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First noscapine glycoconjugates inspired by click chemistry†

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A number of novel 7-*O*-noscapine glycoconjugates have been synthesized starting from noscapine, an alkaloid found in the opium plant, *via* two successive steps. The first step is a selective 7-*O*-demethylation of noscapine and the next is a subsequent propargylation which affords 7-*O*-propargyl noscapine (**3**) in good yield. The structure was confirmed by extensive spectroscopic data including single crystal X-ray data. The 1,3-dipolar cycloaddition of the developed noscapine derivative **3** with glycosyl *azides* **6a–m** was investigated to give the triazole-linked second-generation noscapine analogs in their glycoconjugate forms (**8a–m**) to augment the therapeutic efficacy of noscapine.

Introduction

Natural products and their derivatives are now well established biologically relevant moieties and participate in critical roles in modern drug discovery and development.[1] Alkaloids obtained from nature are the most potent and pharmaceutically interesting scaffolds.[2] One member of this group, noscapine ('a phthalideisoquinoline alkaloid'), has a benzofuranone ring attached to the hetero ring of isoquinoline. Noscapine is available in about 7% abundance during opium harvesting.[3] It has been used as an antitussive agent for several decades because of its favourable toxicity profile. Recently, it was found to bind tubulin and alter its conformation and properties, and alter microtubule dynamics.[4,5] Additionally, noscapine has also shown the successful inhibition of various neoplasms *in vitro* as well as *in vivo*, such as leukaemia and lymphoma,[6–8] along with melanoma,[9] ovarian cancer,[10] gliomas,[11] and breast,[12] lung[13] and colon[14] cancers. Recently, Joshi *et al.* have assessed the mechanistic path of this anticancer effect after performing several studies where they found that noscapine can perturb tubulin dynamics.[15] Recent literature has revealed that chemical modifications at its 7-position *via* selective demethylation on the benzofuranone ring system has been achieved and showed that the *O*-alkylated derivatives, including the 7-hydroxyl compounds, were 100-fold more effective than the parent noscapine.[16,17] This strongly suggests that the presence and modification of the benzofuranone ring in the parent molecule has a significant impact on its biological activity (Fig. 1).

Carbohydrates and their diverse saccharide forms (mono to poly) always attract synthetic chemists for their utilization in medicinal chemistry because their use yields effective control over biological functions.[18] Additionally, the multivalent nature of carbohydrate molecules is frequently used to enhance their affinities for targets in different biological processes, such as the binding of bacteria, bacterial toxins, galectins and other lectins.[19] Although the carbohydrates alone demonstrate no therapeutic action, their presence in synthetic and naturally occurring molecules creates a prominent change in their physical, chemical and biological properties. This also influences the biological activity of most of the drugs which incorporate them.[20]

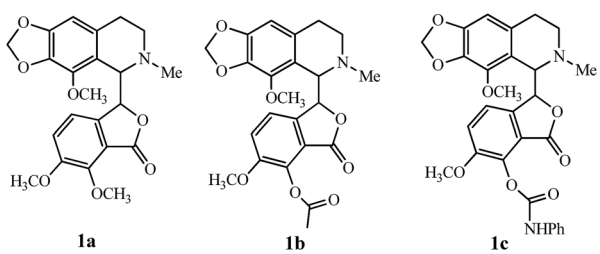

Fig. 1 Structure of noscapine (**1a**) and its potent biologically active 7-*O*-analogs (**1b**, **1c**), against tubulin polymerization.

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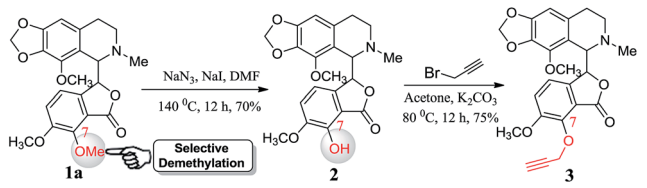
† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of all the new compounds and single crystal X-ray data of **3** have been provided. CCDC 1022189. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra07321a



Scheme 1 Synthesis of 7-*O*-propargyl noscapine derivative *via* selective demethylation and subsequent propargylation.

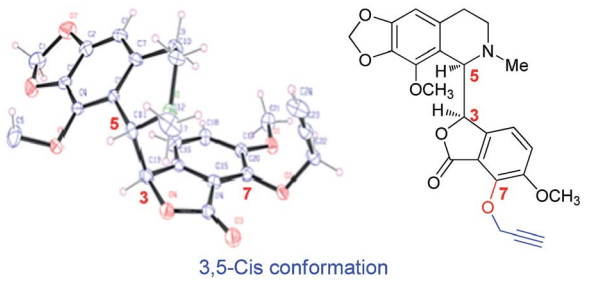
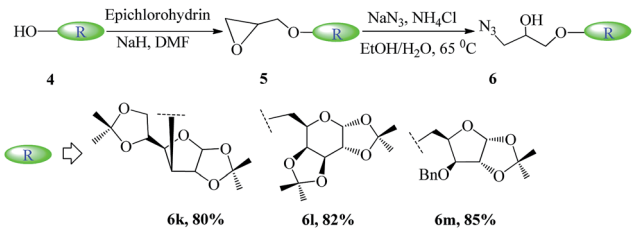
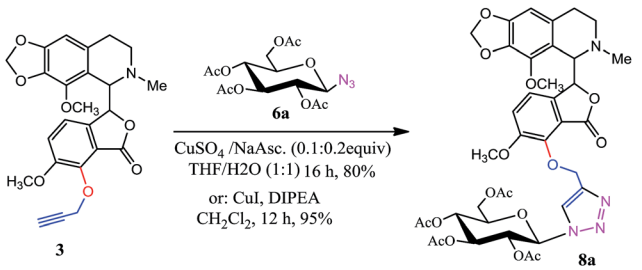


Fig. 2 Molecular structure of **3**. Thermal ellipsoids of C, N, and O are set at 40% probability.



Scheme 2 Synthesis of glycosyl azido alcohols **6k–m** using orthogonally protected sugars and epichlorohydrin.



Scheme 3 Optimization of reaction medium and Cu(I) catalyst for CuAAC reaction of **3** and **6a**.

The Cu(I)-catalysed click reaction[21,22] is a precise tool for the joining of two dissimilar moieties having azide and terminal alkyne functionalities and has emerged as an important strategy for the discovery and optimization of leads. This strategy is also being used in the exploration of effective drug candidates against various therapeutic strains.[23–28] Based upon this impetus and with our previous experience,[29–32] herein we have successfully incorporated a terminal alkyne functionality in naturally occurring α-noscapine at its C-7 position. This strategy afforded novel 7-*O*-analogs which were further utilized for developing second-generation noscapine derivatives in their glycoconjugate forms using Cu(I)-catalyzed click chemistry. We hope this will satisfy the increasing demand for more potent analogs of this molecule to modulate microtubules more effectively.

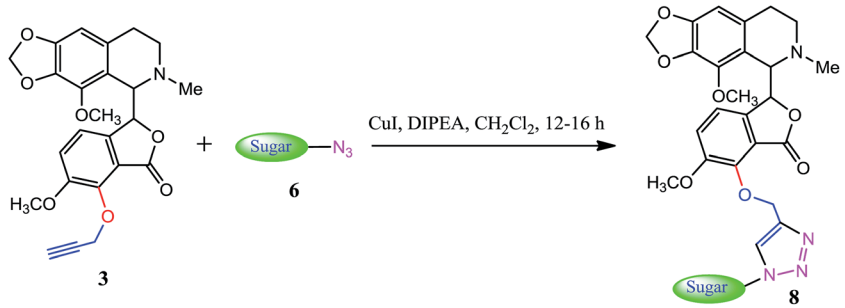
Results and discussion

Our strategy started with the demethylation of the parent compound noscapine. Sodium azide and sodium iodide in dimethylformamide (DMF) were used to cleave the methyl group selectively at position 7 of the benzofuranone ring.[17b] Briefly, noscapine was dissolved in anhydrous DMF along with sodium azide and sodium iodide followed by stirring at 140 °C for 4 h to obtain 7-hydroxy noscapine **2** (Scheme 1). Compound **2** was then propargylated at its hydroxyl moiety using K_2CO_3 in refluxing acetone at 80 °C to afford 7-*O*-propargylated noscapine **3** in 75% yield (Scheme 1). Surprisingly, this reaction did not occur in DMF at room temperature using the same base. Compound **3** served as a scaffold to synthesize various C-7-modified derivatives of noscapine **8a–m** in their glycoconjugate form. The structures of the new C-7 analogs of noscapine **3** were deduced from their extensive spectral studies (IR, NMR, and MS). Single crystal X-ray analysis of compound **3** confirmed the selective demethylation of the parent molecule at the C-7 position.

The ^{1}H NMR spectrum of compound **3** exhibited one singlet signal at δ 2.62, merged with the 3 protons of N–Me, which was assigned to the acetylene proton. Shifting of the *ortho*-coupled aromatic protons from δ 5.11 (d, $J = 8.4$ Hz) to 6.10 (d, $J = 8.4$ Hz) for C-9 and from δ 6.44 (d, $J = 8.4$ Hz) to 6.96 (d, $J = 8.4$ Hz) for C-10 also confirmed the substitution at the 7-hydroxy group. In addition to other signals, the appearance of a multiplet at δ 5.05 attributed to OCH_2 finally confirmed the addition of the propargyl group, leading to the formation of compound **3**. In the ^{13}C NMR, two new resonances were observed at δ 81.9 and δ 75.4 which were assigned to both acetylene carbons. The molecular structure of compound **3** was also confirmed by single crystal X-ray analysis (Fig. 2, see ESI Table 1†).

Once we achieved the second generation (C-7) noscapine analogue **3**, having one terminal alkyne, we attempted the synthesis of various sugar azides for glycoconjugation of the novel noscapine derivative. We prepared sugar azides with the economical and readily available monosaccharides, *i.e.* D-glucose, D-galactose, D-xylose and a disaccharide, lactose, which, after processing through a number of high-yielding steps involving protections and diverse modifications, afforded deoxy-*azido* sugars **6a–j** in good yields.[33] The sugar azides **6k–m** were synthesised *via* a substitution reaction on the orthogonally protected carbohydrate with epichlorohydrin in the presence of NaH in dry DMF at 0 °C–r.t., which afforded a diastereoisomeric mixture of glycosyl epoxides **5k–m**. These epoxides, on reaction with NaN_3 and NH_4Cl in $EtOH/H_2O$ at 65 °C, afforded their respective O-substituted glycosyl azido alcohols **6k–m** (Scheme 2).

Table 1 Synthesis of 7-*O*-Noscapine glycoconjugates **8a–m** *via* Cu-catalyzed click chemistry



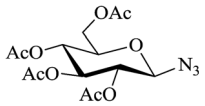
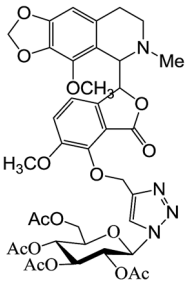
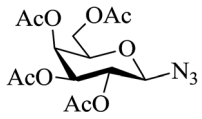
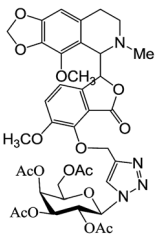
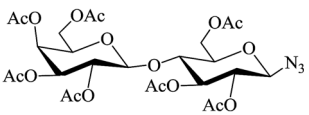
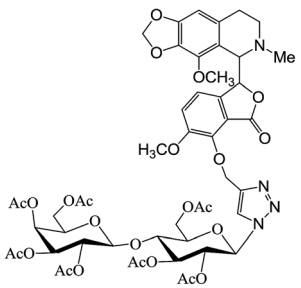
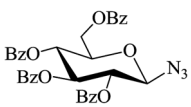
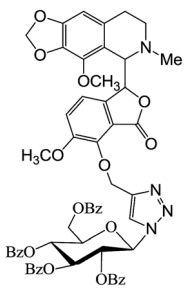
Entry	Sugar azides (**6a–m**)[a]	Noscapine glycoconjugates (**8a–m**)[b]	Time (h)	Yield[c] (%)
1	 **6a**	 **8a**	14	95
2	 **6b**	 **8b**	12	90
3	 **6c**	 **8c**	12	84
4	 **6d**	 **8d**	16	88

Table 1 (*Contd.*)

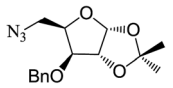
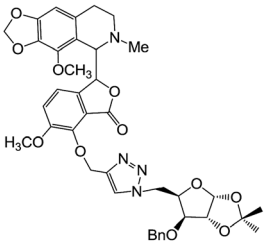
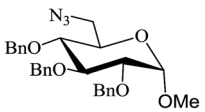
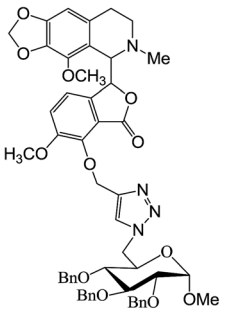
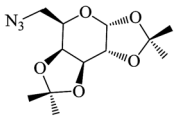
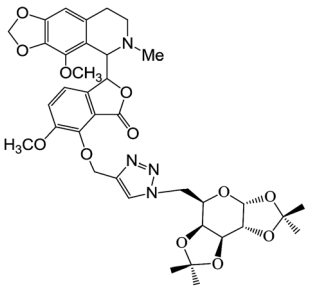
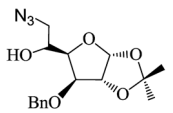
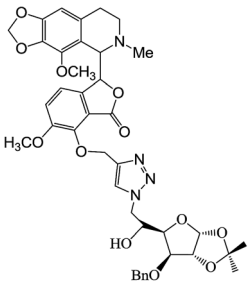
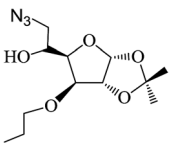
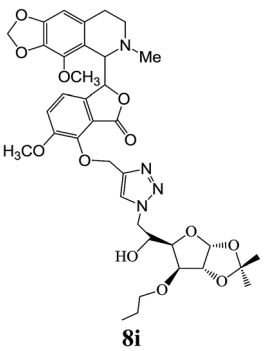
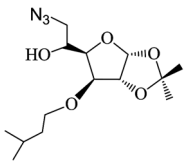
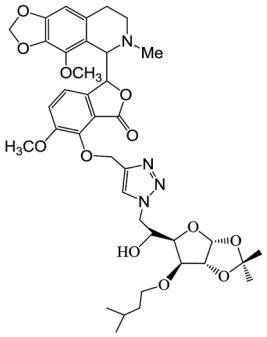
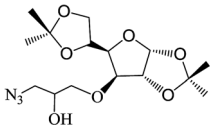
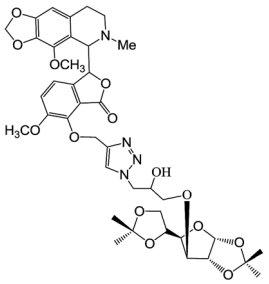
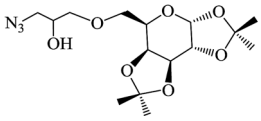
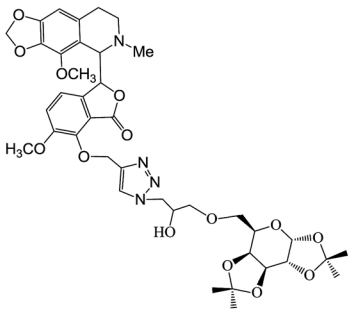
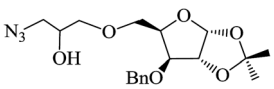
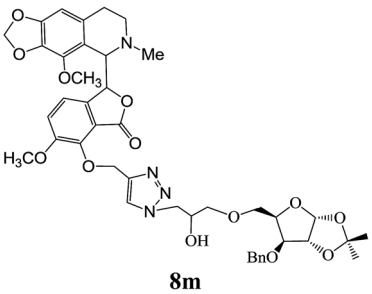
5	 **6e**	 **8e**	12	94
6	 **6f**	 **8f**	14	85
7	 **6g**	 **8g**	15	90
8	 **6h**	 **8h**	13	86
9	 **6i**	 **8i**	12	85

Table 1 (*Contd.*)

10	 **6j**	 **8j**	12	80
11	 **6k**	 **8k**	14	82
12	 **6l**	 **8l**	14	84
13	 **6m**	 **8m**	15	90

[a] Molar ratios: deoxy-azido sugar (1.0 equiv.), 7-*O*-propargylated noscapine (1.0 equiv.), CuI (0.5 equiv.) and DIPEA (1.0 equiv.). [b] Noscapine glycoconjugates. [c] Isolated yield by column chromatography (SiO_2).

All the developed *azido*sugars **6a–m** underwent glycoconjugation using compound **3** *via* the copper-catalyzed azide–alkyne click reaction. Generally, copper-catalyzed azide–alkyne click reactions require the presence of Cu(I) species which may be provided directly or *in situ* depending on the catalyst. Hence, we carried out the reaction using both methods, first using CuI/DIPEA in dichloromethane and then $CuSO_4 \cdot 5H_2O$/sodium ascorbate in aqueous medium. We preferred the former reaction system due to its better yield and shorter reaction time (Scheme 3). Hence, the click reaction of deoxy-azido sugar **6a** (0.19 mmol) with **3** (0.16 mmol) in the presence of CuI (0.08 mmol) and DIPEA (0.16 mmol) was carried out in anhydrous CH_2Cl_2 under argon atmosphere at ambient temperature to afford 7-*O*-noscapine triazolyl glycoconjugate **8a** regioselectively in 95% yield. The regioisomeric nature of compound **8a** was established based on its spectroscopic data

(IR, MS, ^{1}H NMR and ^{13}C NMR) and the purity (evidenced by HRMS) is in close agreement with calculated values.

In the ^{1}H NMR spectrum, two doublets and one singlet of the aromatic protons resonated at δ 6.95 (d, J = 8.4 Hz), 6.07 (d, J = 8.4 Hz) and δ 6.30, along with a triazolyl proton singlet observed at δ 8.25. The anomeric proton of the glucopyranose sugar resonated as a doublet at δ 5.86 (J = 9.6 Hz), while four other sugar protons, along with one noscapine and two oxymethylene protons, appeared at their usual chemical shift values, *i.e.* between δ 5.60–5.22. Two singlets of methyl protons appeared at δ 4.03, 3.84 and were established as the methoxy signals present at the aromatic rings of noscapine and another singlet at δ 2.54 was established as the *N*–Me protons of the hetero carbon ring. The twelve protons of the acetyl moieties on the sugar scaffold were observed as four singlets having three protons each at δ 2.10, 2.07, 2.04 and 1.85. A total of seven remaining protons of noscapine were assigned at δ 5.93 (s, 2H), 4.40 (d, J = 3.9 Hz, 1H), 2.33 (m, 2H), one merged with the acetyl protons and the last one with the *N*-methyl protons. One of the remaining sugar protons in compound **8a** resonated at δ 4.28 (dd, J = 4.8 & 12.6 Hz) and the next one appeared as a multiplet at δ 4.16, which confirms the structure.

Further, having established the reaction conditions for the regioselective cycloaddition of the 7-*O*-propargyl noscapine **3**, we explored the scope of other sugar azides in this cycloaddition and prepared a library of 7-*O*-noscapine triazolyl glycoconjugates **8b–m** in efficient yields (Table 1). Using extensive spectral studies (IR, MS, ^{1}H, and ^{13}C NMR), the structures of all the developed noscapine glycoconjugates **8a–m** were elucidated.

Weak interactions in compound 3 and their biological importance *via* stabilisation of geometrical conformations

Noncovalent inter- and intramolecular interactions play a subtle role in molecular recognition and conformational stabilization within the crystal lattice for biological assays.[34,35] Therefore, it is important to quantify the various interactions within the molecules in the crystal structures. Compound **3** is rich in C–H donors and O, π acceptors. In the isoquinoline ring, the *N*-methyl hydrogens, methylene hydrogens and also the acetylene acidic hydrogen act as a donor whenever oxygen atoms and the π-electron ring system act as acceptors. Intramolecular and intermolecular CH···O and CH···π interactions stabilize the geometry of the molecule and show their effects in the relative changes in the geometrical conformations of compound **3**.

These weak interactions generate a number of six member ring systems which were known for their crucial role in biological activities.[35] Intramolecular interactions have been shown with two six member ring along with a CH···π ring system.

Out of various types of intramolecular interactions (Fig. 3), three of them that cause conformational changes have been presented. A CH···O (I) interaction between the *N*-methyl hydrogens and furanone ring oxygen, with a measured distance of 2.538 Å, and a CH···π (III) interaction between the methylene hydrogen of quinoline and aromatic system fused with the

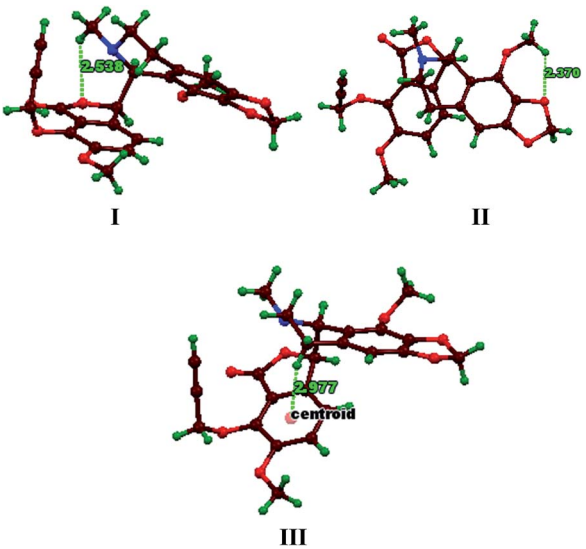


Fig. 3 Intramolecular CH···O and CH···π interactions. Weak interactions are represented by broken light green lines. Carbon atoms are colored brown, hydrogen atoms green, oxygen atoms red, and nitrogen atoms blue.

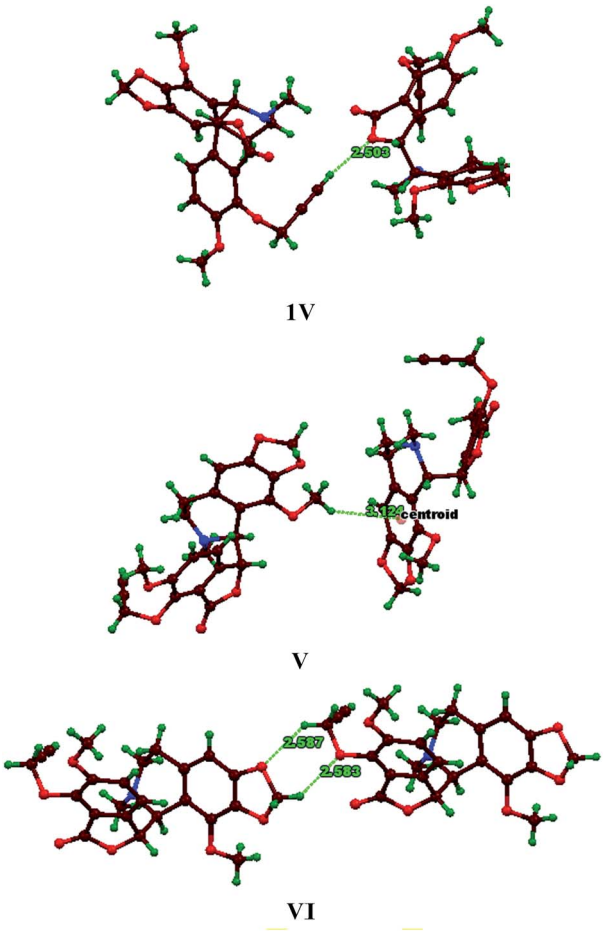


Fig. 4 Intermolecular CH···O and CH···π interactions. Weak interactions are represented by broken light green lines. Carbon atoms are brown, hydrogen atoms green, oxygen atoms red, and nitrogen atoms blue.

lactone ring, with a measured distance of 2.977 Å, are attempting to place both of the fused ring systems in parallel planes, but the repulsion between the oxygen lone pairs of both fused ring systems pushes them to their maximum distances and overcomes the effect of a possible π···π interaction between both of the benzene rings. One of the CH···O (II) interactions, with a measured distance of 2.37 Å, generates a six-membered ring system. All these weak interactions confirm the efficacy of the developed molecules in a biological system due to the presence of a number of interacting sites, which create the effect of interacting with problematic enzymes and proteins to reduce their activities during clinical treatment.[36] Also, intermolecular interactions within the crystal packing have an effect on geometrical conformations and form dimeric structures. The dimeric structures (IV, V, VI) appeared in three forms depending on the type of interactions and the positions of their sites (Fig. 4).

Substitution at the C-7 position in the parent noscapine scaffold creates new interaction sites, such as CH···O, with measured distances of 2.503 Å (IV) and 2.587 Å (VI), between the acetylene and methylene hydrogens of the adjoining part and the oxygen of the parent molecule. An intermolecular CH···π (2.503 Å, V) interaction has effects on the conformations in the crystal packing. Thus, the creation of new binding sites in noscapine C-7 analog **3** is evidenced for the well-known potency towards modulating tublin polymerization. Furthermore, because of the multivalent nature of carbohydrates,[18] their introduction to noscapine is envisaged to provide more binding sites and could result in increased efficacy; however, continued efforts are required for the conclusive investigation to this end.

Conclusion

In conclusion, a number of sugar azides were prepared and further subjected to a Cu(I)-catalyzed azide alkyne cycloaddition reaction (click) with 7-*O*-propargylated noscapine. We have developed thirteen second generation noscapine triazolyl glycoconjugates at the C-7 position in good to excellent yields. Also, the role of weak interactions has been correlated with the biological action of noscapine analogs. The methodology is efficient for the preparation of modified conjugates of noscapine to improve its therapeutic efficacy and its pharmacological properties. Further research into the development of noscapine glycoconjugates as potential anti-cancer agents is in progress in our laboratory.

Experimental

General methods

All of the reactions were performed in anhydrous solvents (where required) under an argon atmosphere in oven dried glassware at 100 °C. All reagents and solvents were of pure analytical grade. Thin-layer chromatography (TLC) was performed on 60 F_{254} silica gel, pre-coated on aluminum plates, and revealed with either a UV lamp ($\lambda_{max} = 254$ nm), a specific colour reagent (*Draggendorff* reagent or iodine vapour) or by spraying with methanolic-H_2SO_4 solution and subsequent charring by heating at 100 °C. ^{1}H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively. Chemical shifts are given in ppm downfield from internal TMS; *J* values are in Hz. The high resolution mass spectrometry (HRMS) was carried out using electrospray ionization mass spectrometry. The infrared spectra were recorded as Nujol mulls on KBr plates. Single-crystal X-ray data were collected on an Xcalibur Eos (Oxford) CCD-diffractometer.

General procedure for synthesis of sugar azides (6a–g). The compounds **6a–g** were prepared from readily available carbohydrates (D-glucose, D-galactose, and D-ribose *etc.*) using standard protection and modification methodologies.[33]

General procedure for the synthesis of glycosyl epoxides (5k–m). A solution of orthogonally protected sugar **4k–m** having one free hydroxyl group (1.0 mmol) in anhydrous DMF was cooled to 0 °C and sodium hydride (2.0 equiv.) was added portion-wise. The reaction mixture was stirred at 0 °C under argon atmosphere for 20 minutes. Epichlorohydrin (1.2 mmol) was added at 0 °C and allowed to stir for 12 hour at room temperature. Upon completion of the reaction, the remaining sodium hydride was quenched with water; the solvent was removed under reduced pressure followed by extraction with ethyl acetate. The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product. Purification using flash chromatography (ethyl acetate/*n*-hexane) afforded the desired glycosyl epoxide **5k–m**.

General procedure for the synthesis of glycosyl azido alcohols 6k–m. A solution of glycosyl epoxide **5k–m** in EtOH–H_2O (1 : 1) was treated with NaN_3 and NH_4Cl at 65 °C for 8 h. Upon completion of the reaction, the solvent was removed under reduced pressure, and extracted with ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum, followed by flash chromatography (ethyl acetate/hexane) affording the desired glycosyl azido alcohol **6k–m** in good yield.

General procedure for 7-*O*-propargyl noscapine 3. To a stirring solution of compound **2** (1.0 g, 2.5 mmol) in dry acetone (25 mL), propargyl bromide (0.291 mL, 3.2 mmol) and K_2CO_3 (690 mg, 5.0 mmol) were added at room temperature. The reaction was fitted with a water condenser and refluxed at 80 °C under inert conditions for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated *in vacuo*, extracted with CH_2Cl_2 (2 × 50 mL) and washed with H_2O (10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure followed by purification (flash column chromatography using gradient mixtures of *n*-hexane/ethyl acetate) to afford compound **3** as a yellowish solid (819 mg, yield 75%). IR (KBr) ν_{max}: 2949, 2850, 1753, 1622, 1514, 1497, 1479, 1362, 1243, 1033 cm^{-1}; MS: *m/z* 457 [M + Na]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (d, $J = 8.4$ Hz, 1H), 6.29 (s, 1H), 6.10 (d, $J = 8.1$ Hz, 1H), 5.93 (s, 2H), 5.58 (d, $J = 4.2$ Hz, 1H), 5.05 (s, 2H), 4.39 (d, $J = 4.2$ Hz, 1H), 4.03 (s, 3H), 3.86 (s, 3H), 2.62–2.54 (m, 4H), 2.40–2.30 (m, 3H), 1.90–1.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 152.7, 148.3, 140.9, 140.4, 133.9, 132.1, 120.8, 118.5, 118.4,

118.1, 117.0, 102.3, 102.2, 100.7, 81.9, 81.8, 75.4, 62.5, 61.2, 60.7, 56.9, 49.9, 46.2, 27.9 ppm.

General procedure for the synthesis of noscapine glycoconjugates (8a–m)

*Noscapine glycoconjugate **8a**.* To a stirring solution of compound **3** (70 mg, 0.16 mmol) and *azido*-sugar **6a** (71 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (10 mL), CuI (15 mg, 0.08 mmol) and DIPEA (0.027 ml, 0.16 mmol) were added and stirring was continued at room temperature for 14 h under argon atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated *in vacuo* to obtain a crude residue which was purified using silica gel (230–400 mesh) column chromatography (ethyl acetate/*n*-hexane) to afford the desired noscapine glycoconjugate **8a** as a brown solid (124 mg, yield 95%); $R_f = 0.35$ (60% ethyl acetate/*n*-hexane); IR (KBr) cm^{-1}: 2960, 2854, 1756, 1622, 1497, 1479, 1377, 1225, 1037; ^1H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 6.30 (s, 1H), 6.07 (d, $J = 8.1$ Hz, 1H), 5.93–5.84 (m, 3H), 5.60–5.24 (m, 7H), 4.40 (d, $J = 3.9$ Hz, 1H), 4.28 (dd, $J = 4.8$ and 12.6 Hz, 1H), 4.16–4.08 (m, 1H), 4.03 (m, 3H), 3.84 (s, 3H), 2.54 (m, 4H), 2.33 (m, 2H), 2.10–2.03 (m, 10H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 170.0, 169.2, 168.6, 168.2, 152.3, 148.3, 145.4, 140.8, 140.4, 132.1, 133.4, 122.6, 120.6, 118.2, 118.1, 116.9, 102.3, 102.2, 100.8, 85.5, 81.8, 74.9, 72.8, 70.2, 67.6, 67.6, 60.8, 60.6, 59.3, 56.6, 50.0, 46.3, 28.1, 20.6, 20.5, 20.4, 20.1 ppm; HRMS: calcd for $C_{38}H_{43}N_4O_{16}$ [M + H]: 811.2674; found 811.2671.

*Noscapine glycoconjugate **8b**.* Compound **3** (50 mg, 0.11 mmol), on treatment with *azido*-sugar **6b** (51 mg, 0.13 mmol), DIPEA (0.018 ml, 0.13 mmol) and CuI (10 mg, 0.05 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 12 h and workup as described in the general procedure, afforded compound **8b** as a brown solid (80 mg, yield 90%); $R_f =$ 0.3 (60% ethyl acetate/*n*-hexane); IR (KBr) cm^{-1}: 3454, 2924, 2853, 1755, 1622, 1498, 1479, 1460, 1371, 1218; ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 6.23 (s, 1H), 6.02 (d, $J = 8.1$ Hz, 1H), 5.86 (s, 2H), 5.76 (d, $J = 9.3$ Hz, 1H), 5.61–5.22 (m, 4H), 5.19–5.15 (m, 2H), 4.34 (d, $J = 3.6$ Hz, 1H), 4.14–4.05 (m, 3H), 3.94 (s, 3H), 3.77 (s, 3H), 2.47 (m, 4H), 2.26–2.18 (m, 4H), 1.98–1.94 (m, 7H), 1.79 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 170.1, 169.8, 168.7, 168.1, 152.4, 148.3, 145.2, 140.8, 140.3, 133.9, 132.0, 122.6, 120.6, 118.1, 116.7, 102.3, 102.1, 100.7, 86.2, 81.9, 73.8, 70.9, 67.7, 67.5, 66.7, 61.2, 60.6, 59.2, 56.5, 49.8, 46.1, 27.9, 20.6, 20.5, 20.4, 20.1 ppm; HRMS: calcd for $C_{38}H_{43}N_4O_{16}$ [M + H]: 811.2674; found 811.2670.

*Noscapine glycoconjugate **8c**.* Compound **3** (50 mg, 0.11 mmol), on treatment with *azido*-sugar **6c** (90 mg, 0.13 mmol), DIPEA (0.018 ml, 0.13 mmol) and CuI (10 mg, 0.05 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 12 h and workup as described in the general procedure, afforded compound **8c** as a brown solid (101 mg, yield 84%); $R_f = 0.3$ (80% ethyl acetate/*n*-hexane); IR (KBr) cm^{-1}: 3472, 2955, 2925, 2853, 1755, 1622, 1498, 1480, 1456, 1371, 1227, 1046; MS: m/z 1122 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H), 6.97 (d, $J = 8.1$ Hz, 1H), 6.30 (s, 1H), 5.93 (s, 2H), 5.82 (d, $J = 9.0$ Hz, 1H), 5.63 (d, $J = 3.3$ Hz, 1H), 5.48–5.37 (m, 6H), 5.17–5.11 (m, 1H), 4.98 (dd, $J = 3.3$ Hz, 10.8 Hz, 1H), 4.55–4.46 (m, 3H), 4.17–4.08 (m, 3H), 4.02 (m, 1H), 3.98 (s, 3H), 3.93–3.88 (m, 2H), 3.85 (s, 3H), 2.67–2.55 (m, 4H), 2.46–2.38 (m, 3H), 2.16, 2.12, 2.09, 2.06, 2.04, 1.97, 1.84 (each s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.3, 170.0, 169.5, 169.0, 168.8, 152.4, 148.7, 145.2, 140.2, 133.9, 131.9, 122.8, 120.2, 118.4, 115.3, 102.3, 102.2, 100.9, 100.8, 85.4, 75.7, 75.6, 72.73, 70.8, 70.7, 70.7, 69.0, 67.5, 66.5, 61.7, 60.7, 60.6, 56.7, 48.9, 45.0, 20.6, 20.6 ppm.

*Noscapine glycoconjugate **8d**.* Compound **3** (50 mg, 0.11 mmol), on treatment with *azido*-sugar **6d** (80 mg, 0.13 mmol), DIPEA (0.018 ml, 0.13 mmol) and CuI (10 mg, 0.05 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 16 h and workup as described in the general procedure, afforded compound **8d** as a brown solid (102 mg, yield 88%); $R_f = 0.25$ (60% ethyl acetate/*n*-hexane); MS: m/z 1081 $[M + Na]^+$; IR (KBr) cm^{-1}: 3444, 3065, 2925, 2852, 2798, 1738, 1621, 1584, 1496, 1452, 1269; ^1H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.01 (d, $J = 7.2$ Hz, 2H), 7.92 (d, $J = 7.2$ Hz, 2H), 7.82 (d, $J = 7.2$ Hz, 2H), 7.73 (d, $J = 7.2$ Hz, 2H), 7.54–7.35 (m, 9H), 7.30–7.28 (m, 3H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.32–6.23 (m, 2H), 6.09–6.06 (m, 3H), 5.92–5.82 (m, 3H), 5.60 (m, 1H), 5.49–5.36 (m, 2H), 4.62–4.41 (m, 4H), 4.00 (s, 3H), 3.71 (s, 3H), 2.54 (m, 4H),2.33 (m, 2H), 1.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 166.0, 165.5, 165.0, 164.3, 152.3, 148.3, 145.4, 140.9, 140.3, 133.9, 133.5, 133.4, 133.3, 133.1, 132.0, 129.8, 129.7, 129.2, 128.4, 128.3, 128.3, 128.1, 122.6, 120.6, 118.2, 116.9, 102.2, 100.7, 86.0, 81.8, 75.4, 73.1, 70.9, 68.8, 67.6, 62.7, 60.7, 59.3, 56.6, 49.9, 46.2, 28.0 ppm.

*Noscapine glycoconjugate **8e**.* Compound **3** (70 mg, 0.16 mmol), on treatment with *azido*-sugar **6e** (58 mg, 0.19 mmol), DIPEA (0.027 mL, 0.16 mmol) and CuI (15 mg, 0.07 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 12 h and workup as described in the general procedure, afforded compound **8e** as a brown solid (111 mg, yield 94%); $R_f = 0.3$ (60% ethyl acetate/*n*-hexane); IR (KBr) cm^{-1}: 3425, 2928, 2797, 1759, 1622, 1497, 1479, 1376, 1271; ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.35 (m, 5H), 6.94 (d, $J = 8.4$ Hz, 1H), 6.28 (s, 1H), 6.06 (d, $J = 8.1$ Hz, 1H), 5.96–5.92 (m, 3H), 5.58–5.29 (m, 3H), 4.74–4.39 (m, 7H), 4.01–3.99 (m, 4H), 3.82 (s, 3H), 2.25 (m, 4H), 2.34–2.31 (m, 2H), 1.89–1.85 (m, 1H), 1.42, 1.30 (each s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 152.4, 148.2, 145.4, 144.4, 140.6, 140.2, 136.8, 133.9, 132.0, 128.5, 128.1, 127.9, 125.0, 124.9, 120.6, 118.0, 116.7, 111.9, 105.0, 102.2, 102.1, 100.6, 81.8, 81.6, 81.3, 78.7, 71.8, 67.6, 60.7, 60.5, 59.3, 56.5, 49.8, 48.9, 46.1, 27.9, 26.5, 26.0 ppm; HRMS: calcd for $C_{39}H_{42}N_4NaO_{11}$ [M + Na]: 765.2748; found 765.2742.

*Noscapine glycoconjugate **8f**.* Compound **3** (90 mg, 0.20 mmol), on treatment with *azido*-sugar **6f** (120 mg, 0.24 mmol), DIPEA (0.034 mL, 0.2 mmol) and CuI (19 mg, 0.1 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 12 h and workup as described in the general procedure, afforded compound **8f** as a brown solid (157 mg, yield 85%); $R_f = 0.35$ (60% ethyl acetate/*n*-hexane); MS: m/z 927 $[M + H]^+$; IR (KBr) cm^{-1}: 2963, 2926, 2855, 1760, 1621, 1496, 1454, 1401, 1261, 1095; ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.25–7.23 (m, 15H), 6.88 (d, $J = 8.4$ Hz, 1H), 6.21 (s, 1H), 6.07 (d, $J = 8.1$ Hz, 1H), 5.83 (s, 2H), 5.54 (m, 1H), 5.40–5.27 (m, 2H), 4.92–4.37 (m, 11H), 3.95–3.75 (m, 8H), 3.40 (d, $J = 9.6$ Hz, 1H), 3.10 (m, 3H),

2.58–1.81 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 152.5, 148.4, 145.6, 144.4, 140.7, 140.3, 138.4, 137.9, 133.9, 131.7, 128.4, 128.3, 128.1, 127.9, 127.8, 127.5, 125.4, 120.4, 118.4, 116.3, 102.2, 100.7, 97.8, 81.8, 81.6, 79.9, 77.9, 75.6, 74.8, 73.3, 69.0, 67.7, 60.7, 59.2, 56.7, 55.2, 50.6, 49.5, 45.8, 27.5 ppm.

Noscapine glycoconjugate ***8g***. Compound **3** (50 mg, 0.13 mmol), on treatment with *azido*-sugar **6g** (46 mg, 0.16 mmol), DIPEA (0.022 mL, 0.13 mmol) and CuI (12 mg, 0.06 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 14 h and workup as described in the general procedure, afforded compound **8g** as a brown solid (89 mg, yield 90%); R_f = 0.25 (60% ethyl acetate/*n*-hexane); MS: *m*/*z* 745 $[M + Na]^+$; IR (KBr) cm^{-1}: 2988, 2934, 2876, 1764, 1624, 1500, 1479, 1382, 1274; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.22 (s, 1H), 6.01 (d, J = 8.1 Hz, 1H), 5.85 (s, 2H), 5.51–5.31 (m, 4H), 4.56–4.10 (m, 7H), 3.92 (s, 3H), 3.77 (s, 3H), 2.45 (s, 3H), 2.29–2.26 (m, 2H), 1.98 (d, J = 3.3 Hz, 1H), 1.82–1.77 (m, 1H), 1.43, 1.31, 1.29, 1.20 (each s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 152.2, 148.3, 144.0, 140.8, 140.3, 133.9, 132.0, 125.3, 120.6, 118.2, 116.7, 109.7, 108.9, 102.3, 102.2, 100.7, 96.0, 81.8, 71.0, 70.6, 70.2, 67.5, 67.0, 60.7, 59.2, 56.6, 50.3, 49.7, 46.1, 27.8, 25.9, 25.9, 24.8, 24.3 ppm.

Noscapine glycoconjugate ***8h***. Compound **3** (100 mg, 0.23 mmol), on treatment with *azido*-sugar **6j** (93 mg, 0.28 mmol), DIPEA (0.039 mL, 0.23 mmol) and CuI (21 mg, 0.12 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 13 h and workup as described in the general procedure, afforded compound **8h** as a brown solid (152 mg, yield 86%); R_f = 0.24 (60% ethyl acetate/*n*-hexane); MS: *m*/*z* 795 $[M + Na]^+$; IR (KBr) cm^{-1}: 3416, 2926, 2854, 1759, 1711, 1622, 1497, 1479, 1457, 1376, 1271; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.28–7.19 (m, 5H), 6.87 (d, J = 8.4 Hz, 1H), 6.20 (s, 1H), 5.98 (d, J = 8.4 Hz, 1H), 5.87–5.84 (m, 3H), 5.47 (d, J = 3.6 Hz, 1H), 5.37–5.22 (m, 4H), 4.73–4.53 (m, 5H), 4.27–4.23 (m, 2H), 3.93 (s, 3H), 3.78 (s, 3H), 2.40 (s, 3H), 2.29–2.19 (m, 2H), 2.10 (m, 1H), 1.79–1.71 (m, 1H), 1.38, 1.24 (each s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 152.6, 148.3, 145.0, 143.9, 140.5, 137.2, 133.8, 132.0, 128.5, 127.9, 125.7, 120.9, 118.0, 116.7, 111.9, 105.1, 102.3, 102.1, 100.7, 82.2, 81.6, 80.9, 80.5, 72.4, 67.7, 67.1, 60.6, 59.2, 56.4, 54.2, 49.7, 46.1, 27.7, 26.7, 26.2 ppm.

Noscapine glycoconjugate ***8i***. Compound **3** (60 mg, 0.14 mmol), on treatment with *azido*-sugar **6i** (48 mg, 0.17 mmol), DIPEA (0.022 mL, 0.13 mmol) and CuI (12 mg, 0.06 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 12 h and workup as described in the general procedure, afforded compound **8i** as a brown solid (80 mg, yield 85%); R_f = 0.25 (60% ethyl acetate/*n*-hexane); MS: *m*/*z* 747 $[M + Na]^+$; IR (KBr) cm^{-1}: 3416, 2926, 2854, 1759, 1711, 1622, 1497, 1479, 1457, 1376, 1271; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.33–6.17 (m, 2H), 5.95–5.92 (m, 3H), 5.61 (d, J = 7.8 Hz, 1H), 5.44–5.31 (m, 2H), 4.73 (d, J = 11.7 Hz, 1H), 4.57 (m, 1H), 4.42–4.31 (m, 3H), 4.02–3.86 (m, 8H), 3.59–3.48 (m, 3H), 2.55–2.51 (m, 4H), 2.41–2.38 (m, 2H), 2.07–1.94 (m, 1H), 1.64–157 (m, 2H), 1.46, 1.32 (each s, 6H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 152.6, 148.4, 145.1, 143.9, 140.5, 140.3, 133.9, 125.8, 118.5, 118.1, 116.8, 111.8, 105.2, 102.3, 102.2, 100.7, 82.2, 82.0, 81.6, 80.4, 72.4, 68.0, 67.1, 60.6, 59.2, 56.5, 54.2, 49.6, 45.9, 27.6, 26.7, 26.2, 22.9, 10.5.

Noscapine glycoconjugate ***8j***. Compound **3** (100 mg, 0.23 mmol), on treatment with *azido*-sugar **6j** (88 mg, 0.28 mmol), DIPEA (0.039 mL, 0.23 mmol) and CuI (21 mg, 0.12 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 12 h and workup as described in the general procedure, afforded compound **8j** as a brown solid (138 mg, yield 80%); R_f = 0.25 (60% ethyl acetate/*n*-hexane); MS: *m*/*z* 775 $[M + Na]^+$; IR (KBr) cm^{-1}: 3416, 2928, 2854, 1759, 1717, 1622, 1497, 1479, 1460, 1376, 1271; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.29–6.20 (m, 2H), 5.93–5.90 (m, 3H), 5.62 (d, J = 3.3 Hz, 1H), 5.45–5.31 (m, 2H), 4.77 (d, J = 12.6 Hz, 1H), 4.56–4.25 (m, 5H), 3.98–3.86 (m, 7H), 3.68–3.49 (m, 3H, OH, OCH_2), 2.68–2.40 (m, 5H), 2.20–2.12 (m, 1H), 1.69–1.61 (m, 2H), 1.51–1.46 (m, 4H), 1.32 (s, 3H), 0.89 (d, J = 7.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 152.6, 148.7, 145.2, 144.0, 140.3, 140.3, 133.9, 125.6, 118.6, 118.3, 111.8, 105.2, 105.1, 102.3, 100.8, 82.3, 82.1, 80.4, 69.1, 67.4, 67.3, 60.8, 60.6, 56.7, 54.1, 38.4, 26.8, 26.7, 26.2, 24.9, 22.5, 22.4 ppm.

Noscapine glycoconjugate ***8k***. Compound **3** (65 mg, 0.15 mmol), on treatment with *azido*-sugar **6k** (64 mg, 0.18 mmol), DIPEA (0.025 mL, 0.14 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 14 h and workup as described in the general procedure, afforded compound **8k** as a brown solid (97 mg, yield 82%); R_f = 0.2 (80% ethyl acetate/*n*-hexane); MS: *m*/*z* 820 $[M + Na]^+$; IR (KBr) cm^{-1}: 3426, 2987, 2937, 2926, 1759, 1622, 1497, 1479, 1382, 1271; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.; ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 152.5, 152.4, 148.3, 148.3, 145.3, 145.2, 144.3, 144.1, 140.5, 140.4, 140.2, 133.8, 131.8, 131.6, 125.7, 125.2, 120.5, 118.2, 116.5, 116.3, 111.7, 109.3, 109.2, 105.5, 105.3, 102.1, 100.6, 83.8, 83.1, 82.2, 81.6, 81.3, 81.1, 81.0, 72.7, 72.5, 72.2, 71.0, 69.3, 68.6, 67.6, 67.5, 60.5, 59.2, 56.5, 53.3, 52.6, 52.3, 49.6, 49.3, 46.0, 45.7, 27.6, 27.1, 26.6, 26.0, 25.0, 25.0 ppm.

Noscapine glycoconjugate ***8l***. Compound **3** (90 mg, 0.21 mmol), on treatment with *azido*-sugar **6l** (89 mg, 0.25 mmol), DIPEA (0.035 mL, 0.2 mmol) and CuI (19 mg, 0.1) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 14 h and workup as described in the general procedure, afforded compound **8l** as a brown solid (140 mg, yield 84%); R_f = 0.2 (80% ethyl acetate/*n*-hexane); MS: *m*/*z* 820 $[M + Na]^+$; IR (KBr) cm^{-1}: 3439, 2988, 2925, 2853, 1759, 1622, 1497, 1461, 1384, 1272, 1069; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.22 (s, 1H), 6.02 (m, 1H), 5.85 (s, 2H), 5.51–5.22 (m, 5H), 4.52–4.00 (m, 7H), 3.92 (s, 3H), 3.78 (s, 3H), 3.61–3.47 (m, 5H), 2.44–2.27 (m, 5H), 1.96–1.80 (m, 2H), 1.46–1.26 (merge 4 s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 152.6, 148.4, 145.3, 140.6, 140.3, 133.9, 131.9, 131.5, 125.4, 120.6, 118.3, 118.2, 109.3, 108.6, 102.3, 102.2, 100.7, 96.2, 81.6, 81.1, 72.7, 72.2, 71.0, 70.5, 70.1, 69.2, 67.4, 66.8, 60.6, 60.8 59.3, 56.6, 52.9, 49.6, 49.0, 46.0, 45.5, 27.6, 26.6, 26.0, 25.9, 24.8, 24.4 ppm.

Noscapine glycoconjugate ***8m***. Compound **3** (50 mg, 0.11 mmol), on treatment with *azido*-sugar **6m** (50 mg, 0.13 mmol), DIPEA (0.018 mL, 0.14 mmol) and CuI (10 mg, 0.05 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under argon atmosphere for 15 h and workup as described in the general procedure,

afforded compound **8m** as a brown solid (80 mg, yield 90%); $R_f = 0.2$ (80% ethyl acetate/*n*-hexane); MS: *m*/*z* 817 $[M + H]^+$; IR (KBr) cm^{-1}: 3417, 2926, 1759, 1622, 1497, 1479, 1456, 1272; ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.30 (m, 5H), 6.96 (d, $J =$ 8.1 Hz, 1H), 6.30 (s, 1H), 6.11 (d, J = 5.7 Hz, 1H), 5.93 (s, 2H), 5.49–5.29 (m, 2H), 4.70–4.30 (m, 7H), 4.13–3.51 (m, 13H), 2.51–2.35 (m, 5H), 2.04–1.93 (m, 2H), 1.49, 1.32 (each s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 152.7, 148.5, 144.2, 140.4, 140.2, 137.3, 128.5, 127.9, 127.6, 125.8, 120.5, 118.4, 118.2, 111.7, 105.0, 102.2, 102.2, 100.7, 82.1, 81.7, 81.1, 79.1, 72.5, 71.8, 69.3, 67.2, 60.7, 60.4, 59.3, 56.6, 53.3, 53.0, 49.6, 48.9, 45.9, 45.4, 27.6, 26.8, 26.5, 26.2 ppm.

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