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Review article

# Taking aim at a dynamic target: Noscapinoids as microtubule-targeted cancer therapeutics

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ABSTRACT

Noscapine and its synthetic derivatives called noscapinoids have been shown to possess potential anticancer properties. These alkaloids target microtubules and inhibit cell proliferation. Noscapinoids are microtubule poisons that induce minor alterations in the innate dynamic instability of microtubules leading to mitotic arrest and cell death. Over the past decade, a number of noscapine derivatives have been synthesized that, compared to the parent compound, show superior anticancer potential, enhanced tumor specificity and tumor regression, and little or no toxicity to normal tissues. Based on their successive synthetic modifications at different points in the scaffold structure of noscapine, aided by computational design and structure–activity relationship studies, the derivatives of noscapine have been classified into different "generations" based on modifications. Several studies have reported the potential to develop noscapinoids as anticancer drugs. Increasing their tumor specificity - either through antibody conjugation or nanoparticle-based carriers - may facilitate the progression of maytansinoid-based cancer drugs to the clinic.



**Contents**



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## Introduction

French chemist Pierre Robiquet first isolated noscapine, a cough-depressant benzylisoquinoline alkaloid, in 1817, and it became known as *narcotine* until the late 1950s [1]. Noscapine's ability to interact with microtubules and suppress the dynamic instability of microtubules and thereby inhibit cell proliferation prompted a number of studies on its potential as an anticancer agent [2]. Over the past decade, numerous derivatives of noscapine have been synthesized and their anti-proliferative mechanism of action, ability to inhibit tumor progression in xenograft animal models, tumor specificity, and side effects evaluated [3].

Microtubules, the target protein of noscapine, are cylindrical, linear, cytoskeletal polymers composed of α and β tubulin heterodimers [4]. Microtubules exhibit an intrinsic behavior called *dynamic instability*, shifting frequently between periods of growth and shortening phases [5]. Microtubules play a number of roles in various cellular functions, including cell division, intracellular transport, and the positioning of cellular organelles [4]. During normal mitosis, microtubules segregate sister chromosomes into daughter cells through a spatially and temporally synchronized mechanism mediated by cell cycle checkpoints [4]. This crucial role in cell division makes microtubules an attractive target for cancer chemotherapy. A number of tubulin-binding molecules with anticancer potential have been discovered in recent years. These agents interact with microtubules through diverse mechanisms to inhibit cancer cell proliferation [6]. For example, compounds such as vinca alkaloids [7] and maytansine [8] bind at growing microtubule tips and suppress dynamic instability. Taxol [6,7], taccalonolide [9], and taxol derivatives suppress microtubule dynamics by stabilizing the lateral interactions between protofilaments [7]. Many of these drug molecules are thought to mimic cellular proteins that stabilize or destabilize microtubule dynamics by binding to tubulin and microtubules. For example, end binding protein 1 (EB1) and the cytoplasmic linker protein CLIP-170 are known to stabilize microtubule dynamics [10], whereas cellular proteins such as stathmin [11] and G proteins increase microtubule dynamics [12].

Suppression of dynamic instability arrests cell cycle progression by adversely affecting the formation and maintenance of a functional mitotic spindle [7]. In fact, even minor perturbations in microtubule dynamics have been reported to induce mitotic arrest [13]. Drug-induced alterations of microtubule dynamics are known to induce a loss of tension across sister kinetochores at the metaphase plate [13,14]. (The tension is generated during metaphase when microtubules attach properly to the kinetochores of sister chromosomes). The loss of tension activates checkpoint proteins such as Mad2 and BubR1, which prevent progression of the cell cycle to anaphase by inhibiting the activation of the anaphase promoting complex, leading to cell cycle arrest [14]. Though chemically diverse, microtubule-targeted compounds are characterized by their ability to disrupt the normal assembly dynamics of the mitotic spindle, thereby inhibiting cell division at the metaphase/anaphase transition [7].

## Noscapine, a microtubule-modulating agent

Noscapine ((3S)-6,7-Dimethoxy-3-((5R)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo(4,5-g) isoquinolin-5-yl)-1(3H)-isobenzofuranone; Fig. 1) is a phthalideisoquinoline alkaloid originally isolated from plants of the papaveracea family, including *papaver somniferum* (opium poppy) [15]. Also known as narcotine, nectodon, nospen, and anarcotine, noscapine has been used as a cough depressant in several clinical formulations [14,15].

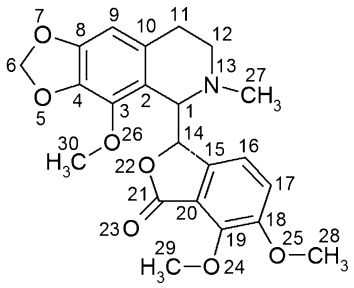


**Fig. 1.** Molecular structure of noscapine with numbering of carbon atoms. Noscapine structure consists of two ring systems, isoquinoline and isobenzofuranone, linked by a rotatable C–C bond between two chiral centers.

The anticancer properties of noscapine have been well documented in a number of studies. It induces mitotic arrest and programmed cell death in several types of cancer cells. In glioma cells, for example, it promotes apoptosis through a C-Jun-N-terminal kinase pathway [16]. In colon cancer cells, noscapine induces mitotic arrest and cell death through a p53- and p21-dependent mechanism [17]. It was found to promote cell death in both apoptosis-resistant and -prone leukemia cell lines [18]. It suppresses the growth of xenograft tumors (non-small cell lung cancer) in mice [19]. From a clinical point of view, noscapine is distinguished from many other microtubule-targeted agents by its lack of considerable cytotoxicity to normal cells [20]. Moreover, it has a good pharmacokinetic and absorption, distribution, metabolism, and excretion (ADME) profile [20] and does not produce major organ toxicities [20]. Noscapine interacts with tubulin and microtubules in a distinctive manner [21,22]. This review focuses on the current understanding of noscapine's mechanism of action and the development of novel noscapine derivatives (collectively called noscapinoids). The review concludes with future perspectives for noscapine's potential as an effective anticancer drug.

## Interactions of noscapine with tubulin and microtubules

Screening for microtubule-targeted agents with functional groups similar to colchicine, podophyllotoxin, and like agents, Harish Joshi's group at Emory University, Atlanta, first reported noscapine's microtubule-interfering action and the correlation between mitotic arrest and microtubule disorganization caused by this alkaloid [22]. Abnormal, multipolar spindle microtubules were observed in noscapine-treated HeLa cells. The cells thus arrested in mitosis eventually underwent apoptosis. While investigating noscapine's molecular mechanism of action, it was found to bind to tubulin, as evidenced by a concentration-dependent quenching of the intrinsic tryptophan fluorescence of tubulin [22]. The mechanism of mitotic arrest induced by noscapine was later discovered by the same group, in collaboration with Leslie Wilson's laboratory at the University of California, Santa Barbara. They found that noscapine arrests cancer cells by altering the dynamic instability of microtubules, primarily by increasing the attenuated state [23]. Specifically, noscapine (50 μM) increases the time microtubules spent in "attenuated state" (a phase in the dynamic instability where no detectable growth or shortening happens). In addition, noscapine substantially reduces the "catastrophe frequency" (occurrences of rapid shortening of microtubules) and increases the "rescue frequency" (occurrences of transition from shortening phase to growth phase). The net effect of noscapine on dynamic instability is suppression of the overall dynamicity of microtubules by ~60% [23].

## Development of noscapine analogs as potential anticancer agents

In recent years, a number of noscapine analogs have been reported to have superior efficacy at inhibiting cancer cell proliferation without inducing significant, adverse effects in normal cells. Three generations of noscapinoids have been synthesized utilizing structure–activity relationship studies [24–30]. *First-generation* analogs were synthesized by chemical alterations of noscapine's isoquinoline (diversity point A) and benzofuranone (diversity point B) ring system (Figs. 1 and 2). The group attached to the diversity point A included nitro (Fig. 3) [24], azido (Fig. 4) [25], amino (Fig. 5) [26] and halogenated (fluoro, chloro, bromo, and iodo) groups (Fig. 6) [27]. The *first-generation* analogs also include all the halogenated-noscapine with reduced oxygen at diversity point B (*viz.* reduced-fluoronoscapine (Rd-F-nos); reduced-chloronoscapine (Rd-Cl-nos); reduced-bromonoscapine (Rd-Br-nos) and reduced-iodonoscapine (Rd-I-nos)) (Fig. 7) [28]. These synthetic derivatives were found to be more effective antitumor agents than the parent compound [24–28]. The *second generation* of noscapine analogs was produced by manipulating noscapine's benzofuranone ring system at diversity point C (Fig. 2), creating O-alkylated and acylated noscapinoids (Fig. 8) [29]. These derivatives were also reported to have better activity than noscapine. *Third generation* noscapinoids were produced through alterations to the isoquinoline ring system at diversity point D (Fig. 2) by functionalization of 'N' (Fig. 9) [30]. The noscapinoids were found to bind to tubulin at site a site that partially overlaps colchicine site (Fig. 10) [30]. The following major noscapine analogs have been shown to possess superior clinical potential compared to the parent compound.

### *Nitro-derivative of noscapine*

To improve the *in vivo* efficacy of noscapine (Fig. 1), novel noscapine analogs were synthesized through chemical modifications, including the addition of a nitro group to noscapine (Fig. 3). Nitro-noscapine inhibits proliferation of ovarian cancer cells and their paclitaxel-resistant variant cells and of human lymphoblastoid cells and their vinblastine- and teniposide-resistant variants [24]. This derivative arrests cells at G2/M phase before apoptosis. Interestingly, the nitro derivative of noscapine did not show any considerable inhibition on the proliferation of normal human fibroblast cells, indicating a selective affinity to the cancer cells [24].

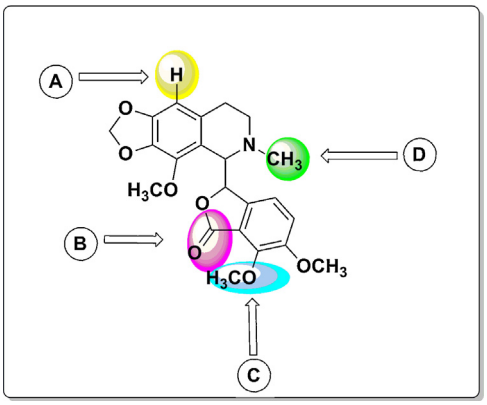


**Fig. 2.** Diversity points for derivatization of α-noscapine [(S)-3-((R)4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3H)-one]. Structural modifications at diversity point A and B generated 1st generation noscapinoids. Modifications at diversity point C and D gave rise to 2nd and 3rd generation noscapinoids, respectively.

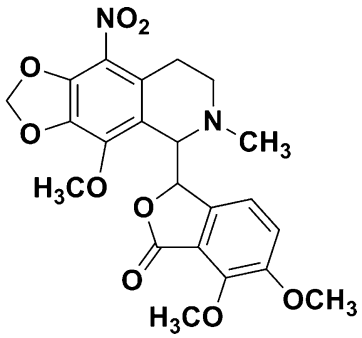


**Fig. 3.** Nitronoscapine: Nitronoscapine (9-Nitro noscapine) is a product of aromatic nitration of noscapine in the presence of silver nitrate in trifluoroacetic anhydride and acetonitrile [24].

### *Azido noscapine*

Azido noscapine [((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-dimethoxyisobenzofuran-1(3H))] (Fig. 4) is another potent analog of noscapine. It has shown superior efficacy at killing human acute lymphoblastic leukemia cells [25]. Reported in 2011, this compound was developed using a quantitative structure activity relationship (QSAR) model.

### *Amino noscapine*

In 2011, Naik et al. [26] reported the synthesis and evaluation of a novel noscapine analog called amino noscapine [(S)-3-((R)-9-amino-4-methoxy-6-methyl-5,6,7,8-tetrahydro [1,3] dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxy isobenzo-furan-1(3H)-one] (Fig. 5). This compound was designed based on the binding free energies of various noscapinoids, calculated using the linear interaction energy (LIE) method combined with a surface generalized Born (SGB) continuum solvation model [26]. The binding free energy determination indicated that amino noscapine binds tubulin more strongly than the parent compound.

### *Halogenated noscapinoids*

Halogenated noscapinoids (Fig. 6) are among the classes of noscapinoids extensively evaluated for their effects on cancer cell proliferation, antitumor efficacy, and potential side effects [27]. These compounds were synthesized by halogenating noscapine through various reactions, as described in the legend of Fig. 6. The key findings from the biological evaluation of the halogenated noscapinoids are described below.

#### *Bromo noscapine*

Among the halogenated noscapinoids investigated, bromo derivative (see Fig. 6) was found to be one of the most potent one. Therefore, bromo noscapine has been chosen as a representative of halogenated noscapine for the ensuing discussion. Bromonoscapine [31], also known as EM011 [32], possesses a bromine atom at position 9 of the parent compound noscapine [31]. EM011 is one of the most extensively studied noscapinoids to date. Bromo noscapine has also shown higher tubulin-binding activity than noscapine. For example, noscapine binds tubulin with an equilibrium dissociation constant ($K_D$) of ~144 μM [31], while bromo noscapine shows stronger binding with a $K_D$ of 54 μM [31]. When tested on the breast cancer cell line MCF-7, the brominated derivative had cell killing activity several times higher than noscapine [31]. Unlike the parent compound, the brominated derivative induced the formation of multipolar spindles in cells

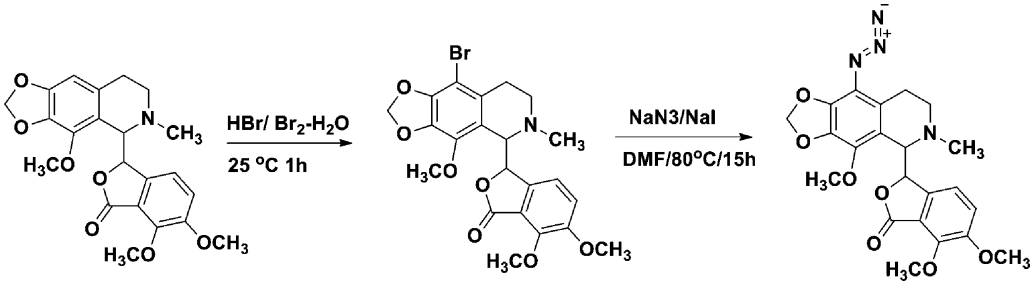


**Fig. 4.** Azido noscapine: Azido noscapine (9-azido noscapine) was synthesized by first converting noscapine to bromonoscapine followed by treatment with sodium azide and sodium iodide [25].

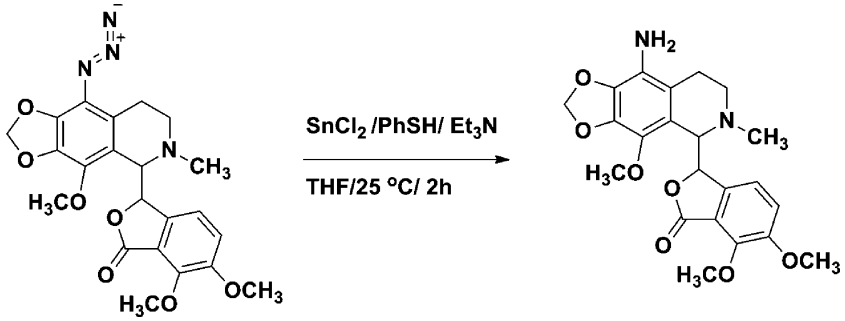


**Fig. 5.** Amino noscapine: Amino noscapine (9-amino noscapine) possesses an amine group at the 9-position of the quinoline ring and is synthesized from azido noscapine [26].

[30]. Similar to the parent compound, the bromo derivative's principal mechanism of action has been the induction of loss of tension across kinetochore pairs [31]. Specifically, the bromo derivative altered the normal dynamics of kinetochore microtubules, as evidenced by a reduction in the distance between sister kinetochores [31]. Bromo noscapine was found to be effective at inhibiting the proliferation of paclitaxel- and epothilone-resistant cancer cells [31]. Notably, brominated noscapine has been found to be active against both vinblastine-sensitive and -resistant cell lines [32]. When given orally (300 mg/kg), the compound significantly reduced tumor volume in tumor xenografts. It significantly increased the survival rate of mice and showed a lack of tissue toxicity [32].

EM012 (Fig. 7), a reduced form of the bromo noscapine, was found to be effective in combination with paclitaxel at inhibiting the proliferation of human breast, prostate, and non-small-cell lung cancer cells at nanomolar concentrations [33], possibly through the additive suppression of microtubule dynamic instability. Specifically, EM012 promoted or complimented the microtubule-stabilizing potential of paclitaxel. In cells, this enhanced stabilization of microtubules was evidenced by an increase in tubulin acetylation [33]. Interestingly, EM012 was found to be capable of inhibiting the proliferation of Pgp-overexpressing, multidrug-resistant ovarian cancer cells, as well [33]. In *in vivo* models, the noscapinoid has also been observed to leave normal tissues intact [34].

*Second-generation noscapinoids: the benzofuranone derivatives*

The second generation of noscapinoids was synthesized by modifying the benzofuranone ring of noscapine at diversity point C (Fig. 8) [29]. These derivatives inhibit microtubule assembly in a concentration-dependent manner and have been found to be effective at inhibiting the proliferation of lymphoma cells and lung, breast, prostate, and pancreatic cancer cell lines [29].

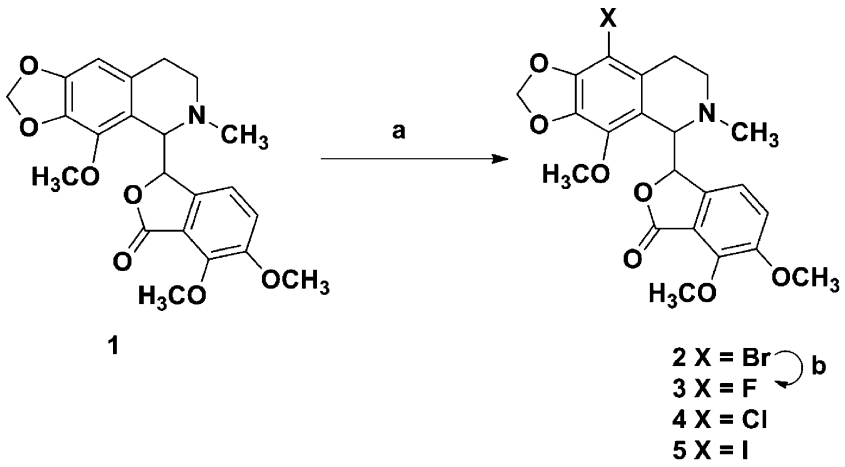


**Fig. 6.** Halogenated noscapinoids: '*a*' represents bromine water and hydrogen bromide for bromo noscapine; sulfuryl chloride and chloroform for chloro noscapine; fluorine, Amberlyst-A (a slightly basic resin with alkyl amine functionality), and tetrahydrofuran for fluoro noscapine; and pyridine–iodine chloride and acetonitrile for iodo noscapine [27].

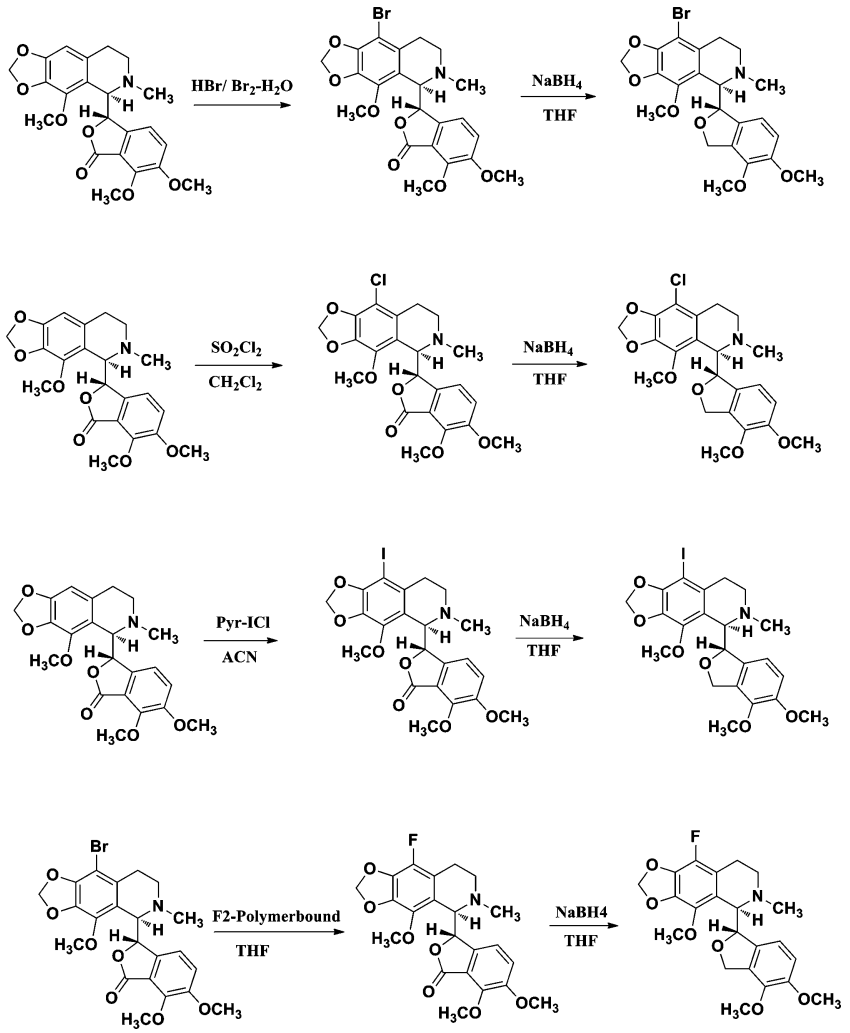


**Fig. 7.** Cyclic ether halogenated derivatives (*viz.* reduced 9-fluoronoscapine (Rd-9-F-nos); reduced 9-chloronoscapine (Rd-9-Cl-nos); reduced 9-bromonoscapine (Rd-9-Br-nos) and reduced 9-iodonoscapine (Rd-9-I-nos)) of noscapine. These derivatives were synthesized from the halogenated derivatives [28].

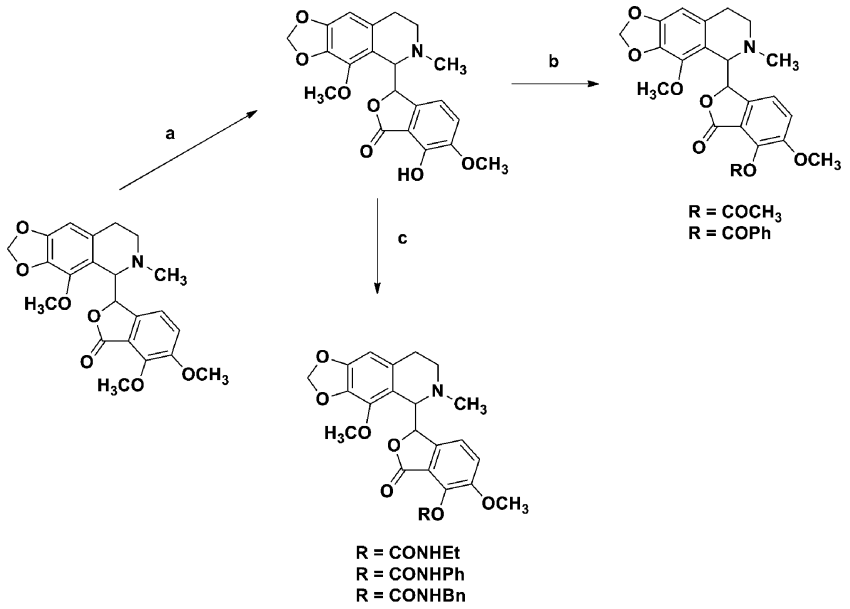


**Fig. 8.** Benzofuranone derivatives of noscapine, the second generation of noscapinoids ***a*** represents sodium azide/sodium iodide, dimethylformamide (DMF) at 140 °C, 4 h ***b***, dimethylamino pyridine, acetic anhydride, acetonitrile, 50 °C, 6 h for compound 3; potassium carbonate, dimethylformamide, and bezoyl chloride at 80 °C for 8 h for compound 4. ***c***, Dimethylamino pyridine, dichloromethane, and isocyanate at room temperature for 6–8 h for compounds 5, 6, and 7 [29].

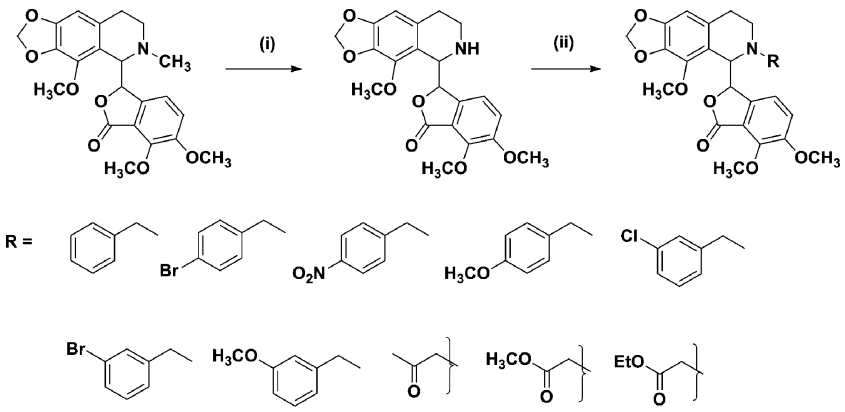


**Fig. 9.** Chemical synthesis of third generation noscapinoids from noscapine as starting material. (i) ***a***, meta-chloroperoxybenzoic acid and dichloromethane; ***b***, 2N hydrochloric acid; ***c***, Iron(II) Sulfate Heptahydrate; (ii) Bromo methane, potassium iodide, $K_2Cr_3$, and Acetone [30].

*Third-generation noscapinoids*

Based on the insights gained from the preceding generations of noscapinoids, a third generation of noscapinoids was designed computationally by inducing structural modification at diversity point D of noscapine (Fig. 9) [30]. Similar to their predecessors, the third-generation noscapinoids fit extremely well within the binding cavity on tubulin, with comparable or improved binding affinities. Moreover, the congeners of noscapine exhibited considerable cytotoxicity toward a variety of cancer cell types [30]. These compounds, delayed cell cycle progression at the $G_2$/M phase, and induced apoptotic cell death in cancer cells. The apoptotic indices for this series of compound were considerably higher than for the parent compound noscapine [30].

Noscapinoids bind tubulin at a site that encompasses both α- and β-tubulin. Fig. 10 shows the binding interaction of the noscapoinoids. Noscapinoids fit well in the colchicine binding site although colchicine binding is limited mostly to the β subunit of tubulin. It has also been found that the interactions of noscapine with tubulin involve several residues that are not part of colchicine binding to tubulin. The residues, Thr B238 Thr B238, Cys B239, Ala B248 take part in the binding of noscapinoid to tubulin. Among the above residues, only Ala B248 takes part in the binding interaction of colchicine to tubulin [30].

## Concluding remarks and future perspectives

With a relatively safe pharmacological profile and high cancer specificity, noscapine has been used to synthesize more potent and cancer-cell-specific analogs. The common characteristic of these analogs is the ability to effectively kill multidrug-resistant cells and promote tumor regression in experimental animal models. As well, most of these agents are bioavailable orally. Further supporting their potential as anticancer drugs, several studies have noted that they do not induce significant tissue or organ toxicity. Clinical trials have been conducted to assess the pharmacokinetic and safety profile of noscapine [35].

An emerging strategy to ensure tumor-specific delivery of microtubule-targeted agents is the use of antibody–drug conjugates (ADC) [36]. For example, Kadcyla, or ado-trastuzumab

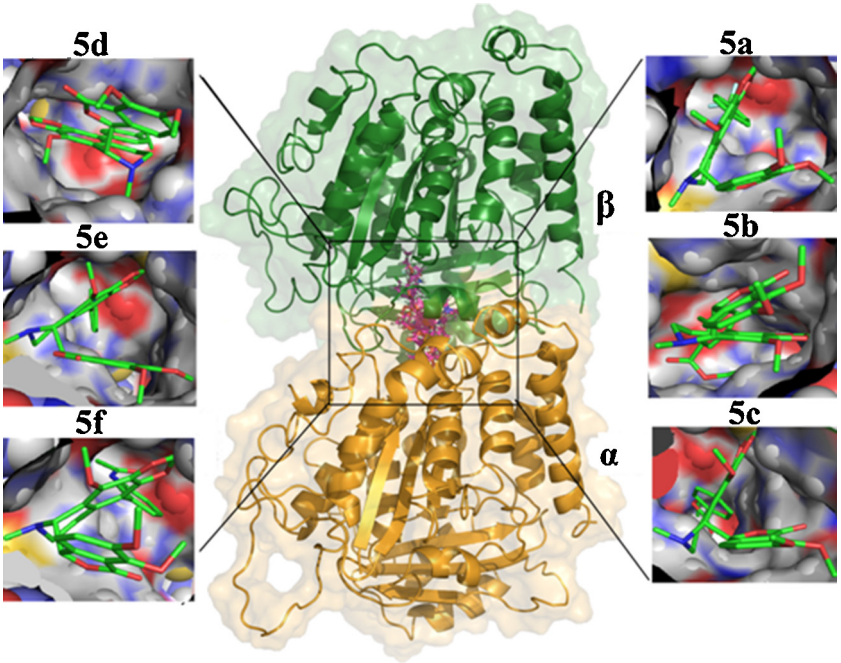


**Fig. 10.** Binding of noscapinoids to tubulin. The third generation noscapinoids have been docked into the binding cavity at the interface between α- and β-tubulin heterodimer. The binding site is very close to the colchicine binding site and it is partially overlapped.

DM1, is an ADC of the potent anti-tubulin agent maytansinoid and the HER2-targeted antibody trastuzumab. Maytansine suppresses microtubule dynamics by binding at the growing tips of microtubules [8,37]. Linking maytansinoid to trastuzumab achieved the specific delivery of the drug molecule (DM1) to HER2+ overexpressing tumor cells. Another effective ADC candidate is dolastatin 15 [38,39], a microtubule-targeted anticancer agent that inhibits cell division by inducing a loss of tension across kinetochore pairs in metaphase cells [38]. Therefore, if highly potent noscapinoids can be engineered as ADCs, targeted therapies for a variety of neoplasms could be introduced. Another clinical use of noscapine and its derivatives lies in their potential for use in nanoparticles for enhanced drug delivery. Several reports have confirmed this possibility and have shown that noscapinoids delivered through nanoparticles retain most of their antiproliferative potential [40,41]. Microtubule plus end tracking proteins (+TIPs) that regulate microtubule dynamics, such as CLIP-170 [10], have been known to facilitate taxol-mediated suppression of microtubule dynamics [42]. Investigating the effects of noscapinoids on +TIP-over expressing cancer cell lines might be useful for the development of novel therapeutics for these types of cancers.

## Conflict of interest

None declared.

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## References

[1] Warolin C. Pierre-Jean Robiquet. Rev Hist Pharm (Paris) 1999;47(321):97–110.
[2] Mahmoudian M, Rahimi-Moghaddam P. The anti-cancer activity of noscapine: a review. Recent Pat Anticancer Drug Discov 2009;4(1):92–7.
[3] Singh H, Singh P, Kumari K, Chandra A, Dass SK, Chandra R. A review on noscapine, and its impact on heme metabolism. Curr Drug Metab 2013;14(3):351–60.
[4] Fojo TA. In: Fojo TA, editor. The role of microtubules in cell biology, neurobiology, and oncology. London: Humana Press; 2008.
[5] Yenjerla M, Lopus M, Wilson L. Analysis of dynamic instability of steady-state microtubules in vitro by video-enhanced differential interference contrast microscopy with an appendix by Emin Oroudjev. Method Cell Biol 2010;95:189–206.
[6] Katsetos CD, Dráber P. Tubulins as therapeutic targets in cancer: from bench to bedside. Curr Pharm Des 2012;18(19):2778–92.
[7] Dumontet C, Jordan MA. Microtubule-binding agents: a dynamic field of cancer therapeutics. Nat Rev Drug Discov 2010;9(10):790–803.
[8] Lopus M, Oroudjev E, Wilson L, Wilhelm S, Widdison W, Chari R, et al. Maytansine and cellular metabolites of antibody-maytansinoid conjugates strongly suppress microtubule dynamics by binding to microtubules. Mol Cancer Ther 2010;9(10):2689–99.
[9] Risinger AL, Riffle SM, Lopus M, Jordan MA, Wilson L, Mooberry SL. The taccalonolides and paclitaxel cause distinct effects on microtubule dynamics and aster formation. Mol Cancer 2014;13:41.
[10] Lopus M, Manatschal C, Buey RM, Bjelić S, Miller HP, Steinmetz MO, et al. Cooperative stabilization of microtubule dynamics by EB1 and CLIP-170 involves displacement of stably bound P(i) at microtubule ends. Biochemistry 2012;51(14):3021–30.
[11] Manna T, Thrower D, Miller HP, Curmi P, Wilson L. Stathmin strongly increases the minus end catastrophe frequency and induces rapid treadmilling of bovine brain microtubules at steady state in vitro. J Biol Chem 2006;281(4):2071–8.
[12] Davé RH, Saengsawang W, Lopus M, Davé S, Wilson L, Rasenick MM. A molecular and structural mechanism for G protein-mediated microtubule destabilization. J Biol Chem 2011;286(6):4319–28.
[13] Kamath K, Okouneva T, Larson G, Panda D, Wilson L, Jordan MA. 2-Methoxyestradiol suppresses microtubule dynamics and arrests mitosis without depolymerizing microtubules. Mol Cancer Ther 2006;5(9):2225–33.
[14] Zhou J, Yao J, Joshi HC. Attachment and tension in the spindle assembly checkpoint. J Cell Sci 2002;115(18):3547–55.
[15] Zhou J, Giannakakou P. Targeting microtubules for cancer chemotherapy. Curr Med Chem Anticancer Agents 2005;5(1):65–71.
[16] Newcomb EW, Lukyanov Y, Smirnova I, Schnee T, Zagzag D. Noscapine induces apoptosis in human glioma cells by an apoptosis-inducing factor-dependent pathway. Anticancer Drugs 2008;19(6):553–63.
[17] Aneja R, Ghaleb AM, Zhou J, Yang VW, Joshi HC. p53 and p21 determine the sensitivity of noscapine-induced apoptosis in colon cancer cells. Cancer Res 2007;67(8):3862–70.
[18] Heidari N, Goliaei B, Moghaddam PR, Rahbar-Roshandel N, Mahmoudian M. Apoptotic pathway induced by noscapine in human myelogenous leukemic cells. Anticancer Drugs 2007;18(10):1139–47.
[19] Jackson T, Chougule MB, Ichite N, Patlolla RR, Singh M. Antitumor activity of noscapine in human non-small cell lung cancer xenograft model. Cancer Chemother Pharmacol 2008;63(1):117–26.
[20] Aneja R, Dhiman N, Idnani J, Awasthi A, Arora SK, Chandra R, et al. Preclinical pharmacokinetics and bioavailability of noscapine, a tubulin-binding anticancer agent. Cancer Chemother Pharmacol 2007;60(6):831–9.
[21] Ke Y, Ye K, Grossniklaus HE, Archer DR, Joshi HC, Kapp JA. Noscapine inhibits tumor growth with little toxicity to normal tissues or inhibition of immune responses. Cancer Immunol Immunother 2000;49(4–5):217–25.
[22] Ye K, Ke Y, Keshava N, Shanks J, Kapp JA, Tekmal RR, et al. Opium alkaloid noscapine is an antitumor agent that arrests metaphase and induces apoptosis in dividing cells. Proc Natl Acad Sci U S A 1998;95(4):1601–6.
[23] Zhou J, Panda D, Landen JW, Wilson L, Joshi HC. Minor alteration of microtubule dynamics causes loss of tension across kinetochore pairs and activates the spindle checkpoint. J Biol Chem 2002;277(19):17200–08.
[24] Aneja R, Vangapandu SN, Lopus M, Chandra R, Panda D, et al. Development of a novel nitro-derivative of noscapine for the potential treatment of drug-resistant ovarian cancer and Tcell lymphoma. Mol Pharmacol 2006;69(6):1801–9.
[25] Santoshi S, Naik PK, Joshi HC. Rational design of novel anti-microtubule agent (9-azido-noscapine) from quantitative structure activity relationship (QSAR) evaluation of noscapinoids. J Biomol Screen 2011;16(9):1047–58.
[26] Naik PK, Chatterji BP, Vangapandu SN, Aneja R, Chandra R, Kanteveri S, et al. Rational design, synthesis and biological evaluations of amino-noscapine: a high affinity tubulin-binding noscapinoid. J Comput Aided Mol Des 2011;25(5):443–54.
[27] Aneja R, Vangapandu SN, Lopus M, Viswesarappa VG, Dhiman N, Verma A, et al. Synthesis of microtubule-interfering halogenated noscapine analogues that perturb mitosis in cancer cells followed by cell death. Biochem Pharmacol 2006;72(4):415–26.
[28] Aneja R, Vangapandu SN, Joshi HC. Synthesis and biological evaluation of a cyclic ether fluorinated noscapine analog. Biorg Med Chem 2006;14:8352–8.
[29] Mishra RC, Karna P, Gundala SR, Pannu V, Stanton RA, Gupta KK, et al. Benzofuranone ring substituted noscapine analogs: synthesis and biological evaluation. Biochem Pharmacol 2011;82(8):110–21.
[30] Manchukonda NK, Naik PK, Santoshi S, Lopus M, Joseph S, Sridhar B, et al. Rational design, synthesis, and biological evaluation of third generation α-noscapine analogues as potent tubulin binding anti-cancer agents. PLOS ONE 2013;8:e77970.
[31] Zhou J, Gupta K, Aggarwal S, Aneja R, Chandra R, Panda D, et al. Brominated derivatives of noscapine are potent microtubule-interfering agents that perturb mitosis and inhibit cell proliferation. Mol Pharmacol 2003;63(4):799–807.
[32] Aneja R, Zhou J, Vangapandu SN, Zhou B, Chandra R, Joshi HC. Drug-resistant T-lymphoid tumors undergo apoptosis selectively in response to an antimicrotubule agent, EM011. Blood 2006;107(6):2486–92.
[33] Zhou J, Liu M, Aneja R, Chandra R, Joshi HC. Enhancement of paclitaxel-induced microtubule stabilization, mitotic arrest, and apoptosis by the microtubule-targeting agent EM012. Biochem Pharmacol 2004;68(12):2435–41.
[34] Zhou J, Liu M, Luthra R, Jones J, Aneja R, Chandra R, et al. EM012, a microtubule-interfering agent, inhibits the progression of multidrug-resistant human ovarian cancer both in cultured cells and in athymic nude mice. Cancer Chemother Pharmacol 2005;55(5):461–5.
[35] A study of noscapine HCl (CB3304) in patients with relapsed or refractory multiple myeloma (ID: NCT00912899), www.clinicaltrials.gov.
[36] Lopus M. Antibody-DM1 conjugates as cancer therapeutics. Cancer Lett 2011;307(2):113–8.
[37] Oroudjev E, Lopus M, Wilson L, Audette C, Provenzano C, Erickson H, et al. Maytansinoid-antibody conjugates induce mitotic arrest by suppressing microtubule dynamic instability. Mol Cancer Ther 2010;9(10):2700–13.
[38] Lopus M. Mechanism of mitotic arrest induced by dolastatin 15 involves loss of tension across kinetochore pairs. Mol Cell Biochem 2013;382(1–2):93–102.
[39] Gianolio DA, Rouleau C, Bauta WE, Lovett D, Cantrell Jr WR, Recio III A, et al. Targeting HER2-positive cancer with dolastatin 15 derivatives conjugated to trastuzumab, novel antibody–drug conjugates. Cancer Chemother Pharmacol 2012;70(3):439–49.
[40] Chandra R, Madan J, Singh P, Chandra A, Kumar P, Tomar V, et al. Implications of nanoscale based drug delivery systems in delivery and targeting tubulin binding agent, noscapine in cancer cells. Curr Drug Metab 2012;13(10):1476–83.
[41] Madan J, Gundala SR, Kasetti Y, Bharatam PV, Aneja R, Katyal A, et al. Enhanced noscapine delivery using estrogen-receptor-targeted nanoparticles for breast cancer therapy. Anticancer Drugs 2014;25(6):704–16. PMID: 24642711.
[42] Sun X, Li D, Yang Y, Ren Y, Li J, Wang Z, et al. Microtubule-binding protein CLIP-170 is a mediator of paclitaxel sensitivity. J Pathol 2012;226(4):666–73.