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A facile synthesis of sugar-pyrazole derivatives

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ABSTRACT

A facile synthesis of sugar-pyrazole derivatives has been accomplished by condensation of sugar-chalcone with hydrazine hydrate under neutral conditions resulting in yields of 70–85%. The products are characterized by FTIR and NMR spectroscopy and by elemental analysis. The β-anomeric forms for these derivatives were assigned by NMR spectroscopy.

1. Introduction

Pyrazole derivatives are important biologically active heterocyclic compounds.[1–9] These derivatives are the subject of many research studies due to their widespread potential biological activities, such as, anti-inflammatory,[1] antipyretic,[2] antimicrobial,[3] antiviral,[4] antitumor,[5] anticonvulsant,[6] antihistaminic,[7] insecticidal[8] and fungicidal activities.[9] Pyrazole derivatives represent important building blocks in organic and medicinal chemistry, such as luminophores, dyes, insecto-acaricides, analgesic, antiphlogistic, antibacterial, and antidepressant drugs.[10–22] In addition, they are of great interest due to their pharmacological properties. For example, pyrazole-3-carboxylic acid (**1**) and pyrazolo[1,5-*c*]quinazoline-2-carboxylates are nicotinic acid receptor agonists[23] and excitatory amino acid antagonists, respectively (Fig. 1).[23,24] Bis(benzo-[g]indazole-3-carboxamide) derivatives exhibit antiproliferative activity against various cancer cell lines.[25] Ethyl-5-propyl-1*H*-pyrazole-3-carboxylate is a key intermediate for the synthesis of Viagra®.[26] Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide, **2**) is the first drug to market amongst a number of selective cyclo-oxygenase-2 (COX-2) inhibitors that are promising anti-inflammatory and analgesic agents without the undesirable side effects associated with other nonsteroidal anti-inflammatory drugs (Fig. 1).[27,28] Recently, Nicolaou et al. reported that a pyrazole-substituted epothilone derivative that shows strong antitumor activity through the stabilization of microtubules by binding with tubulin.[29] Pyrazoles are obtained by 1,3-dipolar cycloaddition reaction of diazoalkanes with alkynes and related transformations.[30–32] Other syntheses rely on cyclization of 1,3-diketones with hydrazine[33–35] and on Michael addition of hydrazines with α,β-unsaturated ketones.[36,37] Due to the importance of sugars in biological systems, recent research focuses on the studies of sugar-based biomolecules.[38–41] In the present study, we have reported a facile synthesis of novel class of sugar-based pyrazole derivatives.

2. Results and discussion

4,6-*O*-Butylidene-D-glucopyranose was synthesized from D-glucose by adopting the literature procedure.[42,43] C-β-Glycosidic ketone **3** was synthesized by the Knoevenagel condensation of 2,4-pentanedione with 4,6-*O*-butylidene-D-glucopyranose in the presence of sodium bicarbonate using THF–H_2O as solvent.[44–46] Aldol condensation of C-β-glycosidic ketones **3**(**a** and **b**) with various substituted aromatic aldehydes **4**(**a–f**) resulted in the formation of the corresponding α,β-unsaturated-C-β-glycosidic ketones **5**(**a–g**) in 70–90% yield (Scheme 1). Acetylation of **5b** using Ac_2O resulted in the formation of the acetylated product (*E*)-1-(2,3-di-*O*-acetyl-4,6-*O*-butylidene-β-D-glucopyranosyl)-4-(4-bromophenyl)-but-3-en-2-one (**5h**) in 90% yield.

Reaction of (*E*)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(4-bromophenyl)-but-3-en-2-one (**5a**) with hydrazine hydrate under neutral conditions leads to the formation of a pyrazoline intermediate, which undergoes self-oxidation resulting in the formation of a sugar-based pyrazole derivative. Under the given reaction conditions, formation of the unprotected saccharide has been observed. However, compound **5h** reacts with hydrazine hydrate

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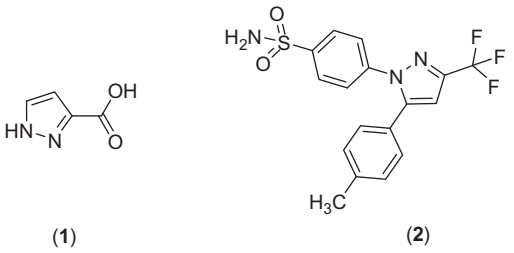


(1) (2)

Figure 1. Representative example of pyrazole class of natural products **1** and **2**.[23,27,28]

under similar conditions resulting in the formation of 3-(4,6-*O*-butylidene-β-D-glucopyranosylmethyl)-5-(4-bromophenyl)-1*H*-pyrazole (**6a**). In this case, hydrazine hydrate selectively hydrolyzes the acetyl group. Reaction of 4,6-O-protected α,β-unsaturated C-β-glycosidic ketones **5**(**b–g**) with hydrazine hydrate under basic conditions resulted in the formation of sugar-based pyrazole derivatives **6**(**a–f**) in 45% yield (Table 1, entry no. 6). The reaction conditions were optimized using different solvents. Thus the reaction of α,β-unsaturated-C-β-glycosidic ketones **5**(**b–g**) with hydrazine hydrate using ethanol as solvent resulted in yields of 70–84% of the corresponding sugar-based pyrazole derivatives (Table 1, entry no. 2). During the course of reaction, the hydrazone was formed as an intermediate, which then subsequently cyclized and underwent self-oxidation to furnish the expected pyrazole derivatives. The structures of resulting sugar-pyrazole derivatives were characterized by FTIR and ^{1}H and ^{13}C NMR spectral techniques. The FTIR spectrum of compound **6a** shows bands around 1661, 1561, and 3251 cm^{-1} that correspond to the $\nu_{C=N}$, $\nu_{C=C}$ and ν_{N-H}, respectively. In the ^{1}H NMR spectrum of compound **6a**, the presence of the sugar-pyrazole core is confirmed from the appearance of a sharp singlet at δ 6.38 ppm that corresponds to the methine proton (H_{pyr}) of the pyrazole ring. The product formations were further confirmed by DEPT-135 experiments (See ESI for more details). The ^{1}H NMR spectrum of **6a** notably exhibited a large coupling constant for the H-1′ signal (δ 4.18 ppm; $^{3}J_{H1',H2'}$ 10.0 Hz), indicating a *trans*-diaxial orientation of H-1′ and H-2′ as expected for the β-D-configured glucopyranose moiety.[47] Absorption spectra of the polycyclic **6d** and **6e** and indole derivative **6f**, showed absorbance bands around 195, 256, and 222 nm, which correspond to π–π and n–π transitions. Among the various α,β-unsaturated C-β-glycosidic ketones synthesized, the 4-allyloxy derivative **5d** showed gelation properties with different solvents, and an investigation in this phenomenon is in progress.

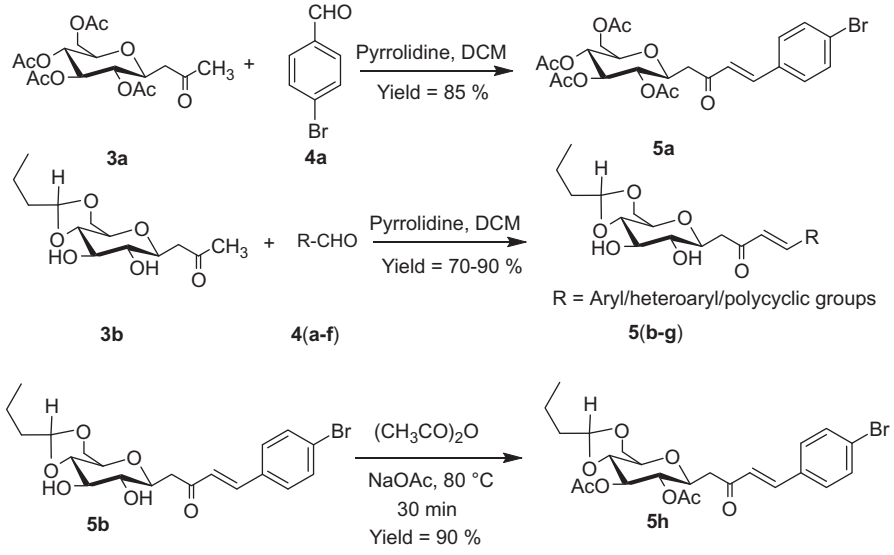
3. Conclusions

In summary, we have effectively synthesized different sugar-based pyrazole derivatives in good yield and characterized them using different spectral techniques. However, using per-O-acetylated sugars resulted in the formation of deacetylated products, which shows that partially protected derivatives are more stable compared to the fully protected derivatives under the reaction conditions. The β-anomeric forms for these sugar derivatives were assigned from NMR studies. Among the various substituted sugar-based pyrazole compounds synthesized, polycyclic and heterocyclic compounds, such as, **6d**, **6e,** and **6f** exhibited strong absorption bands at around 195, 256, 222 nm due to n–π and π–π transitions. Further manipulation of α,β-unsaturated-C-β-glycosidic ketones for the synthesis of several biomolecules and biological investigations of these compounds are in progress in our laboratory.

4. Experimental section

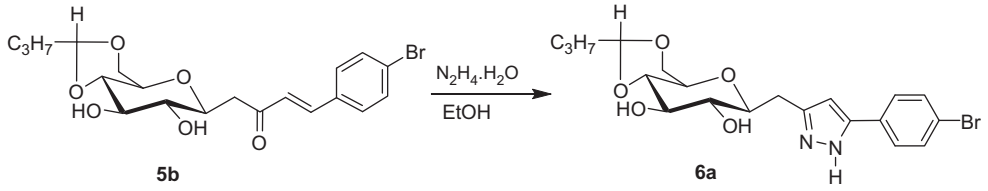
4.1. General methods

D-Glucose, 4-bromobenzaldehyde (**4a**), 5-bromo-3-pyridylbenzaldehyde (**4b**), 4-allyloxybenzaldehyde (**4c**), pyrene carboxaldehyde (**4d**), anthracene-10-carbaldehyde (**4e**), indole-3-carbaldehyde (**4f**), and hydrazine hydrate were purchased from Sigma–Aldrich Chemical Co. (USA) and were of high purity. Butyraldehyde and the organic catalyst (pyrrolidine) were obtained from SRL, India. Other reagents, such as, hydrochloric acid, sodium hydrogen carbonate, sodium hydroxide, potassium hydroxide and solvents (AR Grade) were obtained from Sd-fine, India, in high purity and were used without any further purification. Ac_2O was purchased from Fischer Chemicals Pvt. Ltd, India. The solvents were purified according to the standard methods. Column chromatography was performed on silica gel (100–200 mesh). IR spectra were recorded on a ABB MB 3000 Fourier-transform infrared spectrometer on KBr disks in the range from 400 to 4000 cm^{-1}. Electronic



Scheme 1. Synthesis of sugar-based chalcone derivatives **5**(**a–h**).

Table 1
Optimization of sugar-pyrazole derivatives **6**(**a–f**)



Entry no.	Solvent/mixture of solvent	Reaction conditions	Yield (%)
1	MeOH	Neutral	36
2	EtOH	Neutral	89
3	DMF	Neutral	24
4	MeOH + DMF (1:1)	Neutral	29
5	EtOH + DMF (1:1)	Neutral	34
6	EtOH	Basic (NaOH/KOH)	45
7	EtOH	Acidic ($SnCl_2/CH_3CO_2H$)	[a]

[a] Decomposed product was obtained.

spectral studies were carried out on a 1800 Shimadzu UV spectrophotometer in the range 190–800 nm. NMR spectra were recorded on a Bruker DRX 300 MHz instrument in either $CDCl_3$ or DMSO-d_6. Chemical shifts are referenced to internal TMS. Elemental analyses were performed using a Perkin–Elmer 2400 series CHNS/O analyzer. For assigning the spectral data, several abbreviations were used, including 'Ar' for aromatic, 'Sac' for saccharide, 'Ace-H' for acetal proton, 'Pyr' for pyrazole and 'Ha and Hb' for the methylene protons that connect between the sugar and the pyrazole moieties, respectively.

4.2. Synthesis of α,β-unsaturated C-β-glycosidic ketone (5)

Compounds, **5b**, **5d,** and **5e** were synthesized by following the literature procedures,[45–49] and a similar procedure was adopted to synthesize **5a**, **5c** and **5f**. Spectral data procedures are as follows.

4.2.1. Physicochemical and spectral data for (*E*)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(4-bromophenyl)but-3-en-2-one (5a)

To a solution of compound **3a** (0.39 g, 1.0 mmol) in CH_2Cl_2 (5 mL), pyrrolidine (30 mol %) was added with stirring. To the stirred solution, 4-bromobenzaldehyde (0.22 g, 1.2 mmol) was added. The reaction mixture was then slurried and purified using column chromatography 8:2 $CHCl_3$–MeOH. Yield: 0.48 g (86%); mp 138–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.40 (m, 5H, Ar-*H*, Alk-*H*), 6.72 (d, *J* = 16.2 Hz, 1H, Alk-*H*), 5.23 (t, *J* = 9.3 Hz, 1H, Sac-*H*), 5.07 (t, *J* = 9.9 Hz, 1H, Sac-*H*), 4.98 (t, *J* = 9.6 Hz, 1H, Ace-*H*), 4.29–4.23 (dd, *J* = 5.1 Hz, *J* = 12.6 Hz, 1H, Sac-*H*), 4.15–4.08 (m, 1H, Sac-*H*), 4.05–4.00 (dd, *J* = 5.1 Hz, *J* = 12.6 Hz, 1H, Sac-*H*), 3.74–3.69 (m, 1H, Ha), 3.06–2.97 (dd, *J* = 8.4 Hz, *J* = 16.2 Hz, 1H, Hb), 2.70–2.64 (dd, *J* = 3.0 Hz, *J* = 16.2 Hz, 1H, Sac-*H*), 2.02 (m, 12H, –COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9, 170.6, 170.2, 170.0, 169.6, 142.3, 133.1, 132.3, 129.7, 126.7, 125.1, 75.8, 74.2, 74.1, 71.7, 68.5, 62.0, 42.7, 20.7 (2C), 20.6; Anal. Calcd for $C_{24}H_{27}BrO_{10}$: C, 51.90; H, 4.90. Found: C, 51.34; H, 4.63.

4.2.2. Physicochemical and spectral data for (*E*)-1-(4,6-*O*-butylidene-β-D-glucopyranosyl)-4-(4-bromophenyl)but-3-en-2-one (5b)

To a solution of 1-*C*-(4,6-*O*-butylidene-β-D-glucopyranosyl)propane-2-one (**3b**) (0.27 g, 1.0 mmol) in CH_2Cl_2 (5 mL), 0.1 mL (30 mol %) of pyrrolidine was added with stirring. To the stirred solution 4-bromobenzaldehyde (**4a**) (0.22 g, 1.2 mmol) was added. The white solid that precipitated was filtered off and washed well with CH_2Cl_2. The white solid thus obtained was dissolved in MeOH and purified by using column chromatography (9:1 $CHCl_3$–MeOH). Yield: 0.54 g (67%); mp 228–230 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 7.56–7.45 (m, 5H, Ar-*H*, Alk-*H*), 6.78 (d, 1H, *J* = 16.2 Hz, Alk-*H*), 5.08–5.11 (t, *J* = 5.1 Hz, 1H, Sac-*H*), 4.87–4.91 (d, *J* = 12 Hz, 1H, Sac-*H*), 4.53 (t, *J* = 5.1 Hz, 1H, Ace-*H*), 4.13–4.15 (d, *J* = 10.0 Hz, 2H, Sac-*H*), 3.83–3.89 (t, *J* = 8.9 Hz, 1H, Sac-*H*), 3.56–3.59 (t, *J* = 9.0 Hz, 1H, Sac-*H*), 3.42–3.55 (m, 3H, Hb, Sac-*H*), 3.12–3.13 (m, 2H, Ha, Sac-H), 1.56–1.67 (m, 2H, –C*H*$_2$), 1.38–1.46 (q, *J* = 7.2 Hz, 2H, –C*H*$_2$), 0.88–0.92 (t, *J* = 7.2 Hz, 3H, –C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.8, 141.1, 133.8, 132.0, 130.4, 127.4, 123.9, 101.3, 80.7, 76.8, 74.3, 74.1, 70.3, 67.5, 43.3, 36.0, 17.2, 13.9; Anal. Calcd for $C_{20}H_{25}BrO_6$: C, 54.43; H, 5.71. Found: C, 54.82; H, 5.93.

4.2.3. Physicochemical and spectral data for (*E*)-1-(4,6-*O*-butylidene-β-D-glucopyranosyl)-4-(4-allyloxy)but-3-en-2-one (5c)

To a solution of 1-*C*-(4,6-*O*-butylidene-*β*-D-glucopyranosyl)propane-2-one (**3b**) (0.27 g, 1.0 mmol) in CH_2Cl_2, 0.1 mL (30 mol %) of pyrrolidine was added with stirring. To the stirred solution 4-allyloxybenzaldehyde (**4c**) (0.18 mL, 1.2 mmol) was added, and the reaction mixture was monitored by TLC. The pale-brown residue thus obtained was purified by column chromatography [8.5:1.5 $CHCl_3$–MeOH]. Yield: 0.55 g (45%); mp 228–230 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 7.55–7.40 (m, 3H, Ar-*H*, Alk-*H*), 6.93 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.65 (d, *J* = 16.2 Hz, 1H, Alk-*H*), 5.98–6.11 (m, 1H, Alk-*H*), 5.29–5.46 (dd, *J* = 10.0 Hz, J = 17.4 Hz, 2H, Alk-*H*), 4.70 (s, 1H, Sac-*H*), 4.52–4.59 (m, 2H, Ace-*H*, Sac-*H*), 4.43 (s, 1H, Sac-*H*), 4.07–4.12 (dd, *J* = 3.9 Hz, *J* = 9.8 Hz, 1H, Sac-H), 3.91 (t, *J* = 9.0 Hz, 2H, Sac-H), 3.66 (t, *J* = 8.0 Hz, 1H, Sac-H), 3.41 (t, *J* = 9.6 Hz, 1H, Sac-H), 3.22–3.35 (m, 3H, Ha, Hb, Sac-*H*), 3.10–3.16 (dd, *J* = 2.4 Hz, *J* = 15.9 Hz, 1H, Sac-*H*), 2.78–2.87 (q, *J* = 7.2 Hz, 1H, Sac-*H*), 1.56–1.65 (m, 2H, –C*H*$_2$), 1.35–1.42 (q, *J* = 7.2 Hz, 2H, –C*H*$_2$), 0.87–0.90 (t, *J* = 7.2 Hz, 3H, –C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 197.5, 160.1, 142.2, 133.3, 130.2, 127.0, 124.5, 117.7, 115.1, 101.2, 80.6, 76.8, 74.2, 74.0, 70.3, 68.3, 67.5, 42.9, 35.9, 17.0, 13.8; Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.78; H, 7.58.

4.2.4. Physicochemical and spectral data for (*E*)-1-(4,6-*O*-butylidene-β-D-glucopyranosyl)-4-(3-indole)but-3-en-2-one (5f)

To a solution of 1-*C*-(4,6-*O*-butylidene-β-D-glucopyranosyl)propane-2-one (**3b**) (0.27 g, 1 mmol) in CH_2Cl_2, 0.1 mL (30 mol %) of pyrrolidine was added with stirring. To the stirred solution indole-3-carbaldehyde (0.18 g, 1.2 mmol) was added, and the reaction mixture was monitored by TLC. The pale-brown residue thus obtained was purified by column chromatography (1:1 hexane–EtOAc). Yield: 0.30 g (75%); mp 195–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 11.23 (s, 1H, –N*H*), 7.86 (d, *J* = 16.2 Hz, 1H, Alk-*H*), 7.61–7.47 (m, 3H, Ar-*H*), 7.25–7.22 (m, 1H, Ar-*H*), 6.81 (d, *J* = 15.9 Hz, 1H, Alk-*H*), 4.96–4.90 (m, 1H, Sac-*H*), 4.70–4.64 (m, 1H, Sac-*H*), 4.55 (t, *J* = 5.1 Hz, 1H, Ace-*H*), 4.12–4.08 (dd, *J* = 9.0 Hz, *J* = 3.3 Hz, 1H, Sac-*H*), 3.93 (t, *J* = 7.5 Hz, 1H, Sac-*H*), 3.65 (t, *J* = 7.5 Hz, 1H, Sac-*H*), 3.43 (t, *J* = 9.6 Hz, 1H, Sac-*H*), 3.33–3.26 (m, 3H, Hb, Sac-*H*), 3.18–3.12 (m, 2H, Ha, Sac-*H*), 2.88–2.80 (m, 1H, Sac-*H*), 1.68–1.59 (m, 2H, –CH_2), 1.47–1.39 (m, 2H, –CH_2), 0.91 (t, *J* = 7.2 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 202.8, 142.5, 142.4, 135.9, 130.1, 127.6, 126.1, 125.9, 124.9, 117.5, 117.2, 107.0, 85.4, 79.8, 79.6, 75.4, 73.1, 48.0, 41.0, 22.1, 18.7; Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.51; H, 6.42; N, 3.81.

4.2.5. Physicochemical and spectral data for (*E*)-1-(2,3-di-*O*-acetyl-4,6-*O*-butylidene-β-D-glucopyranosyl)-4-(4-bromophenyl)but-3-en-2-one (5h)

To a solution of compound **5b** (0.44 g, 1.0 mmol) in Ac_2O (0.94 mL, 10 mmol), NaOAc (0.08 g, 1.0 mmol) was added, the mixture was heated under reflux for 1 h. The reaction mixture was then poured over crushed ice. The white solid that precipitated was then filtered off and dried. Yield: 0.45 g (85%); mp 146–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55–7.39 (m, 5H, Ar-*H*, Alk-*H*), 6.70 (d, *J* = 15.9 Hz, 1H, Alk-*H*), 5.23 (t, *J* = 9.0 Hz, 1H, Ace-*H*), 4.93 (t, *J* = 9.3 Hz, 1H, Sac-*H*), 4.48 (t, *J* = 5.1 Hz, 1H, Sac-*H*), 4.19–4.13 (m, 3H, Hb, Sac-*H*), 3.40 (d, *J* = 7.5 Hz, 2H, Ha, Sac-*H*), 2.97–2.88 (dd, *J* = 8.7 Hz, *J* = 15.2 Hz, 1H, Sac-*H*), 2.68–2.61 (dd, *J* = 3.3 Hz, *J* = 16.2 Hz, 1H, Sac-*H*), 2.03 (s, 6H, –COCH_3), 1.50–1.54 (m, 2H, –CH_2), 1.43–1.31 (m, 2H, –CH_2), 0.92–0.87 (t, *J* = 7.5 Hz, 3H, –CH_3); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 195.9, 170.2, 142.2, 133.2, 132.3, 131.9, 129.7, 128.4, 126.6, 125.1, 102.6, 78.4, 74.5, 73.1, 72.5, 70.8, 68.1, 43.0, 36.0, 20.8, 17.4, 13.8; Anal. Calcd for $C_{24}H_{29}BrO_8$: C, 54.87; H, 5.56. Found: C, 55.23; H, 5.13.

4.3. General procedure for the synthesis of sugar-pyrazole derivatives, 6(a–f)

To a solution of (*E*)-1-(4,6-*O*-butylidene-β-D-glucopyranosyl)-4-(phenyl)but-3-en-2-one, (1.0 mmol) in abs EtOH were added hydrazine hydrate (11.0 mmol). After stirring under reflux for a given period of time (see Table 2), the solvent was evaporated under reduced pressure. The crude product was slurried using silica gel and purified by flash column chromatography using 7:3 hexane–EtOAc as eluent to get the corresponding sugar-pyrazole derivatives.

4.3.1. Physicochemical and spectral data for 5-(4-bromophenyl)-3-(4,6-*O*-butylidene-β-D-glucopyranosylmethyl)-1*H*-pyrazole (6a)

Yellow solid; Yield: 0.39 g (89%); mp 107–110 °C; $[\alpha]_D^{28}$ −90.8 (*c* 90 mmol, $CHCl_3$); FTIR (KBr, *v* cm^{-1}): 1661, 1561, 3251; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.51 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.38 (s, 1H, Pyr-*H*), 4.52 (t, *J* = 6.0 Hz, 1H, Ace-*H*), 4.18 (dd, *J* = 4.8 Hz, *J* = 10.2 Hz, 1H, Sac-*H*), 3.70 (t, *J* = 8.7 Hz, 1H, Sac-*H*), 3.58–3.61 (m, 1H, Sac-*H*), 3.49 (t, *J* = 10.2 Hz, 1H, Sac-*H*), 3.35–3.28 (m, 2H, Hb, Sac-*H*), 3.25 (d, *J* = 4.2 Hz, 3H, Sac-H), 3.22–3.19 (m, 2H, Ha, Sac-*H*), 2.98 (dd, *J* = 6.0 Hz, *J* = 15.6 Hz, 1H, Sac-*H*), 1.65–1.58 (m, 2H, –CH_2), 1.45–1.37 (m, 2H, –CH_2), 0.93–0.88 (t, 3H, *J* = 7.5 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.9, 131.0, 127.2, 122.0, 103.2, 102.5, 80.3, 78.7, 75.1, 73.2, 70.6, 68.3, 36.2, 28.6, 17.5, 13.9; Anal. Calcd for $C_{20}H_{25}BrN_2O_5$: C, 52.99; H, 5.56; N, 6.18. Found: C, 53.45; H, 5.29; N, 6.39.

4.3.2. Physicochemical and spectral data for 5-(5-bromo-3-pyridyl)-3-(4,6-*O*-butylidene-β-D-glucopyranosylmethyl)-1*H*-pyrazole (6b)

Yellow solid; Yield: 0.36 g (81%); mp 102–104 °C; FTIR (KBr, *v* cm^{-1}): 1656, 1556; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (s, 1H, Ar-*H*), 8.56 (s, 1H, Ar-*H*), 8.16 (s, 1H, Ar-*H*), 6.43 (s, 1H, Pyr-*H*), 4.51 (t, *J* = 6.0 Hz, 1H, Ace-*H*), 4.16 (dd, *J* = 4.5 Hz, *J* = 10.5 Hz, 1H, Sac-*H*), 3.72 (t, *J* = 8.4 Hz, 1H, Sac-*H*), 3.55–3.63 (m, 2H, Sac-*H*), 3.47 (t, *J* = 9.9 Hz, 1H, Sac-*H*), 3.31 (t, *J* = 8.4 Hz, 1H, Sac-*H*), 3.28 (m, 2H, Hb, Sac-*H*), 3.23–3.17 (m, 3H, Ha, Sac-*H*), 2.97 (dd, *J* = 4.8 Hz, *J* = 15.0 Hz, 1H, Sac-*H*), 1.67–1.58 (m, 2H, –CH_2), 1.43–1.31 (m, 2H, –CH_2), 0.88–0.83 (m, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 149.8, 139.7, 107.5, 107.0, 85.2, 83.6, 79.6, 78.4, 75.4, 73.1, 41.0, 36.2, 32.8, 22.1, 18.7; Anal. Calcd for $C_{19}H_{24}BrN_3O_5$: C, 50.23; H, 5.32; N, 9.25. Found: C, 50.66; H, 4.99; N, 9.38.

4.3.3. Physicochemical and spectral data for 5-(4-allyloxyphenyl)-3-(4,6-*O*-butylidene-β-D-glucopyranosylmethyl)-1*H*-pyrazole (6c)

Yellow solid; Yield: 0.34 g (83%); mp 135–137 °C; $[\alpha]_D^{28}$ −354.1 (*c* 30 mmol, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J* = 6.9 Hz, 2H, Ar-*H*), 6.86 (d, *J* = 6.3 Hz, 2H, Ar-*H*), 6.09–5.98 (m, 1H, Alk-*H*), 6.32 (s, 1H, Pyr-*H*), 5.43–5.27 (dd, *J* = 17.1 Hz, *J* = 10.5 Hz, 2H, Alk-*H*), 4.51 (t, *J* = 9.0 Hz, 2H, Ace-*H*, Sac-*H*), 4.08 (dd, *J* = 3.6 Hz, *J* = 9.0 Hz, 1H, Sac-*H*), 3.89 (t, *J* = 6.5 Hz, 1H, Sac-*H*), 3.70–3.58 (m, 2H, Sac-*H*), 3.37–3.41 (m, 3H, Hb, Sac-*H*), 3.24 (d, *J* = 8.1 Hz, 2H, Sac-*H*), 3.20–3.04 (m, 3H, Ha, Sac-*H*), 2.74–2.60 (m, 1H, Sac-*H*), 1.45–1.37 (m, 2H, –CH_2), 1.05–1.00 (m, 2H, –CH_2), 0.89 (t, *J* = 6.0 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 127.3, 126.9, 115.0, 114.8, 102.4, 102.0, 80.5, 78.3, 74.8, 73.7, 70.6, 69.6, 68.9, 68.4, 45.2, 36.2, 32.4, 22.6, 17.5, 13.9. Anal. Calcd for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51. Found: C, 63.65; H, 7.36; N, 5.76.

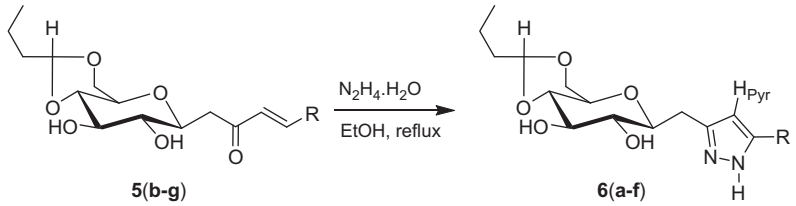
4.3.4. Physicochemical and spectral data for 3-(4,6-*O*-butylidene-β-D-glucopyranosylmethyl)-5-(pyren-3-yl)-1*H*-pyrazole (6d)

Brown syrup; Yield: 0.35 g (73%); $[\alpha]_D^{28}$ −10.3 (*c* 30 mmol, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50–8.47 (d, *J* = 9.2 Hz, 1H, Ar-*H*), 8.24–7.91 (m, 8H, Ar-*H*), 6.55 (s, 1H, Pyr-*H*), 4.45 (t, *J* = 6.0 Hz, 1H, Ace-*H*), 4.17 (dd, *J* = 4.5 Hz, *J* = 9.6 Hz, 1H, Sac-*H*), 3.78 (t, *J* = 8.7 Hz, 1H, Sac-*H*), 3.73–3.68 (m, 1H, Sac-*H*), 3.45 (t, *J* = 9.0 Hz, 2H, Sac-*H*), 3.35 (dd, *J* = 4.5 Hz, 1H, Sac-*H*), 3.29 (d, *J* = 6.6 Hz, 2H, Hb, Sac-*H*), 3.25–3.19 (m, 3H, Ha, Sac-*H*), 3.14–3.07 (dd, *J* = 5.4 Hz, *J* = 15.6 Hz, 1H, Sac-*H*), 1.59–1.55 (m, 2H, –CH_2), 1.43–1.27 (m, 2H, –CH_2), 0.90–0.83 (m, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.3, 128.0, 127.8, 127.3, 127.0, 126.1, 125.4, 125.1, 124.9, 124.8, 124.7, 102.5, 80.4, 78.8, 75.2, 73.5, 70.6, 68.4, 36.2, 30.9, 29.7, 17.5, 13.9; Anal. Calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 71.79; H, 6.34; N, 5.91.

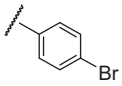
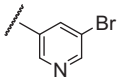
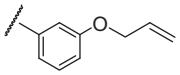
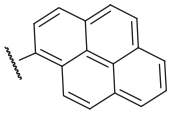
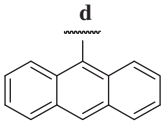
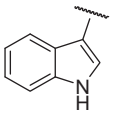
4.3.5. Physicochemical and spectral data for 5-(anthracen-9-yl)-3-(4,6-*O*-butylidene-β-D-glucopyranosylmethyl)-1*H*-pyrazole (6e)

Yellow solid; Yield: 0.32 g (70%); mp 120–122 °C; FTIR (KBr, *v* cm^{-1}) 1662, 1559; $[\alpha]_D^{28}$ −10.4 (*c* 100 mmol, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42–8.23 (m, 3H, Ar-*H*), 8.01–7.98 (m, 2H, Ar-*H*), 7.46–7.41 (m, 4H, Ar-*H*), 6.70 (s, 1H, Pyr-*H*), 4.50

Table 2
Synthesis of sugar-based pyrazole derivatives **6**(**a–f**)



5(**b-g**) **6**(**a-f**)

Entry	R (**6**)	Time (h)	**5**(**b–g**) (mg)	δ Pyr-*H* (ppm)	δ (Ano-*H*) ppm, $^3J_{H1',H2}$ (Hz)	Yield of **6**(**a–f**) in mg (%)
1	 **a**	3	440	6.38	4.18, 10.2	390 (84)
2	 **b**	3	440	6.43	4.16, 10.5	360 (81)
3	 **c**	4	420	6.32	4.08, 9.0	340 (73)
4	 **d**	3	490	6.55	4.17, 9.6	350 (83)
5	 **e**	4	460	6.70	4.19, 10.2	320 (70)
6	 **f**	3	400	6.45	4.10–3.97, —[a]	300 (73)

[a] Proton merged with other sugar skeletal protons and appeared as broad peak.

(t, *J* = 4.8 Hz, 1H, Ace-*H*), 4.19 (dd, *J* = 4.8 Hz, *J* = 10.2 Hz, 1H, Sac-*H*), 4.04–3.99 (t, *J* = 6.0 Hz, 1H, Sac-*H*), 3.78–3.72 (m, 2H, Sac-*H*), 3.51–3.44 (m, 2H, Sac-*H*), 3.37–3.31 (m, 2H, Sac-*H*), 3.25 (d, *J* = 11.4 Hz, 2H, Hb, Sac-*H*), 2.99–2.89 (m, 1H, Ha), 2.83–2.76 (dd, *J* = 6.3 Hz, *J* = 14.4 Hz, 1H, Sac-*H*), 1.61–1.57 (m, 2H, $-CH_2$), 1.41–1.34 (m, 2H, $-CH_2$), 0.88–0.83 (m, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4, 131.0, 129.4, 129.1, 128.9, 128.7, 128.1, 127.2, 126.2, 126.1, 125.3, 125.2, 124.8, 103.1, 102.4, 80.4, 77.2, 74.8, 68.3, 36.2, 17.5, 13.9; Anal. Calcd for $C_{28}H_{30}N_2O_5$: C, 70.87; H, 6.37; N, 5.90. Found: C, 71.43; H, 5.98; N, 5.72.

4.3.6. Physicochemical and spectral data for 3-(4,6-*O*-butylidene-β-D-glucopyranosylmethyl)-5-(indole-3-yl)-1*H*-pyrazole (6f)

Orange solid, Yield: 0.30 g (73%); mp 132–135 °C; $[\alpha]_D^{28}$ −1.63 (*c* 60 mmol, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.99 (s, 1H, –N*H*), 8.78 (s, 1H, –N*H*), 7.50–7.08 (m, 5H, Ar-*H*), 6.45 (s, 1H, Pyr-*H*), 4.99 (s, 1H, Sac-*H*), 4.44–4.35 (m, 2H, Ace-*H*, Sac-*H*), 4.10–3.97 (m, 2H, Sac-*H*), 3.63 (m, 3H, Sac-*H*), 3.32–3.16 (m, 2H, Hb, Sac-*H*), 2.94–2.80 (m, 1H, Ha), 2.62–2.59 (m, 1H, Sac-*H*), 1.52–1.40 (m, 2H, $-CH_2$), 1.33–1.26 (m, 2H, $-CH_2$), 0.86–0.84 (m, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.5, 127.2, 126.5, 126.0, 124.8, 123.8, 123.5, 116.5, 107.5, 107.0, 85.3, 79.6, 79.4, 75.4, 73.1, 41.0, 22.1, 18.7; Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.57; H, 6.91; N, 10.40.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.06.019.

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