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

Mridul Misra [a], Rahul Sharma [a], Ruchir Kant [b], P.R. Maulik [b], R.P. Tripathi [a,*]

[a] Medicinal and Process Chemistry Division, Central Drug Research Institute (CSIR), Lucknow 226001, UP, India
[b] Molecular and Structural Biology Division, Central Drug Research Institute (CSIR), Lucknow 226001, India

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ABSTRACT

One pot synthesis of the butenonyl-*C*-β-D-glycosides with malononitrile in the presence of K_2CO_3 in water under mild and green reaction conditions leading to the formation of small library of multifunctional biphenyl methyl-*C*-β-D-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.

1. Introduction

C-Glycosides have received increasing interest in medicinal chemistry as carbohydrate biomimetics.[1–3] As compared to *O*-glycosidic 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 possess 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 have been studied in great detail for different biological activity. Among the naturally occurring β-*C*-aryl glycosides several *C*-glycosyl flavonoids and antibiotics of gilvocarcin family, the pluramycins and others are of great importance due to their interesting biological activities.[4–6] Most of the naturally occurring *C*-glycosides with sugar as hexapyranoid unit, the thermodynamically more favourable 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 different plants and two of the representatives[15,16] (**A** and **B**) are shown in Fig. 1a. These phenolic β-*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]

Different synthetic strategies are known to synthesize aryl-β-*C*-glycosides.[21–24] The above aryl-β-*C*-glycosides as SGLT2 inhibitors have been synthesised involving multistep synthesis. The synthesis is associated with many drawbacks such as use of BuLi, potentially hazardous and costly reagents, and sophisticated reaction conditions.[25,26] The Stille coupling reaction of *C*-glycosylated aryl tins with aryl bromide is also known to give biphenyl glycosides.[27] Biphenyl system has been developed via multi-component reactions of substituted enones, malononitriles and other reagents under various reaction conditions.[28–30] A solvent free approach to synthesise polysubstituted benzene from enones and malononitrile under basic conditions[31] and a recent report on use of ionic liquids in MCR of chalcones and malanonitrile to give polysubstituted biphenyls is noteworthy.[32] Yi et al. has also reported the synthesis of above type of skeleton using ynones and malanonitrile as starting material in MCR.[33]

Most of the methods for the synthesis of the biphenyls suffer from drawbacks of unwanted side products, costly reagents, non eco-friendly catalysts and harsh refluxing conditions etc.[34–36] In one of our continuing programs towards the development of new

* Corresponding author. Tel.: +91 0522 2612411; fax: +91 522 2623405/2623938/2629504; e-mail address: rpt.cdri@gmail.com (R.P. Tripathi).

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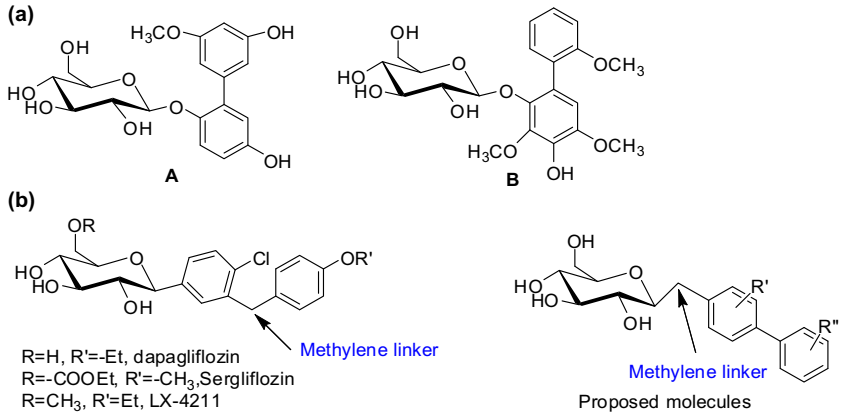


Fig. 1. a). Naturally occurring biphenyl glycosides **A** from leaves of *Eriobotrya japonica* **B** from fruits of *Pyracantha fortuneana*. (b) SGLT2 inhibitors in clinical trial for diabetes and our proposed molecules.

antidiabetic agents we were interested to prepare the analogues of the above SGLT2 inhibitors, the aryl-β-*C*-glycosides where the oxygen atom in glycosides is replaced by a methylene group (Fig. 1b) using a simple and economical method.

In order to address the simplicity, economics and environment we have developed one-pot protection free and eco-friendly synthesis of biphenyl methyl β-*C*-glycosides in aqueous medium. Our synthetic protocol involves the one step MCR of unprotected butenoyl-*C*-β-D-glycosides and malononitrile in presence of K_2CO_3 as catalyst and water as solvent. Method developed by us is devoid of any protection or deprotection step and quite economical and eco-friendly and no sophisticated reaction conditions are required during reaction.

2. Results and discussion

The starting butenonyl-*C*-glycosides (**1a**–**o**) could be accessed from abundantly available D-glucose following our recently reported and literature methods.[37–40] The biphenyl methyl β-*C*-glucopyranosides were obtained by reaction of butenoyl-*C*-glucopyranosides with malononitrile in presence of a base as catalyst.

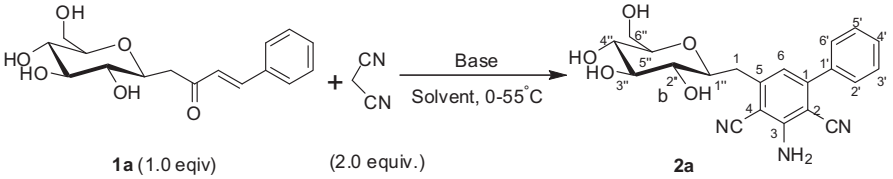
To optimize the reaction condition, reaction of 1 equiv of (*E*)-1-(β-D-glucopyranosylmethyl)-4-phenyl-but-3-en-2-one (**1a**) with malononitrile (2.0 equiv) in the different organic solvents under the influence of various bases at different temperatures was investigated to get the desired 3-amino-5-[(β-D-glucopyranosyl) methyl]biphenyl-2,4-dicarbonitrile (**2a**) (Scheme 1). 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.

Out of the secondary (pyrrolidine) and tertiary amines (Et_3N and DBU) used 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. Among the alkali metal hydroxides used, sodium hydroxide was

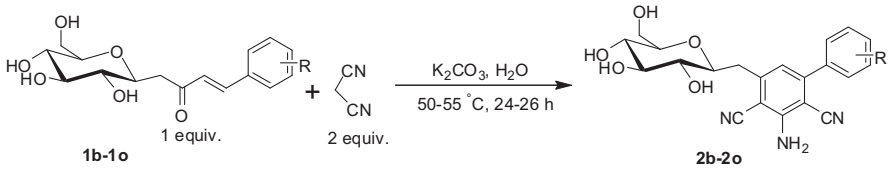
Table 1
Optimization of reaction condition for the synthesis of biphenyl methyl-β-D-glycoside

Entry	Catalyst (1.0)	Solvent	Reaction time (h)	Isolated yield (%)
1	Pyrrolidine	Water	28	30
2	Triethylamine	Water	30	18
3	DBU	Water	29	5
4	K_2CO_3	Water	24	78
5	K_2CO_3	DMSO	27	5
6	K_2CO_3	CH_2Cl_2	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

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 as 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, 1 equiv of potassium carbonate as base, water as solvent and reaction temperature of 50–55 °C was found to be the most optimal reaction condition to give the desired compound **2a** in 78% yield (entry 4, Table 1).

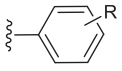


Scheme 1. Reaction of (*E*)-1-(β-D-glucopyranosylmethyl)-4-phenyl-but-3-en-2-one (**1a**) with malononitrile under different reaction conditions.



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

Table 2
Syntheses of biphenyl methyl-*C*-β-D-glucopyranosides (**2b**–**o**)

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-Diethylenedioxyphenyl	26	70

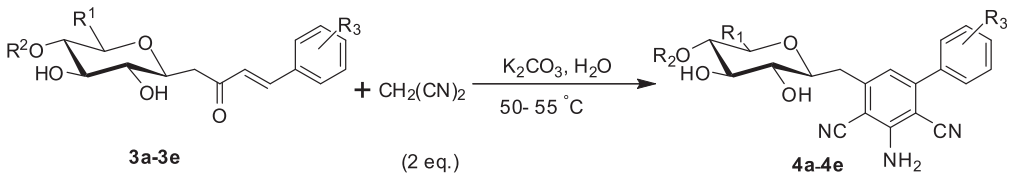
[a] Isolated yields are based on the butenonyl glycosides substrates.

The structure of (**2a**) was established on the basis of its spectroscopic data and microanalysis. The IR spectrum of compound **3a** 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 as $[M+H]^+$ peak corresponding to its molecular formula. In the ^1H NMR spectrum, compound **3a**, 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 sugar at C-2″, C-3″and C-4″ were observed 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 moiety 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. In the ^{13}C NMR spectrum 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, respectively.

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

It is clear from Table 2, that the yield of the biphenyl methyl-*C*-β-D-glucopyranosides with butenonyl glycosides as substrates bearing 2- or 4-halo and methoxy substituents in the aromatic moiety (entries 1, 3, 5, 6, 13, Table 2) is better than with the glycosyl substrates having the 4-hydroxy, 4-*N*,*N*-dimethylamine and 4-benzyloxysubstituents in the phenyl ring. 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 disubstitution and substitution with bulky naphthyl group in aromatic ring of glucosyl butenone offers comparable yields. However, when the aromatic ring in the substrate was replaced by a heteroaromatic ring, thiophenyl 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 glycosides with any sort of aromatic ring.

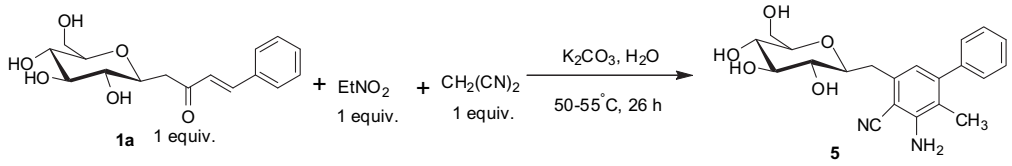
We have extended this work to see the scope of this reaction with butenonyl xylopyranose and a butenonyl cellobiose also. Thus the reaction 1-(β-D-xylopyranosyl)-4-(aryl)-but-3-en-2-ones (**3a**–**d**) and a disaccharide (cellobiose) derived butenonyl-*C*-glycoside (**3e**)[23] with malononitrile separately under the above optimal reaction condition resulted respective biphenyl methyl-*C*-β-D-xylopyranosides (**4a**–**d**) 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**–**d**) 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**–**d**) and 3-amino-5-[(β-D-cellobiosyl)methyl]biphenyl-2,4-dicarbonitrile (**4e**).



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

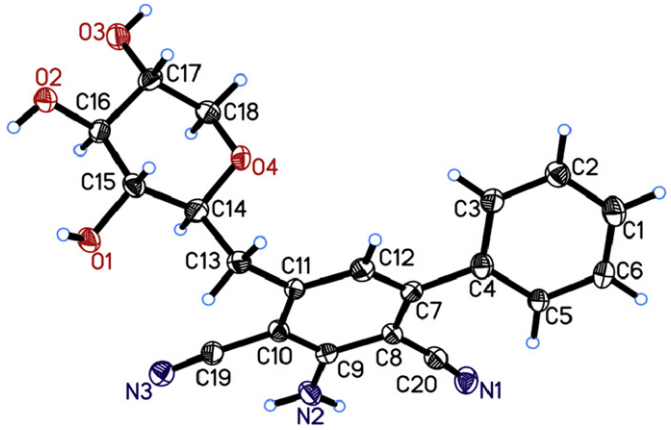


Fig. 2. Ortep diagram of 3-amino-5-[(β-D-xylopyranosyl)methyl] biphenyl-2,4-dicarbonitrile (**4a**).

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 Knoevenagel reaction with another 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 cycloaddition product (**IV**). The base catalysed elimination of HCN gave an intermediate imine (**V**), which on aerial oxidation afforded the biphenyl methyl glycosides (**VI**).

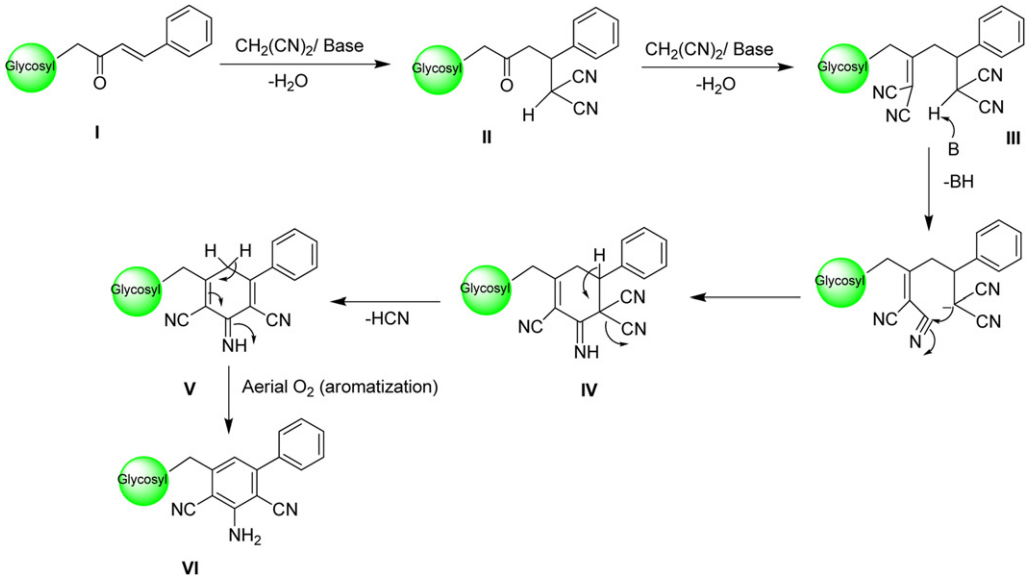


Fig. 3. Reaction mechanism proposed for the formation of biphenyl methyl-C-β-D-glycosides.

To enhance the scope of this reaction to get biphenyl methyl glycosides with different substituents in the aromatic ring and to gain an insight into the reaction mechanism the above glucopyranosyl butenone **1a** was reacted with nitroethane (1.0 equiv) and malononitrile (1.0 equiv) instead of 2 equiv of malanonitrile alone as above. The reaction led to the formation of 3-amino-2-methyl-5-[(β-D-glucopyranosyl)methyl]biphenyl-4-carbonitrile (**5**) as the only isolable product in 65% yield (Scheme 4).

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).

3. 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 nontoxic 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 eco-friendly nature, 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.

4. Experimental section

4.1. 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% $KMnO_4$ aqueous 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 on KBr or in solution 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 parts per million 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), br s (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 on German made Vario-EL (III) elemental analyzer. All spectroscopic data including elemental analyses were carried out in SAIF (sophisticated analytical instrumental facility), Division, Central Drug research Institute, Lucknow. The X-ray crystallographic data were obtained from IIT Kanpur India.

4.2. General procedure for the preparation of compounds (2a–o, 4a–e)

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. The reaction mixture was stirred magnetically at 50–55 °C. After completion of the reaction, the reaction mixture was extracted by ethyl acetate/water. The organic layer was dried (anhyd Na_2SO_4) and concentrated under reduced pressure to give a crude mass. The latter was purified by column chromatography on silica gel (60–120 mesh) using methanol/chloroform as eluant to give the respective 3-amino-5-[(β-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**2a**–**o**) or 3-amino-5-[(β-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**4a**–**d**) or 3-amino-5-[(β-D-cellobiosyl) methyl]biphenyl-2,4-dicarbonitrile (**4e**).

*4.2.1. 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 K_2CO_3 (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; mp 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=11.1 Hz, 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 $(M+H)^+$.

*4.2.2. 3-Amino-4′-bromo-5-[(β-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**2b**).* It was obtained by reaction of compound **1b** (1.2 g, 3.10 mmol), malononitrile (0.40 g, 6.20 mmol) and K_2CO_3 (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; mp 119–122 °C; R_f 0.45 (20% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ −18.5 (*c* 0.1, DMSO); IR (KBr) ν_{max} cm^{-1} 3352 (OH), 2217 (C≡N), 1638, 1578, 1437; ^1H 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, br s, OH), 4.87 (1H, br s, OH), 4.22 (1H, br s, OH), 3.65 (1H, dd, J_1=3.6, J_2=11.2 Hz, H-6″a), 3.39–3.27 (3H, m, 2×CH, H-6″b), 3.17 (1H, br s, 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 $(M+H)^+$.

*4.2.3. 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 K_2CO_3 (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; mp 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; ^1H 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, 2×CH, H-6″a), 3.32–3.26 (3H, m, 2×CH, 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 $(M+7)^+$.

*4.2.4. 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 K_2CO_3 (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; mp 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; ^1H 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, 2×CH, H-6″b), 3.16–3.12 (1H, m, H-1″), 3.04–2.91 (3H, m, 2×CH, 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 $(M+H)^+$.

*4.2.5. 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 K_2CO_3 (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; mp 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; ^1H NMR (300 MHz, DMSO) δ=7.17 (3H, m, ArH), 6.88 (1H, s, ArH), 6.48 (2H, s, $ArNH_2$), 5.14 (1H, br s, OH), 4.88 (2H, br s, OH), 4.20 (1H, br s, OH), 4.26 (1H, t, *J*=5.3 Hz, OH), 3.82 (6H, br s, 2×OCH_3), 3.64–3.57 (1H, m, H-6″a), 3.40–3.34 (3H, m, 2×CH, 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 $(M+H)^+$.

*4.2.6. 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 K_2CO_3 (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; mp 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; ^1H 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 $(M+H)^+$.

*4.2.7. 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 K_2CO_3 (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; mp 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; ^1H 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×CH, 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 $(M+Na+H)^+$.

*4.2.8. 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/$CHCl_3$); mp 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; ^1H 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, br s, OH), 4.33 (1H, br s, OH), 3.67–3.65 (1H, m, H-6″a), 3.37–3.31 (3H, m, 2×CH, 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 $(M+21)^+$.

*4.2.9. 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 K_2CO_3 (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; mp 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; ^1H 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, br s, OH), 4.26 (1H, t, *J*=5.3 Hz, OH), 3.65 (1H, dd, J_1=4.9, J_2=11.0 Hz, H-6″a), 3.41–3.25 (3H, m, 2×CH, H-6″b), 3.17–3.16 (1H, m, H-1″), 3.05 (2H, br s, 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 $(M+H)^+$.

*4.2.10. 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 K_2CO_3 (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; mp 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; ^1H NMR (300 MHz, DMSO) δ=7.49 (2H, d, *J*=8.7 Hz, ArH), 6.83 (3H, m, ArH), 6.43 (2H, s, $ArNH_2$), 5.17 (1H, d, *J*=5.4 Hz, OH), 4.95 (1H, d, *J*=4.6 Hz, OH), 4.89 (1H, br s, OH), 4.25 (1H, t, *J*=5.5 Hz, OH), 3.65 (1H, dd, J_1=5.0, J_2=11.2 Hz, H-6″a), 3.36–3.24 (3H, m, 2×CH, H-6″b), 3.17–3.15 (1H, m, H-1″), 3.05 (2H, br s, CH), 2.97–2.85 (7H, m, 2×NCH_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 $(M+H)^+$.

*4.2.11. 2-Amino-4′-(thiophen-2-yl)-6-[(β-D-glucopyranosyl)methyl] isophthalonitrile (**2k**).* It was obtained by the reaction of compound **1k** (1.2 g, 3.81 mmol), malononitrile (0.50 g, 7.64 mmol) and K_2CO_3 (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; mp 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; ^1H 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, 2×CH, 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 $(M+H)^+$.

*4.2.12. 3-Amino-3′-nitro-5-[(β-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**2l**).* It was obtained by the reaction of compound **1l** (1.1 g, 3.10 mmol), malononitrile (0.41 g, 6.20 mmol) and K_2CO_3 (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; mp 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, 2×CH, 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 $(M+H)^+$.

*4.2.13. 2-Amino-4′-(pyridin-3-yl)-6-[(β-D-glucopyranosyl)methyl] isophthalonitrile (**2m**).* It was obtained by the reaction of compound **1m** (1.1 g, 3.55 mmol), malononitrile (0.47 g, 7.11 mmol) and K_2CO_3 (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; mp 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*=6.0 Hz, ArH), 7.56–7.52 (1H, m, ArH), 6.91 (1H, s, ArH), 6.74 (2H, s, $ArNH_2$), 5.23 (1H, d, *J*=5.4 Hz, OH), 5.00 (1H, d, *J*=4.5 Hz, OH), 4.94 (1H, d, *J*=4.2 Hz, OH), 4.30 (1H, t, *J*=5.4 Hz, OH), 3.60–3.58 (1H, m, H-6″a), 3.39–3.28 (3H, m, 2×CH, H-6″b), 3.17–3.15 (1H, m, H-1″), 3.00–2.94 (3H, m, 2×CH, 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 $(M+H)^+$.

*4.2.14. 3-Amino-2′-chloro-5-[(β-D-glucopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**2n**).* It was obtained by the reaction of compound **1n** (1.2 g, 3.50 mmol), malononitrile (0.46 g, 7.01 mmol) and K_2CO_3 (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; mp 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*=6.6 Hz, ArH), 7.46–7.43 (3H, m, ArH), 6.74 (1H, s, ArH), 6.64 (2H, s, $ArNH_2$), 5.12 (1H, d, *J*=3.99 Hz, OH), 4.91 (1H, br s, OH), 4.84 (1H, br s, OH), 4.41 (1H, br s, OH), 3.56–3.16 (6H, m, 4×CH, H-6″a and 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 $(M+H)^+$.

*4.2.15. 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** (1.1 g, 3.12 mmol), malononitrile (0.41 g, 6.24 mmol) and K_2CO_3 (0.43 g, 3.12 mmol) in water as yellow solid (0.96 g, 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; mp 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, br s, CH_2), 5.19 (1H, d, *J*=5.4 Hz, OH), 4.97 (1H, d, *J*=4.4 Hz, OH), 4.91 (1H, br s, 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, 2×CH, 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 $(M+22)^+$.

*4.2.16. 3-Amino-5-[(β-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**4a**).* It was obtained by the reaction of compound **3a** (1.0 g, 3.59 mmol), malononitrile (0.47 g, 7.19 mmol) and K_2CO_3 (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; mp 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*=5.5 Hz, OH), 5.04 (1H, d, *J*=4.6 Hz, OH), 4.98 (1H, d, *J*=4.8 Hz, OH), 3.66 (1H, dd, J_1=5.1, J_2=10.8 Hz, H-5″a), 3.40–3.21 (3H, m, 2×CH, 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 $(M+H)^+$.

*4.2.17. 3-Amino-4′-chloro-5-[(β-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**4b**).* It was obtained by the reaction of compound **3b** (1.0 g, 3.20 mmol), malononitrile (0.42 g, 6.41 mmol) and K_2CO_3 (0.44 g, 3.20 mmol) in water as white solid (0.96 g, 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; mp 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, br s, ArH), 6.72 (1H, s, ArH), 6.62 (2H, s, $ArNH_2$), 5.20 (1H, d, *J*=5.3 Hz, OH), 4.96 (1H, d, *J*=4.3 Hz, OH), 4.91 (1H, d, *J*=4.8 Hz, 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 $(M+H)^+$.

*4.2.18. 3-Amino-3′-nitro-5-[(β-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**4c**).* It was obtained by the reaction of compound **3c** (1.0 g, 3.09 mmol), malononitrile (0.40 g, 6.19 mmol) and K_2CO_3 (0.42 g, 3.09 mmol) in water as white solid (0.89 g, 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; mp 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*=7.6 Hz, ArH), 7.85 (1H, t, *J*=7.8 Hz, ArH), 6.83 (1H, s, ArH), 6.71 (2H, s, $ArNH_2$), 5.21 (1H, d,

J=5.3 Hz, OH), 4.96 (1H, d, J=4.2 Hz, OH), 4.91 (1H, d, J=4.7 Hz, 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 $(M+H)^+$.

*4.2.19. 3-Amino-4′-methoxy-5-[(β-D-xylopyranosyl)methyl]biphenyl-2,4-dicarbonitrile (**4d**).* It was obtained by the reaction of compound **3d** (1.1 g, 3.57 mmol), malononitrile (0.47 g, 7.14 mmol) and K_2CO_3 (0.49 g, 3.57 mmol) in water as white solid (0.98 g, 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; mp 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=8.6 Hz, ArH), 7.08 (2H, d, J=8.6 Hz, ArH), 6.70 (1H, s, ArH), 6.52 (2H, s, $ArNH_2$), 5.19 (1H, d, J=5.4 Hz, OH), 4.95 (1H, d, J=4.5 Hz, OH), 4.91 (1H, d, J=4.8 Hz, 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, 2×CH, 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 $(M+H)^+$.

*4.2.20. 3-Amino-5-[(β-D-cellobiosyl)methyl]biphenyl-2,4-dicarbonitrile (**4e**).* It was obtained by the reaction of compound **3e** (1.2 g, 2.55 mmol), malononitrile (0.33 g, 5.10 mmol) and K_2CO_3 (0.35 g, 2.55 mmol) in water as white solid (0.71 g, 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; mp 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=5.4 Hz, OH), 5.27 (1H, d, J=4.7 Hz, OH), 5.05–5.04 (1H, d, J=4.7 Hz, OH), 5.03–5.01 (1H, d, J=5.3 Hz, OH), 4.73 (1H, br s, OH), 4.63 (1H, t, J=5.1 Hz, OH), 4.38(1H, t, J=5.7 Hz, OH), 4.27 (1H, d, J=7.7 Hz, H-1‴), 3.70–3.67 (2H, m, H-6a and 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, 2×CH, 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 $(M+H)^+$.

*4.2.21. 3-Amino-2-methyl-5-[(β-D-glucopyranosyl)methyl]biphenyl-4-carbonitrile (**5**).* It was obtained by the reaction of compound **2a** (1.0 g, 3.24 mmol), with nitroethane (0.23 ml, 3.12 mmol) in the presence of K_2CO_3 (0.44 g, 3.24 mmol), followed by addition of malononitrile (0.21 g, 3.24 mmol) in water as yellow solid (0.84 g, 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; mp 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; ^{1}H 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=4.5 Hz, 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 g cm^{-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 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: SMART 32 (Bruker), SAINT (Bruker) and SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997]. CCDC (deposit No: 784,739) 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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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.067.

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