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Synthesis and click reaction of tubulin polymerization inhibitor 9-azido-α-noscapine

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Abstract An efficient protocol for the synthesis of tubulin polymerization inhibitor, 9-azido-α-noscapine **2h** from 9-amino-α-noscapine **2g** is developed using mild reaction conditions (*t*-butyl nitrite/trimethylsilyl azide in acetonitrile at room temperature). Operational simplicity, high product yield without formation of any side products are the advantages of this protocol. Further copper catalyzed click reactions of 9-azido-α-noscapine **2h** with alkynes **6a–f** resulted 9-triazolyl noscapinoids **7a–f** resulted in excellent yields.

Graphical Abstract Developed an amicable protocol for the synthesis of 9-azido-α-noscapine from 9-amino-α-noscapineunder mild reaction conditions; was further derivatized to triazoles using click chemistry.

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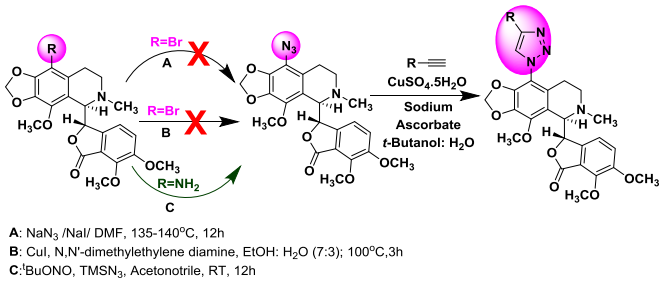


Keywords Noscapine · Heterocycle · Tubulin · Inhibitor · Click chemistry · Azide · Alkaloid

Introduction

Natural products were and are playing vital roles in drug discovery and development [1–3]. Several blockbuster and life saving drugs currently on the market are either from natural sources or generated through manifestation of the structures of natural products [4–6]. Alkaloids are one such class of natural products that contribute significantly in identifying pharmaceutically relevant scaffolds [7–9]. Among several natural alkaloids, α-noscapine **1**, (also known as Narcotine, Anarcotine and Nospen) with benzyl isoquinoline architecture attracted attention of several groups worldwide [10–14]. It is isolated from plants of the Papaveraceae family at about 7 % during opium harvesting [15–17]. It has been commonly used for several decades as an oral antitussive agent without any side effects [17]. With a favourable toxicity profile, Zhou et al. [18] and Ye et al. [19] repurposed α-noscapine as a tubulin-binding anticancer agent that arrested cancer cells in mitosis and induced apoptosis. Unlike the other tubulin-targeting agents, α-noscapine binds at the colchicine binding site and does not alter the steady state monomer/polymer ratio of tubulin [18, 19]. In addition, α-noscapine has some other advantageous properties [20] as lead molecule: (1) it has favourable pharmacokinetics (clearance in 6–10 h); (2) it retains activity against the epothilone-resistant cell line (1A9/A8) and paclitaxel-resistant cell lines (1A9/PTX10, 1A9/PTX22); and (3) it is free from immunological and neurological toxicities [10–17].

To enhance anticancer activity of α-noscapine, further efforts were made to add various functional substituents on the noscapine core [12]. For instance, 9-substituted noscapine analogues (9-bromo, 9-fluoro, 9-chloro, 9-iodo, 9-nitro, 9-azido, 9-amino and 9-aryl analogues (Fig. 1) [21–25] exhibited higher anticancer activity than the parent α-noscapine without significant toxicity. Among them, 9-bromo-α-noscapine **2a** (EM011) has been recently introduced into phase I/II clinical trials against non-Hodgkin's lymphoma and chronic lymphocytic leukemia [26–28]. Similarly, 9-nitro-α-noscapine **2f** was active against T cell lymphoma cells and drug-resistant ovarian cancer [29]. Our group also synthesized 9-amino (**2g**, Fig. 1), 9-aryl (**2e**) and other α-noscapine derivatives, and they were found to possess improved tubulin binding anticancer activity [30–34].

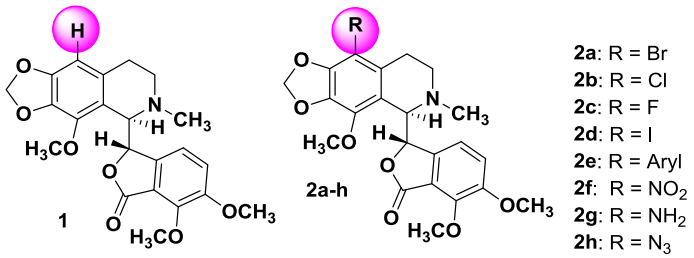


Fig. 1 Structures of natural α-Noscapine **1** and its potent bioactive 9-substituted analogs **2a–g**

Recently, 9-azido-α-noscapine (**2h**) [(*S*)-3-((*R*)-9-azido-4-methoxy-6-methyl-5,6,7,8-tetra hydro-[*1, 3*]dioxolo[*4,5-g*]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-(3*H*)-one] was identified as a potential anticancer clinical agent without any significant toxicity [35]. The IC_{50} value of **2h** is 2.6 μM against human acute lymphoblastic leukemia cells (CEM). Computational methods predicted that **2h** binds to tubulin at a site overlapping with the colchicine-binding site and possesses better antitumor activity than the parent compound **1** [35, 36]. However, further development of **2h** as an anticancer lead molecule is hampered due to non-availability of a suitable procedure for its preparation [12]. In view of the increased utility of 9-azido-α-noscapine in anticancer evaluations, it is desirable to develop an efficient method for the synthesis of **2h**.

In our programme [30–34] on the synthesis of natural products and its analogues for bio-evaluations, we herein report our efforts on development of an amicable procedure for the preparation of 9-azido-α-noscapine **2h** from natural α-noscapine. Further, the azide **2h** thus obtained reacted with alkyl/aryl alkynes to give respective 1,2,3-triazole analogs using copper catalyzed click chemistry.

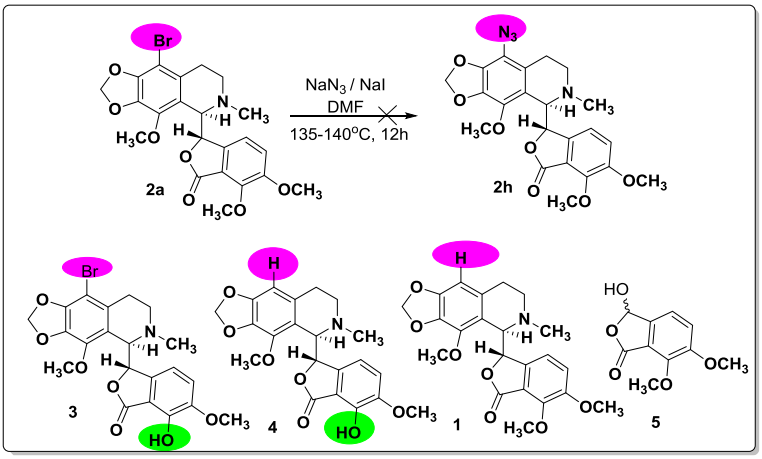
Results and discussion

Previously, synthesis of 9-azido-α-noscapine **2h** was reported via a two step route involving aromatic bromination of α-noscapine using aqueous HBr/Br_2–H_2O followed by azidation using NaN_3 and NaI in DMF [25, 26]. To the best of our knowledge, this is the only method available in the literature [25, 26] for the synthesis of **2h**. Taking it as a starting point, 9-bromo-α-noscapine **2a** required was prepared in excellent yield (90 %) from commercially available natural α-noscapine **1** using bromine water in 48 % aqueous HBr [33]. 9-Bromo-α-noscapine **2a** thus obtained was fully characterized by IR, ^1H and ^{13}C NMR and Mass (ESI and HRMS) spectra data [33]. Following the sequencing, conversion of **2a** with sodium azide/sodium iodide was attempted in DMF heating at 80–85 °C for 15 h. Contrary to our expectation, the reaction did not proceed in our hands and after a prolonged reaction time (48 h) produced 9-azido-α-noscapine **2h** only in a trace amount (∼1 %). Repeated reactions under modified conditions; changing the mole ratio of sodium azide/sodium iodide, temperature, time and solvent did not give a fruitful result.

Further, we replaced sodium azide with trimethylsilyl azide, tosyl azide, tributyltin azide, triethyl ammonium azide, tetrabutyl ammonium azide, but this did not yield the desired product. Reaction of **2a** with 2.0 equiv. of sodium azide and heating at elevated temperatures (135–140 °C) for 4 h, we noticed a sluggish reaction mixture containing several compounds (Scheme 1). Silica gel column chromatography led to separation and identification of a major amount as *O*-demethylated compound **3** (65 %) and minor amounts of **4** (5 %) and regenerated α-noscapine **1** (4 %). Another product, Opianic acid **5**, was identified as generated though cleavage of sensitive C–C bond between two heterocyclic lobes, isoquinoline and isobenzofuran-(3*H*)-one. Such sodium azide mediated regioselective *O*-demethylation of α-noscapine at elevated temperature is consistent with the literature [37, 38].

We next considered copper catalyzed Ullmann type conversion as an alternate method for the preparation of **2h**. Here, the reaction was carried out using CuI, NaN_3 and proline as an additive ligand [39, 40]. However this method also suffered from drawbacks of a low reaction rate and did not yield the desired azide. At elevated reaction temperatures (135–140 °C) 9-bromo-α-noscapine **2a** reacted with sodium azide (2.0 equiv), in the presence of CuI (2.0 equiv), and proline (4.0 equiv) in DMSO for 3.0 h gave 9-amino-α-noscapine **2g** in 62 % yield [33]. The protocol did not give any *O*-demethylated compound **3** or **4** or 9-azido-α-noscapine **2h** and also did not affect the sensitive C–C bond between the two heterocyclic units. Here, 15 % of noscapine **1** was recovered.

A report from Anderson et al. [41] indicated that proline is not a suitable ligand in copper catalyzed conversion of bromo aromatics to azides. The conversion is best achieved using CuI/*N*,*N*′-dimethyl ethylene diamine. With this clue, CuI catalyzed conversion of 9-bromo noscapine **2a** to azide **2h** was carried out with sodium azide and *N*,*N*′-dimethylethylene diamine as a ligand in ethanol: water (7:3) at 100 °C. However, the result was unchanged, to yield 9-amino noscapine **2g** along with re-



Scheme 1 Attempted synthesis of 9-azido-α-noscapine **2h**

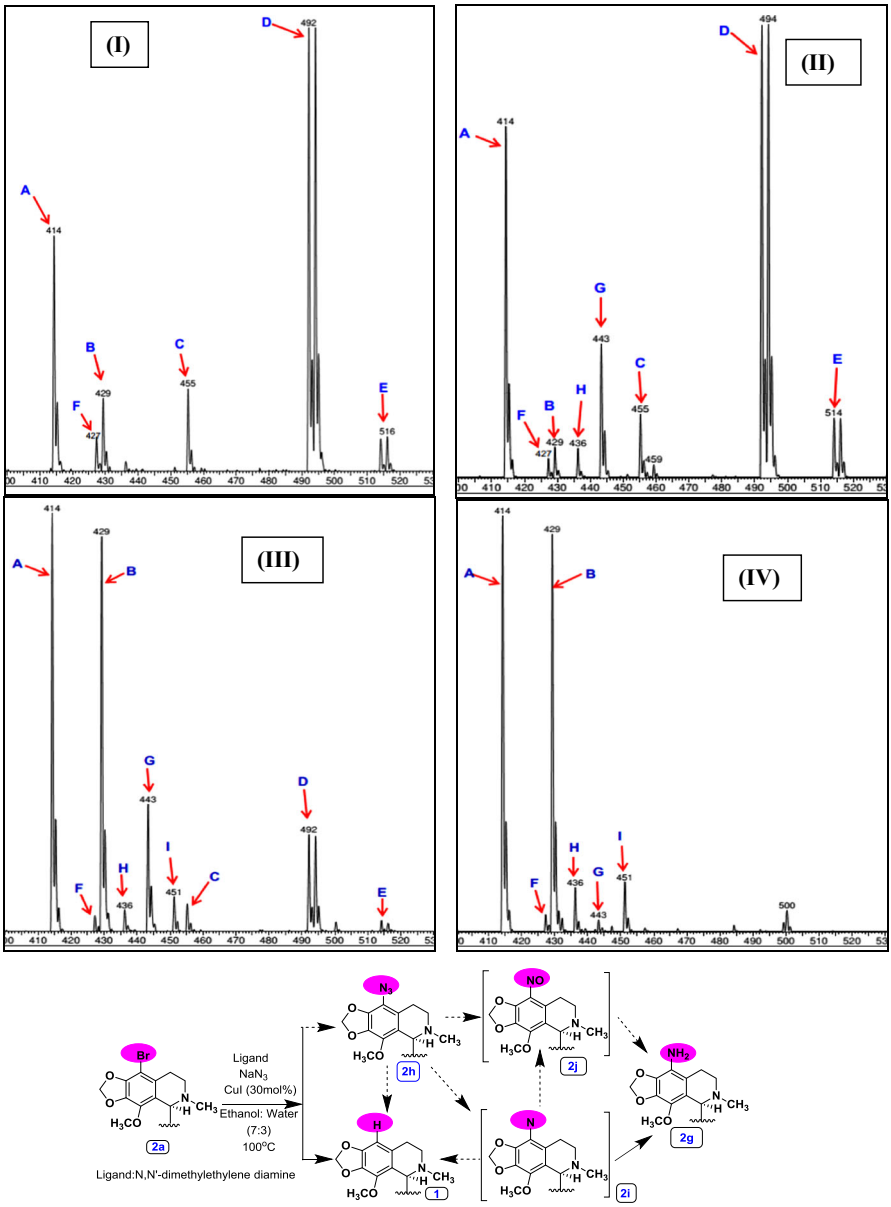


Fig. 2 Time dependent positive ion ESI mass spectra (*Top*) of the CuI catalyzed reaction of 2a with sodium azide. Panels **I**: 1 h, **II**: 3 h, **III**: 5 h and **IV**: 8 h; and schematic representation (*Bottom*) of various intermediates identified in the ESI mass spectra. Peak representations are *A*: *m/z*: 414 $(1 + H)^+$; *B*: *m/z*: 429 $(2\ g + H)^+$; *C*: *m/z*: 455 $(2\ h + H)^+$; *D*: *m/z*: 492 $(2a + H)^+$; *E*: *m/z*: 516 $(2a + Na)^+$; *F*: *m/z*: 427 $(2i + H)^+$; *G*: *m/z*: 443 $(2j + H)^+$; *H*: *m/z*: 436 $(1 + Na)^+$; *I*: *m/z*: 492 $(2\ g + Na)^+$

generated noscapine **1**. Only trace amounts (∼3 %) of 9-azidonospine **2h** was formed. In order to get mechanistic insight into this CuI catalyzed reaction, a time dependentd ESI-mass spectral analysis was carried out by drawing the samples of

reaction mixture at 1, 3, 5 and 8 h time intervals. From the ESI- mass spectral analysis (panels I–IV, Fig. 2) it is evident that formation of azide **2h** [*m/z*: 455(M + H)] is taking place within 1 h (Panel I, Fig. 2), along with de-brominated product, noscapine **1** [*m/z*: 414 (M + H)] and amine **2g** [*m/z*: 429 (M + H)]. As the time progressed, formation and dissociation/reduction of azide was taking place simultaneously through aryl nitrene [*m/z*: 427 (M + H)] and aryl nitroso [*m/z*: 443 (M + H)] intermediates. After 8 h, as evident from mass spectra (panel IV, Fig. 3), only two significant compounds, 9-amino noscapine **2g** (45 %) and de-brominated product noscapine **1** (38 %) were isolated. The study clearly revealed that 9-azido noscapine thus formed in the reaction mixture is simultaneously undergoing dissociation and reduction to form 9-amino noscapine **2g** and de-brominated product, noscapine **1**.

A literature search indicated that compared to alkyl azides, synthesis of aryl azides relies on limited selection of transformations [42–46]. The most common one is from aryl amine via diazonium salts [44]. This transformation might be problematic due to sensitivity of the C–C bond between two heterocyclic units and functional groups. The alternate Wong's (TfN_3) methodology [45] of converting aryl amines to azides uses excess Triflic anhydride and is also likely to alter noscapine architecture. Later methods of Das et al. (*tert*-butyl nitrite/excess NaN_3) [47] and Barral et al. (*tert*-butyl nitrite/$TMSN_3$) [48] are attractive for the desired conversion. Given the complexity in noscapine architecture, *tert*-butyl nitrite/$TMSN_3$ was envisaged as a choice for exploration in our study due to its applicability under mild reaction conditions [49].

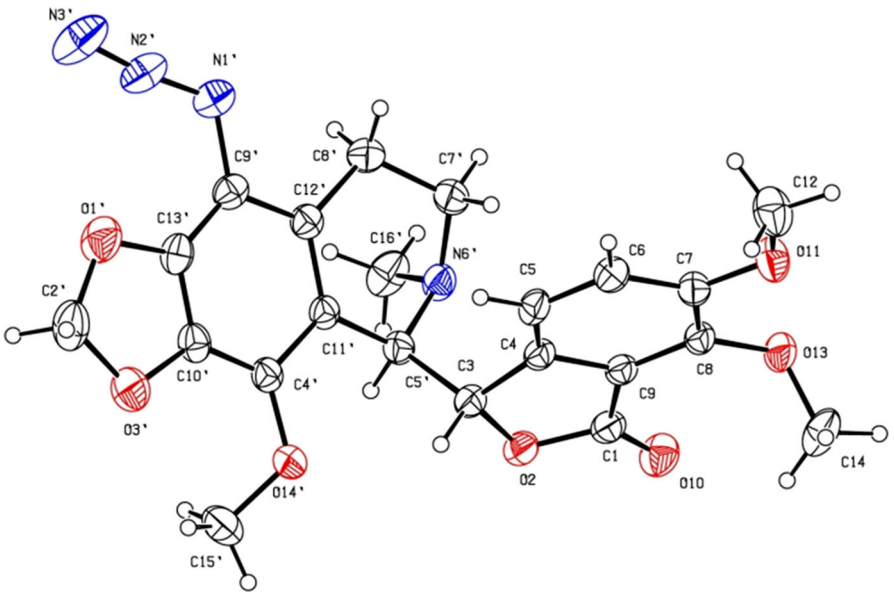


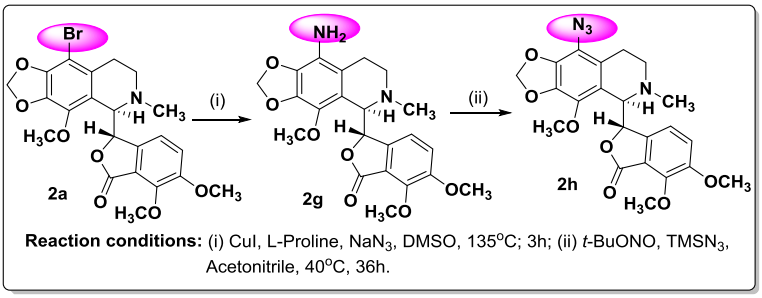
Fig. 3 ORTEP representation of 9-azido α-noscapine **2h** with thermal displacement ellipsoids drawn at the 30 % probability level and H atoms are represented by circles of arbitrary radii

Having 9-amino-α-noscapine **2g** in hand, we next reacted with *tert*-butyl nitrite/$TMSN_3$ (Scheme 2). Initially, **2g** (1.0 equiv.) was reacted with *tert*-butyl nitrite (1.0 equiv.) $TMSN_3$ (1.0 equiv.) stirring at 25 °C in acetonitrile for 24 h to give 46 % of 9-azido noscapine **2h**. After a series of reactions, the optimum yield was obtained reacting **2g** with *tert*-butyl nitrite (2.0 equiv) and $TMSN_3$ (2.0 equiv.) in acetonitrile at 40 °C for 36 h to give azide **2h**. The crude reaction mixture was purified over silica gel column chromatography to give azide **2h** in 74 % yield with >95 % HPLC purity. Azide **2h** was fully characterized by IR, ^1H and ^{13}C NMR and Mass (ESI and HRMS) spectral data. Single crystal X-ray analysis of **2h** unambiguously confirmed the structure (Fig. 3).

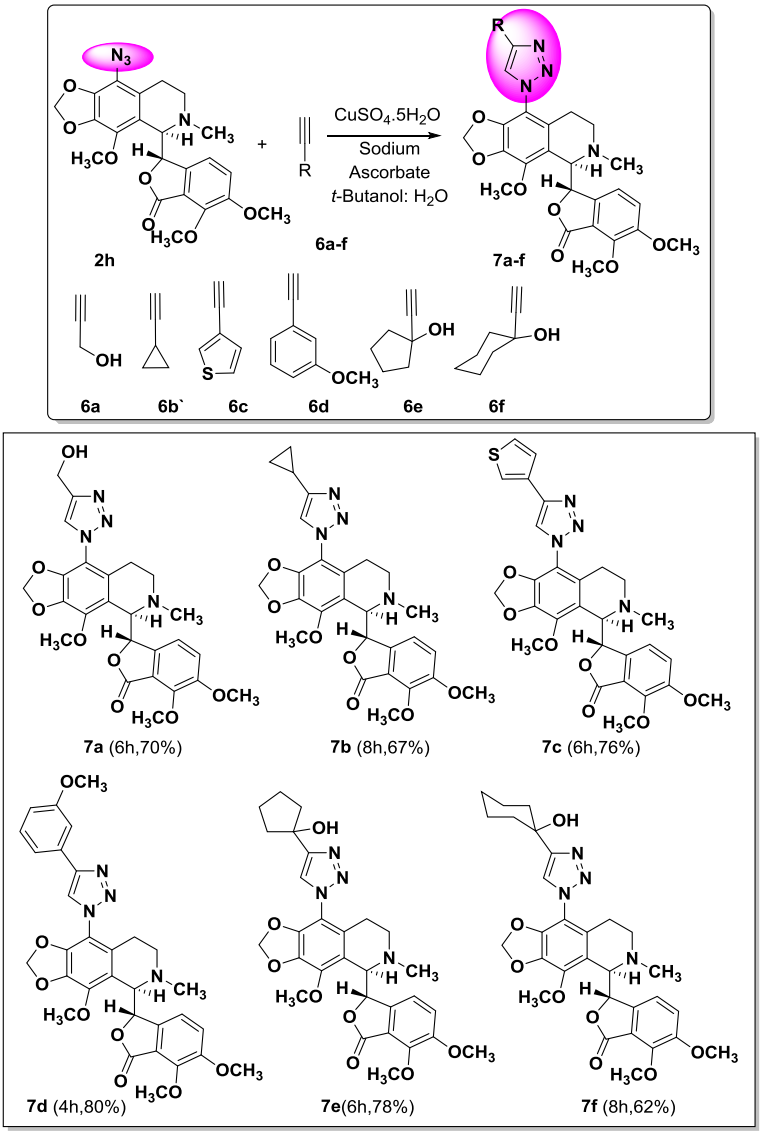
Further, to enhance the scope of 9-azido-α-noscapine **2h** and to develop potent antiproliferative agents, we explored copper catalyzed click chemistry [50–52] and reacted with various alkyl/aryl alkynes **6a–f** (Scheme 3). For example, azide **2h** (1 mmol) was reacted with propagyl alcohol **6a** in the presence of copper sulphate (0.20 mmol) and sodium ascorbate (0.20 mmol) in *tert*-butanol and water (10 mL, 1:1, v/v) for 6 h to produce triazolyl noscapine **7a** in a 70 % yield. Similarly, all other alkynes **6b–f** reacted with azide **2h** to give 9-triazolyl noscapinoids **7b–f** in excellent yields. All the products **7a–f** obtained were fully characterized by IR, ^1H and ^{13}C NMR and mass (ESI and HRMS) spectral data.

Conclusion

In summary, we have developed an efficient and amicable protocol for the synthesis of 9-azido-α-noscapine **2h** from 9-amino-α-noscapine **2g** in 74 % yield using a relatively non-explosive reagent system, *tert*-butyl nitrite/$TMSN_3$. In view of the potential use of 9-azido-α-noscapine **2h** as a tubulin binding anticancer agent, the procedure developed here is highly useful for the preparation of required quantities of **2h** with excellent purity. The azide **2h** was further reacted with various alkynes **6a–f** utilizing copper catalyzed click chemistry to give 9-triazolyl noscapinoids **7a–f** in excellent yields. Antiproliferative evaluation and potential tubulin polymerization inhibition of 9-azido-α-noscapine **2h** and its triazole analogues **7a–f** are in progress and will be reported later as a separate study.



Scheme 2 Synthesis of 9-azido-nospaine **2h**



Scheme 3 Click synthesis of 9-traizolyl α-noscapinoids **7a–f**. Reaction time, % yield of the product

Experimental

General remarks

Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. Melting points were determined on a Fischer-Johns melting point

apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ and DMSO-d6 were recorded on a Bruker UXNMR FT-300 MHz (Avance) spectrometer and Varian FT-500 MHz (Inova). Chemical shifts reported are relative to an internal standard TMS ($\delta = 0.0$). Mass spectra were recorded in ESI or EI conditions at 70 eV on LC-MSD (Agilent technologies) spectrometers. All high-resolution spectra were recorded on a QSTAR XL hybrid MS/MS system (Applied Bio systems/MDS sciex, Foster City, USA), equipped with an ESI source (IICT, Hyderabad). All the reactions were monitored by TLC (Precoated silica plates and visualizing under UV light) using Merck 60 F-254 silica gel plates. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. Analytical HPLC was performed on an 1260 infinity model of Agilent technologies using a C18 column, gradient elution with acetonitrile: water. Commercially available anhydrous solvents were used as such without further purification. Noscapine, TMS-azide, and *t*-butyl nitrite were purchased from Sigma-Aldrich and used as such without any further purification.

Synthesis of (*S*)-3-((*R*)-9-azido-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]-dioxolo[4,5-*g*] isoquinolin-5-yl)-6,7-dimethoxyiso benzo furan-1(3*H*)-one (2h) To a stirred solution of 9-amino-α-noscapine **2g** (2.0 g, 4.66 mol) in dry acetonitrile (15 mL), *t*-butyl nitrite (1.10 mL, 9.33 mol) and trimethylsilyl azide (1.22 mL, 9.33 mol) were sequentially added at 0 °C under nitrogen. The reaction mixture was brought to 40 °C and vigorously stirred for 36 h (monitored by TLC). It was quenched with water (10 mL), extracted with dichloromethane (3 × 25 mL), combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. Crude azide thus obtained was purified over silica gel column chromatography eluted with EtOAc : Hexane (40:60) to give pure azide **2h** (1.56 g, 74 %). White solid, mp 116 °C; $[\alpha]_D^{25}$: −102.3($c = 1$, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$,): δ 7.03(d, $J = 8.2$ Hz, 1H), 6.27(d, $J = 8.0$ Hz, 1H), 6.01 (d, $J = 1.6$ Hz, 2H), 5.51(d, $J = 4.4$ Hz, 1H), 4.31(d, $J = 4.4$ Hz, 1H), 4.09 (s, 3H), 3.97(s, 3H), 3.88(s, 3H), 2.69–2.61(m, 1H), 2.55–2.45(m, 4H), 2.40–2.32(m, 1H), 2.39–2.32(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 152.1, 147.6, 141.0, 140.9, 137.8, 134.6, 123.8, 119.6, 118.1, 118.0, 117.4, 113.8, 101.5, 81.3, 62.2, 60.6, 59.4, 56.6, 48.4, 45.4, 21.6. MS (ESI): *m/z* 455$(M + H)^+$, 427$(M - N_2)^+$. HRMS (ESI): Calcd for $C_{22}H_{23}N_4O_7$ $(M + H)^+$: 455.15613, found: 455.15600.

General procedure for the synthesis of 9-triazolyl noscapinoids 7a–f

To a stirred solution of 9-azido-α-noscapine **2h** (1.0 mmol), alkynes **6a–f** (1.5 mmol) in *tert*-butanol and water (1:1, v/v, 10 mL), copper sulphate pentahydrate (0.20 mmol) and sodium ascorbate (0.20 mmol) were added and stirred at room temperature for an appropriate time. After completion of reaction (TLC), to the reaction mixture was added water (5 mL), extracted with dichloromethane (3 × 25 mL), combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. Crude residue thus

obtained was purified over silica gel column chromatography to give pure 9-triazolyl noscapinoids **7a–f**.

(*S*)-3-((*R*)-9-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one (7a) Colourless solid; yield: 70 %; mp 149 °C; $[\alpha]_D^{25}$: −103.3($c = 1$, CH_2Cl_2). IR (KBr): 3418, 3448, 2925, 2797, 1758, 1618, 1497, 1461, 1217, 1034, 969, 904, 821 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.71(s, 1H), 7.11(d, $J = 8.3$ Hz, 1H), 6.51(d, $J = 8.3$ Hz, 1H), 6.01(d, $J = 11.3$ Hz, 2H), 5.50(d, $J = 4.5$ Hz, 1H), 4.89(s, 2H),4.39(d, $J = 4.5$ Hz, 1H), 4.09(s, 3H), 4.06(s, 3H), 3.90(s, 3H), 2.76–2.69(m, 1H), 2.52(s, 3H), 2.42–2.32(m, 1H), 2.29–2.20(m, 1H),1.90–1.79(m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 168.0, 152.4, 147.7, 147.3, 145.4, 143.5, 141.5, 141.0, 134.2, 128.3, 124.1, 118.4, 118.2, 117.6, 102.1, 81.3, 62.3, 60.8, 59.5, 56.8, 56.5, 48.2, 45.3, 22.3. MS (ESI): *m/z* 511 $(M + H)^+$. HRMS (ESI) Calcd for $C_{25}H_{27}N_4O_8$ $(M + H)^+$: 511.18234, found: 511.17816.

(*S*)-3-((*R*)-9-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3] dioxolo[4,5-*g*]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one (7b) Colourless solid; yield: 67 %; mp 174 °C; $[\alpha]_D^{25}$: −136.0 ($c = 1$, CH_2Cl_2). IR (KBr): 3139, 2926, 2802, 1764, 1617, 1499, 1457, 1270, 1084, 1033, 966, 936, 816, 664, 436 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.41(s, 1H), 7.09 (d, $J = 8.3$ Hz, 2H), 6.47(d, $J = 8.3$ Hz, 1H), 6.03(d, $J = 1.3$ Hz, 1H), 5.99(d, $J = 1.3$, 1H), 5.49(d, $J = 4.3$ Hz, 1H), 4.38(d, $J = 4.3$ Hz, 1H), 4.10 (s, 3H), 4.07(s, 3H), 3.89(s, 3H), 2.74–2.64(m, 1H), 2.52(s, 3H), 2.39–2.28(m, 1H), 2.26–2.13(m, 1H), 1.89–1.75(m, 1H), 1.03–0.92(m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 152.3, 149.7, 147.6, 143.3, 141.3, 141.0, 134.1, 128.5, 122.0, 119.6, 118.4, 117.6, 112.5, 101.9, 81.4, 62.2, 60.8, 59.4, 56.7, 48.4, 45.5, 29.6, 22.5, 7.8, 6.6. MS (ESI): *m/z* 521 $(M + H)^+$. HRMS (ESI): Calcd for $C_{27}H_{29}N_4O_7$ $(M + H)^+$: 521.20308, found: 521.19946.

(*S*)-6,7-dimethoxy-3-((*R*)-4-methoxy-6-methyl-9-(4-(thiophen-3-yl)-1*H*-1,2,3-triazol-1-yl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one (7c) Pale yellow solid; yield: 76 %; mp 111 °C; $[\alpha]_D^{25}$: −97.3($c = 1$, CH_2Cl_2). IR (KBr): 3422, 3103, 2934, 1757, 1620, 1497, 1457, 1268, 1033, 935, 788, 622 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.84(s, 1H), 7.76(d, $J = 3.0$ Hz, 1H), 7.51(dd, $J = 1.5\&5.2$ Hz, 1H), 7.42(dd, $J = 3.0\&5.2$ Hz, 1H), 7.13 (d, $J = 7.5$ Hz, 1H), 6.54(d, $J = 8.3$ Hz, 1H), 6.06(d, $J = 1.5$, 1H), 6.01(d, $J = 1.5$ Hz, 1H), 5.50(d, $J = 4.5$ Hz, 1H), 4.39(d, $J = 4.5$ Hz, 1H), 4.10(s, 3H), 4.08(s, 3H), 3.91(s,3H), 2.84–2.66(m, 1H), 2.54(s, 3H), 2.46–2.20(m, 2H), 2.01–1.81(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 152.4, 147.7, 143.6, 143.4, 141.5, 141.1, 134.1, 131.3, 128.4, 126.4, 125.7, 121.6, 121.4, 119.5, 118.5, 118.3, 117.6, 112.2, 102.0, 81.3, 62.2, 60.9, 59.4, 56.8, 48.2, 45.3, 22.4. MS (ESI): *m/z* 563 $(M + H)^+$. HRMS (ESI): Calcd for $C_{28}H_{27}N_4O_7(M + H)^+$: 563.19950, found: 563.15679.

(*S*)-6,7-dimethoxy-3-((*R*)-4-methoxy-9-(4-(3-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-

one (7d) Colourless solid; yield: 80 %; mp 157 °C; $[\alpha]_D^{25}$: −115.1(c = 1, CH_2Cl_2). IR (KBr): 2936, 2836, 1761, 1618, 1587, 1797, 1468, 1276, 1033, 781, 694 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94(s, 1H), 7.52(s, 1H), 7.42(d, J = 7.4 Hz, 1H), 7.35(t, J = 7.9 Hz, 1H), 7.12(d, J = 8.2 Hz, 1H), 6.92(d, J = 7.4 Hz, 1H), 6.53(d, J = 8.0 Hz, 1H), 6.03(d, J = 19.6 Hz, 2H), 5.50(d, J = 4.2 Hz, 1H), 4.40(d, J = 4.2 Hz, 1H), 4.10(s, 3H), 4.08(s, 3H), 3.91(s, 3H), 3.89(s, 3H), 2.78–2.69(m, 1H), 2.54(s, 3H), 2.42–2.25(m, 2H), 2.01–1.87(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9,159.9, 152.3, 147.6, 147.2, 143.3, 141.5, 141.0, 134.1, 131.4, 129.8, 128.3, 122.0, 119.5, 118.5, 118.3, 118.1, 117.6, 114.3, 112.2, 110.8, 102.0, 81.3, 62.3, 60.8, 59.4, 56.7, 55.3, 48.3, 45.3, 22.5. MS (ESI) m/z 587$(M + H)^+$. HRMS(ESI) Calcd for $C_{31}H_{31}N_4O_8$ $(M + H)^+$: 587.21364, found: 587.21049.

(*S*)-3-((*R*)-9-(4-(1-hydroxycyclopentyl)-1*H*-1,2,3-triazol-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one (7e) Colourless solid; yield: 78 %; mp 144 °C; $[\alpha]_D^{25}$: −147.2(c = 1, CH_2Cl_2). IR (KBr): 3510, 2927, 2804, 1715, 1500, 1458, 1275, 1033, 964, 902, 820 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.64(s, 1H), 7.10(d, J = 8.3 Hz, 1H), 6.48(d, J = 8.3, 1H), 6.03(d, J = 1.1 Hz, 1H), 5.99(d, J = 1.1 Hz, 1H), 5.51(d, J = 4.5 Hz, 1H), 4.40(d, J = 4.5 Hz, 1H), 4.09(s, 3H), 4.06(s, 3H), 3.89(s, 3H), 2.77–2.65(m, 1H), 2.53(s, 3H), 2.41–1.75(m, 11H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.9, 153.8, 152.3, 147.6, 143.3, 141.3, 140.9, 134.1, 128.4, 122.0, 119.5, 118.3, 118.2, 117.5, 112.3, 101.9, 81.3, 78.9, 62.2, 60.7, 59.4, 56.7, 48.4, 45.5, 41.2, 23.5, 22.6. MS (ESI): m/z 565 $(M + H)^+$. HRMS (ESI) Calcd for $C_{29}H_{33}N_4O_8$ $(M + H)^+$: 565.22929, found: 565.22622.

(*S*)-3-((*R*)-9-(4-(1-hydroxycyclohexyl)-1*H*-1,2,3-triazol-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one (7f) Colourless solid; yield: 62 %; mp 91 °C; $[\alpha]_D^{25}$: −77.3(c = 1, CH_2Cl_2). IR (KBr): 3422, 2929, 2854, 1759, 1620, 1498, 1457, 1269, 1034, 969, 935, 818, 727 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.63(s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.50(d, J = 8.3 Hz, 1H), 6.01(d, J = 11.5 Hz, 2H), 5.52 (d, J = 3.9 Hz, 1H), 4.41(d, J = 3.9 Hz, 1H), 4.09(s,3H), 4.05(s, 3H), 3.90 (s, 3H), 2.79–2.66(m, 1H), 2.53(s, 3H), 2.44–0.79(m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 155.4, 152.4, 147.6, 143.4, 141.3, 141.0, 134.1, 128.3, 122.0, 118.4, 117.6, 112.4, 118.1, 119.5, 102.0, 81.3, 69.6, 62.2, 60.8, 59.4, 56.7, 48.3, 45.3, 38.0, 25.3, 22.5, 21.9. MS (ESI) m/z 579$(M + H)^+$. HRMS(ESI) Calcd for $C_{30}H_{35}N_4O_8Na$ $(M + H)^+$: 579.24494, found: 579.24246.

Single crystal X-ray analysis

X-ray data for the azide **2h** were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ = 0.71073 Å) with the ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Integration and scaling of intensity data were accomplished using the SAINT program [53]. The structure was solved by direct methods using SHELXS97 and refinement was carried out by

the full-matrix least-squares technique using SHELXL97 [54]. Anisotropic displacement parameters were included for all non-hydrogen atoms.

Crystal data for **2h**: $C_{22}H_{22}N_4O_7$, $M = 454.44$, colourless plate, $0.18 \times 0.17 \times 0.07$ mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 11.5800(8)$, $b = 12.2181(9)$, $c = 14.9647(11)$ Å, $V = 2117.3(3)$ Å^3, $Z = 4$, $D_c = 1.426$ g/cm^3, $F_{000} = 952$, CCD Area Detector, MoKα radiation, $\lambda = 0.71073$ Å, $T = 294(2)$K, $2\theta_{max} = 50.0°$, 20173 reflections collected, 2121 unique ($R_{int} = 0.0193$). Final $GooF = 1.046$, $R1 = 0.0282$, $wR2 = 0.0765$, R indices based on 2021 reflections with $I > 2\sigma(I)$ (refinement on F^2), 302 parameters, 0 restraint, $\mu = 0.108$ mm^{-1}. **CCDC 944742** contains supplementary Crystallographic data for the structure.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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