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COMMINICATION

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 opium plant, *via* two successive steps. First step is the selective 7-O-demethylation of Noscapine and the next one is the subsequent propargylation which afford 7-*O*-propargyl noscapine (**3**) in good yield. The structure of was confirmed by extensive spectroscopic data including single crystal X-ray. The 1,3-dipolar cycloaddition of developed noscapine derivative **3** with glycosyl *azides* **6a-m** was investigated to give the triazole linked second-generation noscapine analogous 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 of the member of this group, noscapine 'a phthaisoquinoline alkaloid' has a benzofuranone ring attached with hetero ring of isoquinoline. Noscapine is available in about 7% abundance during opium harvesting.[3]It has been used as antitussive agent since several decades because of its favourable toxicity profile. Recently, it was found to bind the tubulin and alter its conformation, properties, and turn the microtubule dynamics.[4,5] Additionally, noscapine has also shown the successful inhibition of various neoplasms *in vitro* as well as *in vivo* such as leukemia and lymphoma,[6-8] along with melanoma,[9] ovarian,[10] gliomas,[11] 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 the noscapine can perturb tubulin dynamics.[15]Recent literature has revealed that chemical modifications at its position-7 *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 suggested that the presence and modification of benzofuranone ring in parent molecule had significant impact on its biological activity (**Figure 1**).

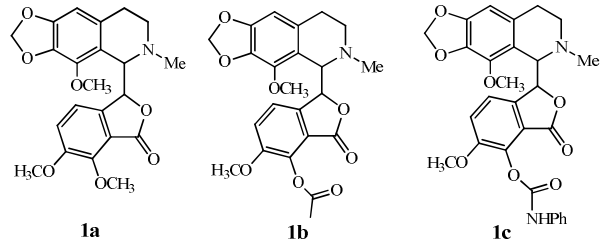

Fig. 1: Structure of Noscapine (**1a**) and its potent biologically active 7-*O*-analogous (**1b, 1c**) against tubulin polymerization

Carbohydrates and its diverse saccharide forms (mono to poly) always attract to synthetic chemist for their utilization in medicinal chemistry because it yields effective control on biological functions.[18] Additionally, multivalent nature of carbohydrate molecules are frequently used to enhance the affinities 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, yet their presence in synthetic and naturally occurring molecules create 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]

Cu(I)-catalysed Click reaction[21,22] is a precise tool for the adjoining of two dissimilar moieties having azide and terminal alkyne functionality and has emerged as an important strategy for the discovery and optimization of leads. This strategy is also being used in exploration of effective drug candidates against various therapeutic strains.[23-28] Based upon these impetus and with our previous experience,[29-32] herein we have incorporated terminal alkyne functionality successfully 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 form using Cu(I)-catalyzed Click Chemistry. We hope it will satisfy the increasing demand of more potent analogs of this molecule to modulate microtubules more effectively.

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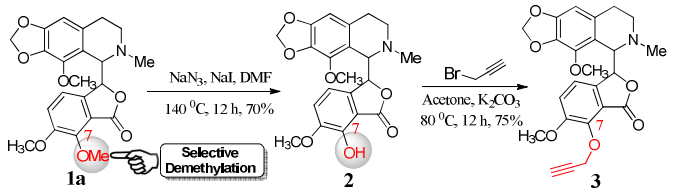
†**Electronic Supplementary Information (ESI) available:** Copies of ^{1}H and ^{13}C NMR for all the new compounds, single crystal X-ray data of **3** has been provided. See DOI: DOI:10.1039/b.

Results and discussion

Our strategy started with the demethylation of parent compound noscapine. Sodium azide and sodium iodide in dimethylformamide (DMF) were used to cleave the methyl group selectively at position-7 of 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 ºC to afford 7-*O*-propargylated noscapine **3** in 75 % yields (Scheme 1). Surprisingly, this reaction did not occur in DMF at room temperature using same base. Compound **3** served as a scaffold to synthesize various C-7-modified derivatives of noscapine **8a-m** in their glycoconjugate form. The structure of new C-7 analogs of noscapine **3** was deduced from their extensive spectral studies (IR, NMR, and MS).Single crystal x-ray analysis of compound **3** confirmed the selective demethylation of parent molecules at C-7 position.



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

The ^{1}H NMR spectrum of compound **3** exhibited one singlet signal observed at δ 2.62 merged with 3 protons of *N*-Me assigned for the acetylene proton. Shifting of *ortho*-coupled aromatic protons from δ 5.11 (d, J = 8.4Hz) 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 respectively also confirmed the substitution at 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 propargyl group leading to the formation of compound **3**. In ^{13}C NMR, two new resonances were observed at δ 81.9 and δ 75.4 which were assigned for both acetylene-carbons. Molecular structure of compound **3** was also confirmed by single crystal X-ray (**Figure 2**, See, Supporting Information Table 1).

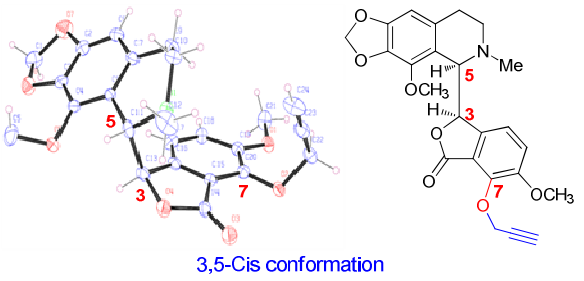
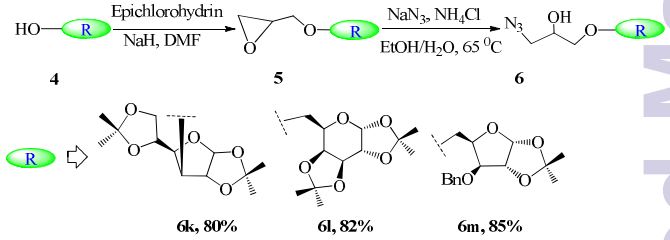


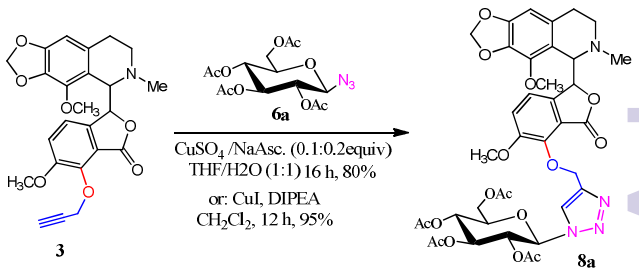
Figure 2. Molecular structure of **3**. Thermal ellipsoids of C, N, and O are set at 40 % probability

Once we achieved the second generation (C-7) noscapine analogs **3** 'having one terminal alkyne' we attempted the synthesis of various sugar azides for glycoconjugation of 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] Sugar azides **6k-m** were developed via substitution reaction on orthogonally protected carbohydrate with epichlorohydrin in presence of NaH in dry DMF at 0 ºC–r.t., which afforded distereoisomeric mixture of glycosyl epoxides **5k-m**. These epoxides on reaction with NaN_3 and NH_4Cl in $EtOH/H_2O$ at 65 ºC, afforded their respective *O*-substituted glycosyl azido alcohols **6k-m** (Scheme 2).



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

All developed *azido*sugar **6a-m** proceeded to the glyco-conjugation using compound **3** *via* copper catalyzed azide-alkyne click reaction. Generally, copper catalyzed azide-alkyne click reactions requires the presence of Cu(I) species which may be provided directly or in situ depending on catalyst. Hence, we carried out the reaction using both methods, first using CuI/DIPEA in dichloromethane and then $CuSO_4.5H_2O$/ sodium ascorbate in aqueous medium. We preferred the former reaction system due to better yield and shorter reaction times (Scheme 3). Hence, the click reaction of deoxy-azido sugar **6a** (0.19 mmol) with **3** (0.16 mmol) in 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 the compound **8a** was established based on its spectroscopic data (IR, MS, ^{1}H NMR and ^{13}C NMR) and purity is in close agreement evidenced in HRMS with calculated values.

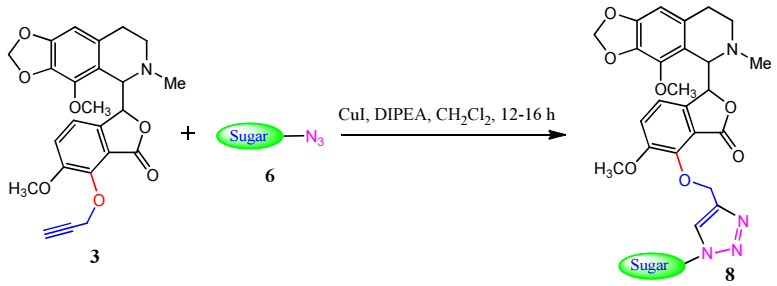


Scheme 3. Optimization of reaction medium and Cu (I) catalyst for CuAAC reaction of **3** and **6a**.

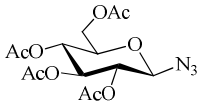
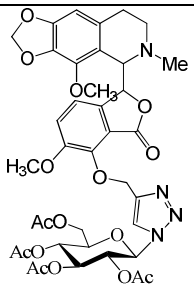
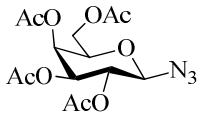
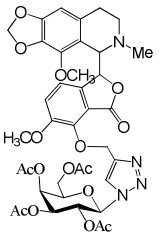
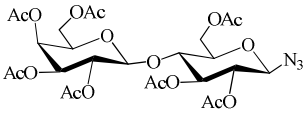
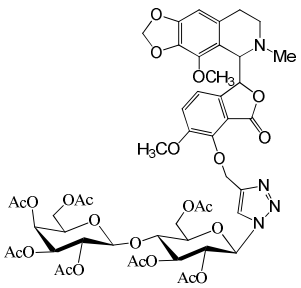
In ^{1}H NMR spectrum, two doublets and one singlet of aromatic protons resonated at δ 6.95 (d, J = 8.4 Hz), 6.07 (d, J = 8.4 Hz) and δ 6.30 along with a triazolyl proton singlet observed at δ 8.25. The anomeric proton of gluco-pyranose sugar resonated as doublet at δ 5.86 (J = 9.6 Hz) while other four 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 proton appeared at δ 4.03, 3.84 were established for methoxy signals present at aromatic rings of noscapine and another singlet at at δ 2.54 established *N*-Me protons of hetero carban ring. Twelve protons of acetyl moiety on sugar scaffold were observed as four singlets having three proton each at δ 2.10, 2.07, 2.04 and 1.85. A total of seven remaining protons of noscapine were atributed at δ 5.93 (s, 2H), 4.40 (d, J = 3.9 Hz, 1H), 2.33 (m, 2H), one merged with acetyl protons and last one with *N*-Methyl protons. Remaining sugar proton in compound **8a** resonated at δ 4.28 (dd, J = 4.8 & 12.6 Hz) and the next one appeared as multiplet at δ 4.16 confirms the structure.

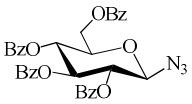
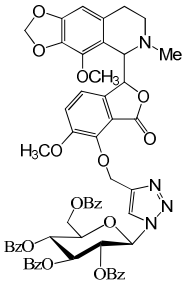
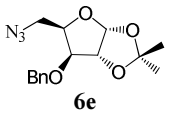
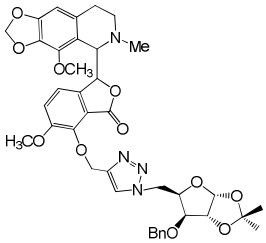
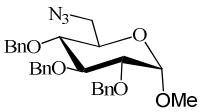
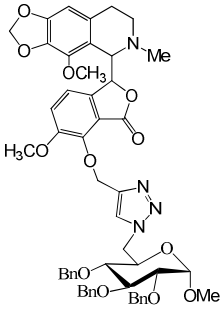
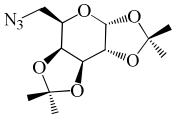
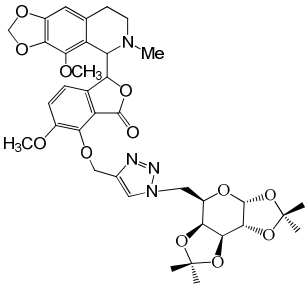
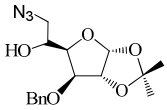
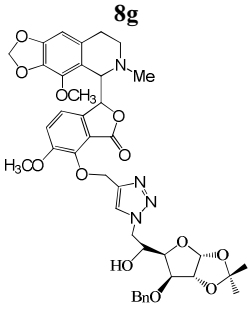
Further, having established the reaction conditions for the regioselective cycloaddition of the 7-*O*-propargyl noscapine **3**, we explored the scope of other sugar azides in this cycloaddition and prepared a library of 7-*O*-noscapine triazolyl glycoconjugates **8b-m** in efficient yield (**Table 1**).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

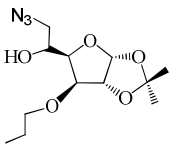
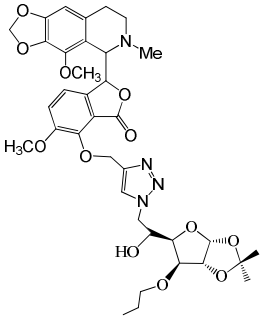
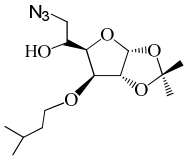
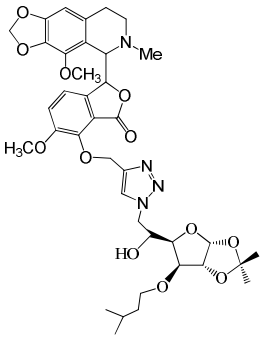
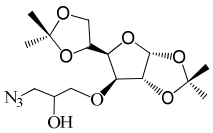
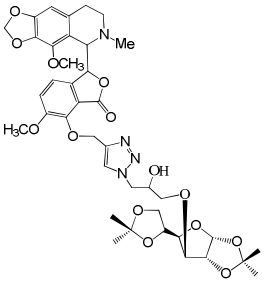
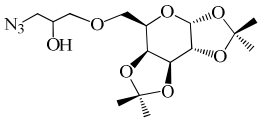
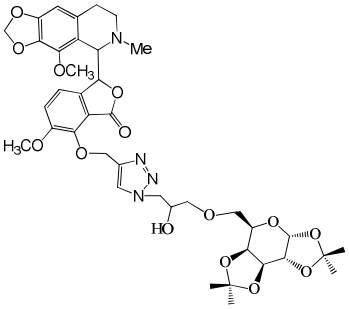
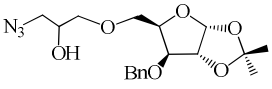
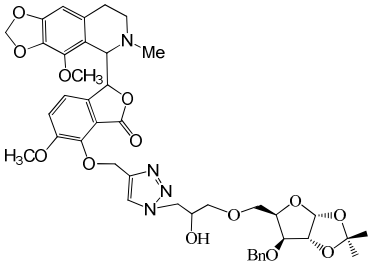
Table 1: Synthesis of 7-*O*-Noscapine glycoconjugates **8** *via* Cu-catalyzed click chemistry



3 6 8

Entry	Sugar Azides (6a-m)[a]	Noscapine Glycoconjugate (6a-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
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
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).

Weak Interactions in compound 3 and their biological importance *via* stabilizing geometrical conformations

The noncovalent inter and intramolecular interactions played the subtle role in molecular recognition and conformational stabilization within the crystal lattice for their biological assay.[34,35] Therefore, it is important to quantify the various interactions within the molecules in the crystal structures. The compound **3** is rich in C-H donors and O, π acceptors. In isoquinoline ring, *N*-methyl hydrogen, methylene hydrogen including acetylene acidic hydrogen take action as donor whenever oxygen atoms and 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 relative changes in geometrical conformations of the 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.

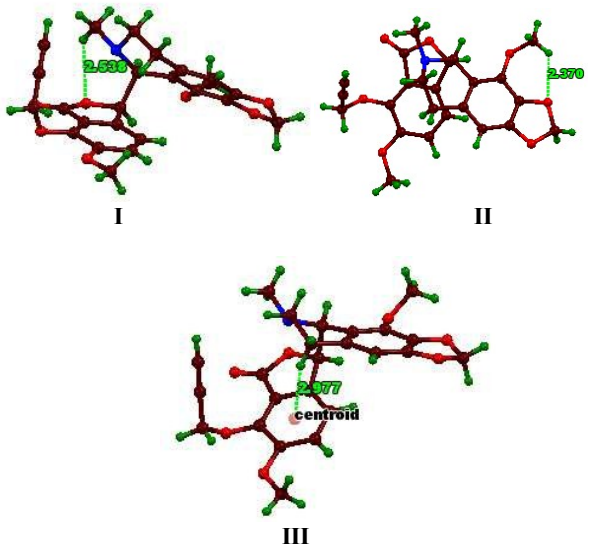


Figure 3. Intramolecular CH···O and CH···π interactions. Weak interactions are represented by broken light green lines. Carbon atoms are colored brownish, hydrogen atoms green, oxygen atoms red, and nitrogen atoms blue.

Out of various types of intramolecular interactions, three of them have been presented which causes conformational changes. CH···O (**I**) interaction between *N*-methyl hydrogens and furanone ring oxygen with measure distance 2.538 Å including CH···π, (**III**) interaction between methyene hydrogen of quinoline and aromatic system fused with lactone ring with measured distance 2.977 Å are attempting to carry both of the fused ring system in parallel planes but the repulsion among oxygen lone pairs of both fused ring systems send to each other at maximum distances and overcome the effect of possible π···π interaction between both of the benzene rings. One of the CH···O (**II**) interactions with measured distance 2.37 Å generates a six member ring system. All these weak interactions confirm the efficacy of the developed molecules in biological system due to presence of number of interacting sites which create their effect on interacting with the problematic enzymes and proteins to reduce their effects during clinical treatment.[36] Also intermolecular interactions with in the crystal packing effect on geometrical conformations and form their dimeric structures. The dimeric structures (**IV, V, VI**) appeared in three forms depending on the type of interactions and position of sites.

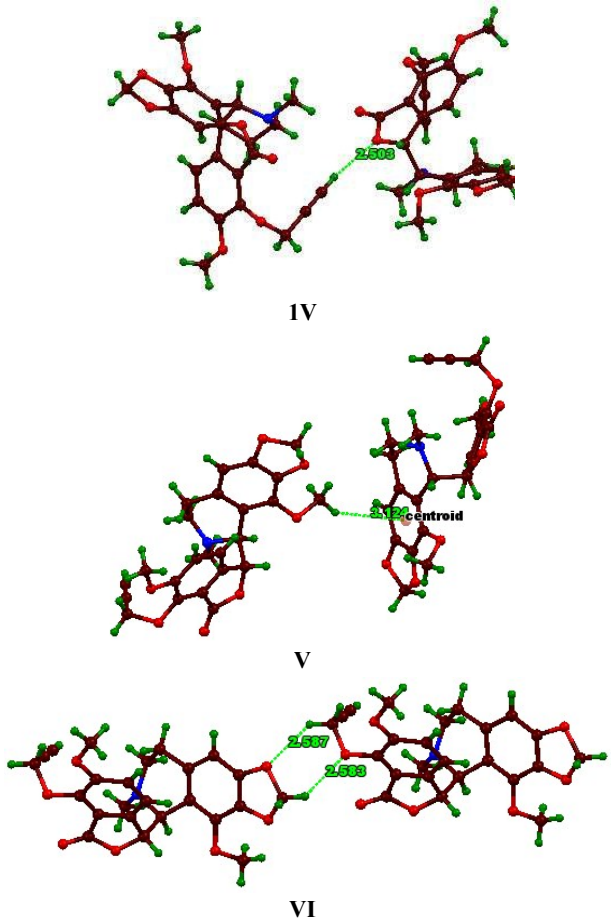


Figure 4. Intermolecular CH···O and CH···π interactions. Weak interactions are represented by broken light green lines. Carbon atoms are brownish, hydrogen atoms green, oxygen atoms red, and nitrogen atoms blue.

Substitution on *C*-7 position in parent noscapine scaffold is creating new interaction sites such as CH···O with measured distances 2.503 Å (**IV**) and 2.587 Å (**VI**) among acetylene, methylene hydrogens of adjoining part and oxygen of parent molecule. Intermolecular CH···π (2.503 Å, **V**) interaction effects on conformations in crystal packing's. Thus, 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 multivalent nature of carbohydrates,[18] their introduction to noscapine is envisaged to provide more binding sites and could result the increased efficacy, however continued efforts need to required for the conclusive investigation in this end.

Conclusion

In conclusion, a number of sugar azides were prepared and further subjected to Cu(I)-Catalyzed Azide Alkyne Cycloaddition reaction (Click) with 7-*O*-propargylated noscapine. We have developed thirteen second generation noscapine triazolyl glycoconjugates at its C-7 position in good to excellent yields. Also, role of weak interactions has been correlated with biological action of noscapine analogs. The methodology is efficient to prepare modified conjugates of noscapine to improve the therapeutic efficacy and its pharmacological properties. Further research on development of noscapine glycoconjugateas as potential anti-cancer agent is under 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 (λ_{max} = 254 nm) or a specific colour reagent (*Draggendorff* reagent or iodine vapours) 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 given in ppm downfield from internal TMS; *J* values in Hz. The high resolution (HRMS) mass spectra were recorded using electro spray ionization mass spectrometry. Infrared spectra were recorded as Nujol mulls in KBr plates. Single-crystal X-ray data collected on 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 ºC and sodium hydride (2.0 equiv.) was added portion wise. The reaction mixture was stirred at 0 ºC under argon atmosphere for 20 minutes. Epichlorohydrin (1.2 mmol) was added at 0 ºC and allowed to stir for 12 hour at room temperature. Upon completion of the reaction, remaining sodium hydride was quenched by 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 the compounds **5k-m** in EtOH/H_2O (1:1) was treated with NaN_3 and NH_4Cl at 65 ºC for 8 h. Upon completion of the reaction, the solvent was removed under reduced pressure, extracted with ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum, followed by flash chromatography (ethyl acetate: hexane) afforded desired glycosyl azido alcohol **6k-m** in good yields.

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) was added at room temperature. Reaction mixture was fitted with water condenser and refluxed at 80 °C under inert condition for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was *in vacuo* concentrated, extracted with CH_2Cl_2 (2 x 50 mL) and washed with H_2O (10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4, solvent evaporated under reduced pressure followed by purification (flash column chromatography using gradient mixtures of *n*-hexane/ethyl acetate) afforded compound **3** as 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, 148.5, 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) was added and sttiring was countinued at room temparature for 14 h under argon atmosphenre. After completion of reaction (monitored by TLC), the reaction mixture was *in vacuo* concentrated to obtain a crude residue which was purified using silica gel (230-400 mesh) column chromatography (Ethyl acetate/*n*-hexane) to afford 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; ^{1}H 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 temparature under argon atmosphenre for 12 h

and workup as described in general procedure afforded compound **8b** as 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 temparature under argon atmosphenre for 12 h and workup as described in general procedure afforded compound **8c** as 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 temparature under argon atmosphenre for 16 h and workup as described in general procedure afforded compound **8d** as 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 temparature under argon atmosphenre for 12 h and workup as described in general procedure afforded compound **8e** as 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 temparature under argon atmosphenre for 12 h and workup as described in general procedure afforded compound **8f** as 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 temparature under argon atmosphenre for 14 h and workup as described in general procedure afforded compound **8g** as 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; ^1H 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, 0.22 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 temparature under argon atmosphenre for 13 h and workup as described in general procedure afforded compound **8h** as 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; ^1H 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 temparature under argon atmosphenre for 12 h and workup as described in general procedure afforded compound **8i** as 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; ^1H 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 temparature under argon atmosphenre for 12 h and workup as described in general procedure afforded compound **8j** as 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; ^1H 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 temparature under argon atmosphenre for 14 h and workup as described in general procedure afforded compound **8k** as 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; ^1H 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 temparature under argon atmosphenre for 14 h and workup as described in general procedure afforded compound **8l** as 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}: 343[illegible], 2988, 2925, 2853, 1759, 1622, 1497, 1461, 1384, 1272, 1069; ^1H 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.[illegible], 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 temparature under argon atmosphenre for 15 [illegible] and workup as described in general procedure afforded compound **8m** as 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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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

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