γ = 90.00°, *V* = 952.4(6) $Å^3$, *Z* = 2, D_c = 1.435 gcm^{-3}, *μ* (Mo-Kα) = 0.10 mm^{-1}, *F*(000) = 436, rectangular block, Colourless crystal, 6157 reflections measured (R_{int} = 0.0566), 4285 unique, wR_2 = 0.236 for all data, conventional *R* = 0.0701 for 3750 Fo > 4sig(Fo) and 0.0905 for all 4285 data, *S* = 1.137 for all data and 278 parameters. Unit cell determination and intensity data collection (2θ= 50°) was performed on a Bruker Smart Apex diffractometer with CCD area detector at 293(2)K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs:XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997]. CCDC (deposit No:**) contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12Union Road, Cambridge, CB2 1EZ, U. K; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk.

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