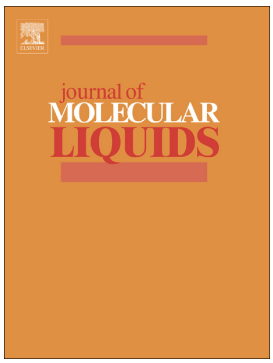

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Synthesis and characterization of novel 1,3-benzodioxole tagged noscapine based ionic liquids with *in silico* and *in vitro* cytotoxicity analysis on *HeLa* cells

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ABSTRACT

Ionic Liquids (ILs) have proven themselves as a new class of anticancer compounds amongst the scientific community in the 21st century. With proven efficiency of ionic liquids here an attempt has been made on a legacy anticancer compound noscapine. In this study, a library of novel Noscapine (Nos) based ionic liquids were synthesized and characterized using various techniques such as ^{1}H-, ^{13}C- NMR spectroscopy and Mass spectrometry. These novel Nos-based ionic liquids were studied by *in silico* assays including molecular docking analysis, which showed the [Pip-Nos]OAc and [Pip-Nos]OTf derivatives of Nos-based ionic liquids have high molecular binding with docking score -336.19 kJ/mol and -326.71 kJ/mol, respectively, much higher than the parent compound noscapine (-267.06 kJ/mol). Also, pharmacokinetics and pharmacodynamics properties analyses showed the favorable results with high drug likeliness. The lead compounds were further well validated with *in vitro* anticancer cytotoxicity assay on *HeLa* cancer cell line. The *in vitro* cytotoxicity analysis depicted the high anticancer potency of lead compounds with lower IC_{50} of acetate and triflate IL derivatives than the parent compound noscapine. In conclusion, the present study paves the way to elucidate the potential anticancer ionic liquids.

1. Introduction

Noscapine (phthalide isoquinoline alkaloid) known as Narcotine, Nectodon, Nospen, Anarcontie, it was the first time isolated from opium plant by a French chemist (Pierre Robiquet) in 1817 as denomination of narcotine till the late of 1950s.[1,2] The opium has contained various alkaloids such as thebaine, papaverine, morphine, codeine, noscapine and narceine but noscapine does not match structurally or chemically with other alkaloids. In 1960, noscapine was considered as inactive drug but later on it was used as an anti-tussive agent which further used for decades in the world including India. The discovery of anti-neoplastic properties of noscapine has attracted the researcher's attention towards its synthesis and biological application. Noscapine was synthesized in 1994 and over the decades, various methods were developed for the total synthesis of noscapine and its derivatives.[3] Generally, noscapine was explored at four positions i.e. 9th position hydrogen was replaced by bromine, fluorine, chlorine, iodine, nitro, amino and others alkyl, carbonyl reduced, 7`th methoxy convert into other ether groups and N-methyl group was also replaced by other groups.[4–8] On the literature survey, we found that there are many compounds (podophyllotoxin, steganacin, noscapine and combretastatin A-2) containing 1,3-benzodioxole motif reported as potential antitumor drugs.[9]

Ionic liquids (ILs) are generally synthesized from various combination of organic cations (imidazolium, pyridinium, piperidinium, quinolinium, pyrrolidinium, quaternary ammonium, so on) with a wide range of anions (halides, tetrafluoroborate, hexafluorophosphate, methylsulphate, dicyanamide, nitrate, trifluoromethanesulphonate, bis(trifluoromethanesulfonyl)amide, etc).[10–12] Ionic liquids have attracted attention of the researchers due to their high thermal & chemical stability, low volatility, low flammability, high aqueous solubility and high ionic conductivity which increases their applications in the various fields like electrochemistry, fuel production & processing, biomass conversion, biotransformation, nanotechnology, catalysis, organic synthesis, pharmaceutics and many other fields.[11–24]

Over the two decades, our laboratory has synthesized various derivatives of noscapine with their *in silico* and *in vivo* studies. To design and development of anticancer drug, molecular docking analysis has been performed in a large number of reports to assess the potency of natural drugs and their analogs.[9,25,26] Molecular docking is a computational algorithm based technique to study the binding potency of the target receptor with ligand and helps in virtual screening of the drugs. Hence, we carried out the *in silico* molecular docking analysis of noscapine and its potential IL analogs. Furthermore, pharmacokinetics and pharmacodynamics studies were performed employing the

advanced pharmacological computational avenues, as also performed in many research studies.[27–29] Pharmacological parameters analysis helps in assessing drug impacts and further validation to reach preclinical stages. Herein, we have reported the synthesis of the noscapine based ionic liquids, *in silico* and *in vitro* studies. Noscapine based ionic liquids were characterized by ^{1}H-, ^{13}C-NMR spectroscopy, mass spectrometry and melting point techniques. In our best knowledge, this is the first study in which noscapine based ionic liquids has been synthesized and explored for biological activity.

2. Experimental

2.1 *Materials*

All the chemicals used were purchased from SRL, TCI, Sigma-Aldrich, Merck, Alfa Aesar and LOBA Chemie. The solvents used were of extra pure quality. Melting points were recorded on Buchi M-560. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Jeol Resonance ASC 64 (400 MHz) spectrometer using $CDCl_3$ and chemical shifts were recorded in ppm with tetramethylsilane (TMS) as an internal standard. High-resolution mass spectroscopy (HRMS) were recorded on the Agilent 6530 Accurate-Mass Q-TOF LC/MS.

2.2 General procedure

*Synthesis procedure of 5-(Bromomethyl)-1,3-benzodioxole **(2)***

5-(Bromomethyl)-1,3-benzodioxole was prepared using reported method.[30] Take a 250 mL round bottom flask **A** charged with 1,3-Benzodioxole-5-methanol (5 g; 32.86 mmol) in dry diethyl ether (50 mL). Take another 100 mL round bottom flask B loaded with 3.1 mL (32.86 mmol; 1 equiv) of phosphorous tribromide dissolved in 40 mL of diethyl ether. A dropwise addition was carried out from Flask **B** to Flask **A** maintaining the temperature at 0°C for and stirred for 15 minutes. After the completion of the reaction, the reaction mixture was worked up with water (3x100 mL) using a separating funnel followed by washing with brine (1:1). After drying over sodium sulphate and filtration, the solvent was evaporated on a vacuum rotary evaporator. The crude was recrystallized in petroleum ether to get the desired white solid product.

*Synthesis procedure of the 6-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium bromide ionic liquid [Pip-Nos]Br **(3)***

1.1 equiv. of 5-(Bromomethyl)-1,3-benzodioxole, 1 equiv. of noscapine were taken in 3 mL of toluene in a 25 mL round bottom flask and at 60° C for 20 hours on a continuous stirring in an oil bath. After the completion of reaction, toluene was decanted and remaining solid residue was washed with ethyl acetate to remove the unreacted part (3x10 mL). Chloroform was added to dissolve the solid product followed by evaporation on a vacuum rotary evaporator to obtain **3** as the solid ionic liquid product.

General procedure for the synthesis of 4-10

Compound **3** was used as precursor for the metathesis reactions. An equal amount of **3** and the salt of desired anion X^- were taken in a 10 mL round bottom flask containing 2 mL of dichloromethane for 8 hours at room temperature. After the completion of reaction time, chloroform was added to dissolve the ionic liquid and filtered to remove the solid residue through the chloroform solution followed by the evaporation on a vacuum rotary evaporator to obtain the desired ionic liquid product.

*5-(Bromomethyl)-1,3-benzodioxole **(2)***: It was obtained as white solid in 70% yield; mp: 97-98 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.88-6.81 (m, 2H), 6.74 (d, J = 7.8 Hz, 1H), 5.95 (s, 2H), 4.44 (s, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): 147.851, 147.756, 131.456, 122.699, 109.4175, 108.273, 101.294, 34.199

[Pip-Nos]Br: 6-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium bromide **(3)**: It was obtained as pale white solid in 90.1 % yield; mp: 198-200 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J = 1.9 Hz, 1H), 6.99 (dd, J = 8.0, 1.8 Hz, 1H), 6.95 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.40 (s, 1H), 6.28 (d, J = 5.5 Hz, 1H), 6.11-5.98 (m, 4H), 5.84 (d, J = 1.4 Hz, 1H), 5.78 (d, J = 1.2 Hz, 1H), 4.78 (d, J = 12.9 Hz, 1H), 4.67 (d, J = 12.9 Hz, 1H), 3.88 (t, J = 4.9 Hz, 8H), 3.80 (s, 3H), 3.51 (s, 3H), 3.44-3.31 (m, 1H), 3.25-3.12 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 166.298, 153.025, 150.936, 149.987, 148.550, 147.582, 139.819, 137.241, 133.810, 127.984, 126.757, 120.892, 119.895, 119.138, 117.327, 112.727, 109.028, 108.012, 102.482, 102.013, 101.409, 75.648, 66.573, 64.992, 62.308, 59.069, 56.942, 53.827, 49.121, 24.367; HRMS (ESI) m/z =548.2426 [M^+]

[Pip-Nos]I : 6-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **(4)** : It was obtained as pale yellow solid in 82.8 % yield; mp: 190-192 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26-7.19 (m, 1H), 7.01-6.89 (m, 2H), 6.78 (d, J = 7.3 Hz, 1H), 6.37 (s, 1H), 6.23 (d, J = 10.1 Hz, 1H), 5.98 (s, 4H), 5.81 (s, 1H), 5.75 (s, 1H), 4.72 (d, J = 12.8 Hz, 1H), 4.60 (d, J = 12.8 Hz, 1H), 3.98-3.79 (m, 8H), 3.76 (s, 3H), 3.50 (d, J = 12.4 Hz, 3H), 3.43-3.29 (1H), 3.22-3.08 (1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 166.250, 153.102, 151.032, 150.121, 148.626, 147.591, 139.953, 136.944, 133.849, 128.060, 126.527, 121.208, 119.675, 119.133, 117.289, 112.679, 109.133, 107.897, 102.434, 102.080, 101.447, 75.581, 66.707, 64.992, 62.327, 59.203, 56.942, 53.721, 49.054, 24.329; HRMS (ESI) m/z =548.2427 [M^+]

[Pip-Nos]BF_4 : 6-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium tetrafluoroborate **(5)** : It was obtained as pale white solid in 85.9 % yield; mp: 197-199 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 8.2 Hz, 1H), 6.92 (t, J = 7.6 Hz, 2H), 6.78 (d, J = 8.2 Hz, 1H), 6.37 (s, 1H), 6.24-6.18 (1H), 6.04-5.95 (m, 3H), 5.89 (d, J = 5.0 Hz, 1H), 5.81 (d, J = 0.9 Hz, 1H), 5.75 (s, 1H), 4.67 (d, J = 12.8 Hz, 1H), 4.58 (d, J = 12.8 Hz, 1H), 3.84 (t, J = 4.6 Hz, 8H), 3.71 (s, 3H), 3.47 (s, 3H), 3.38 (s, 1H), 3.21-3.07 (1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 166.289, 153.044, 150.974, 150.045, 148.588, 147.582, 139.848, 137.165, 133.810, 127.965, 126.680, 120.902, 119.799, 119.148, 117.317, 112.698, 109.056, 107.993, 102.453, 102.032, 101.418, 75.639, 65.212, 62.308, 59.059, 56.932, 53.741, 49.006, 24.367; HRMS (ESI) m/z =548.2462 [M^+]

[Pip-Nos]OAc : 6-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium acetate **(6)** : It was obtained as white solid in 85.2 % yield; mp: 192-194 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26-7.19 (m, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.92 (s, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.37 (s, 1H), 6.29-6.20 (1H), 6.07-5.91 (m, 4H), 5.81 (d, J = 1.4 Hz, 1H), 5.75 (d, J = 0.9 Hz, 1H), 4.73 (s, 1H), 4.64 (s, 1H), 3.85 (t, J = 5.0 Hz, 8H), 3.78 (d, J = 10.5 Hz, 3H), 3.47 (s, 3H), 3.41-3.31 (1H), 3.15 (t, J = 9.4 Hz, 1H), 1.18 (s, 3H); ^{13}C-NMR (100

MHz, $CDCl_3$): 166.514, 166.303, 153.021, 150.942, 149.984, 148.537, 147.569, 139.807, 137.239, 133.808, 127.982, 126.769, 120.890, 119.884, 119.137, 117.330, 112.716, 109.022, 108.002, 102.482, 102.012, 101.409, 75.641, 65.004, 62.302, 59.149, 59.063, 56.935, 53.830, 49.106, 29.768, 24.363; HRMS (ESI) m/z =548.2435 [M^+]

[Pip-Nos]DCA : 6-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium dicyanamide **(7)** : It was obtained as zurich white solid in 86.9 % yield; mp: 191-193 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27-7.19 (m, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.92 (s, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.39-6.34 (1H), 6.24 (d, J = 11.0 Hz, 1H), 5.99 (t, J = 4.4 Hz, 4H), 5.81 (s, 1H), 5.75 (s, 1H), 4.73 (d, J = 12.8 Hz, 1H), 4.63 (d, J = 12.8 Hz, 1H), 3.85 (t, J = 5.0 Hz, 8H), 3.76 (s, 3H), 3.52-3.43 (3H), 3.38 (s, 1H), 3.21-3.07 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 166.284, 153.031, 150.942, 149.988, 148.546, 147.597, 139.831, 137.258, 133.817, 127.982, 126.765, 122.816, 121.331, 120.890, 119.894, 119.170, 117.330, 112.716, 109.027, 108.030, 102.472, 102.003, 101.409, 75.645, 66.642, 65.033, 62.292, 59.072, 56.945, 53.830, 49.125, 24.363; HRMS (ESI) m/z =548.2516 [M^+]

[Pip-Nos]NO_3 : 6-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium nitrate **(8)** : It was obtained as pale white solid in 84.2 % yield; mp: 188-190 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23-7.21 (m, 1H), 6.97-6.91 (m, 2H), 6.78 (q, J = 4.0 Hz, 1H), 6.37 (s, 1H), 6.24 (s, 1H), 5.98-5.92 (m, 4H), 5.81 (s, 1H), 5.75 (s, 1H), 4.72-4.64 (m, 2H), 3.84 (dd, J = 9.4, 3.4 Hz, 8H), 3.76 (s, 3H), 3.47 (d, J = 6.0 Hz, 3H), 3.38-3.33 (m, 1H), 3.19-3.10 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 166.332, 153.026, 150.951, 150.003, 148.556, 147.559, 139.802, 137.215, 133.798, 127.982, 126.755, 120.890, 119.855, 119.132, 117.326, 112.721, 109.041, 107.982, 102.482, 102.022, 101.418, 75.655, 66.623, 65.081, 62.316, 59.067, 56.935, 53.816, 49.125, 24.363; HRMS (ESI) m/z =548.2437 [M^+]

[Pip-Nos]OTf : 6-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium trifluoromethanesulfonate **(9)** : It was obtained as origami white solid in 87.4 % yield; mp: 186-188 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.3 Hz, 1H), 6.96-6.81 (4H), 6.40 (s, 1H), 6.16 (s, 1H), 6.03 (d, J = 3.2 Hz, 2H), 5.85 (s, 1H), 5.79 (s, 1H), 5.68 (s, 1H), 4.53 (d, J = 13.1 Hz, 1H), 4.32 (d, J = 13.1 Hz, 1H), 3.95-3.84 (m, 8H), 3.53 (s, 6H), 3.47 (s, 1H), 3.17 (q, J = 9.3 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 166.230, 153.061, 151.067, 150.166, 148.700, 147.569, 139.776, 136.968, 133.604, 127.824, 126.597, 121.048, 120.770, 119.486, 119.121, 117.272, 112.565, 109.125, 107.773, 102.330, 102.080, 101.390, 75.645, 67.010, 66.080, 62.294, 58.824, 56.907, 53.601, 48.895, 24.367; HRMS (ESI) m/z =548.2400 [M^+]

[Pip-Nos]Cl : 6-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium chloride **(10)** : It was obtained as pale white in 90.2 % yield; mp: 191-193 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29 (t, J = 4.1 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.99 (s, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.44 (s, 1H), 6.32 (s, 1H), 6.05 (d, J = 3.2 Hz, 4H), 5.88 (s, 1H), 5.82 (s, 1H), 4.80 (d, J = 12.8 Hz, 1H), 4.72 (d, J = 13.3 Hz, 1H), 3.92 (t, J = 4.6 Hz, 8H), 3.85 (s, 3H), 3.54 (s, 3H), 3.47-3.37 (m, 1H), 3.28-3.15 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 166.322, 152.993, 150.927, 149.964, 148.517, 147.540, 139.720, 137.277, 133.750, 127.962, 126.836, 120.814, 119.875, 119.122, 117.335, 112.716, 109.008, 107.968, 102.492, 102.003, 101.409, 75.641, 66.566, 65.004, 62.302, 59.048, 56.935, 53.993, 49.231, 24.354; HRMS (ESI) m/z =550.2012 [M^+]

Biological target of Noscapine retrieval and its evaluation

Among the various chemotherapeutic drugs, noscapine is reported to be the potential anticancer compound targeting the tubulin protein. Noscapine targets the tubulin protein, by its high potency towards the binding groove and further induces the conformational changes to the tubulin protein.[5] Noscapine via targeting the tubulin regulates its polymerization into the microtubules and combat the mitotis in cancer cells. Also, mechanistic studies demonstrated the binding of noscapine with tubulin protein; in estimation of one noscapine compound per tubulin dimer.[31,32] Hence, we have retrieved the tubulin protein with PDB ID 1TUB from the protein data bank. The 3D structure was evaluated by employing a multistep process using the preparation wizard module of Maestro version 9.7. 3D structure energy minimized and optimized for its stable conformations. Protein chains and bound ligand consisted of the structure were analyzed. Furthermore, the 3D crystal structure was assessed for its stereochemical properties by Ramachandran plot and its stability using the various computational algorithms, including Swiss-Model, Verify-3D, Saves Server. [33–35]

Preparation of tubulin protein for molecular docking analyses

Prior to molecular docking, the tubulin protein was prepared. The 3D crystal structure was checked, and unwanted ligands were removed by using the protein preparation module of the Whatif server (https://swift.cmbi.umcn.nl/servers). After that, water molecules were removed from the crystal structure of tubulin; to avail to dry trajectories and hydrogen atoms were added to stabilize the protein structure.

Preparation of Noscapine and its IL analogs for molecular docking analyses

Noscapine and its IL analogs were drawn using the Marvin sketch and Chemdraw software. Compounds were saved in the required format (.mol/mol2) for molecular docking. Prepared compounds were assessed for energy minimization through Pymol molecular modeling suites.

Molecular docking analyses

Molecular docking is a computer-aided drug design approach to screen the list of compounds and to define the binding conformation of compounds to the target protein. We have performed the molecular docking through the HEX 8.0. It is the computational approaches to define the interaction geometries of potential drugs with target biological targets. HEX 8.0 works based on Fast Fourier Transformation algorithms to derive the minimal binding energy conformations of the ligand-protein complex using the steric shapes and electrostatic potentials.

The output of molecular docking, a complex system was studied to analyze the involved molecular interaction using the Ligplot server. Ligplot identifies the hydrogen bonds and hydrophobic interactions of the docked complex. Moreover, binding conformations and molecular interactions were analyzed using the Chimera modeling suite.[36]

Pharmacological analyses of Noscapine and lead compounds

Noscapine and lead noscapine based IL derivatives ([Pip-Nos]OAc and [Pip-Nos]OTf) were studied for their pharmacokinetic and pharmacodynamic properties using multiple servers though SwissADME, pkCSM, ACD/I-Lab, and Molinspiration. It involves many pharmacological parameters, including the Lipinski rule of five, drug-likeliness and ADMET (Absorption, metabolism, excretion, toxicity).

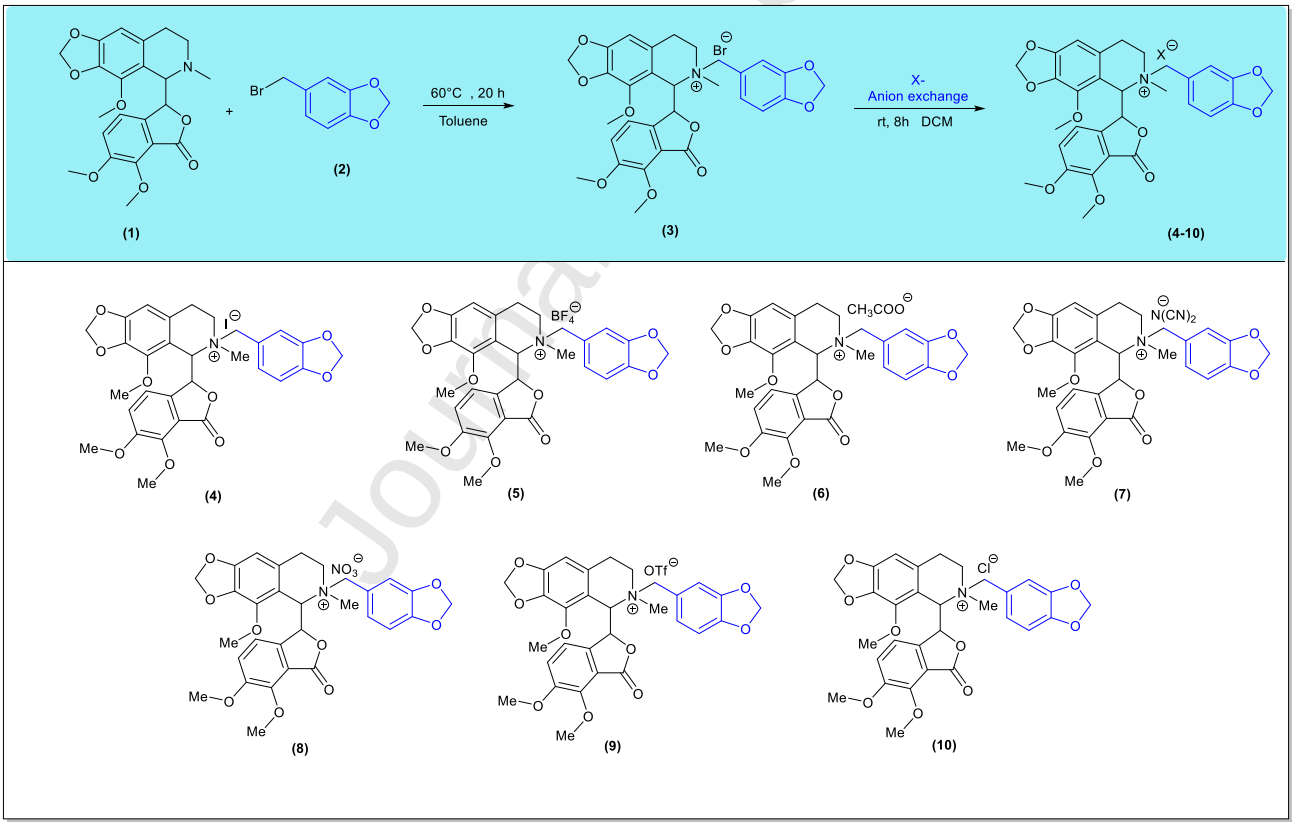
Standard Cell Proliferation Assay against Human Cervical Cancer Cells

The anti-proliferative effect was assessed by employing Standard Cell Proliferation Assay i.e. MTT [3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide] cell assay. Human cervical cancer cells, *HeLa* were employed to evaluate the cytotoxic effect of synthesized compounds using 96-wells microtitre plate. Briefly, 5x103 *HeLa* cells well were plated in 200µl of DMEM medium and incubated for 24 h. After a predetermined incubation period, serum DMEM was replaced with serum-free DMEM. The next day, cells were treated with a gradient concentration (10-70µM) of noscapine, [Pip-Nos]OAc and [Pip-Nos]OTf for 72 h. At the end of treatment, 5 mg/ml of MTT dye was added to each well and the plate was incubated at 37°C in dark for 4 h. The formazan crystals were formed of pink color, which were then dissolved by solubilizing buffer (100 µl) to each well. At reference wavelength of 630 nm, the absorbance value obtained is 560 nm in a plate reader (Tecan, Switzerland).

3. Result and discussion

3.1. Chemistry

In our laboratory, we are focused to design and develop the methodologies for the synthesis of new analogs of noscapine from the last few decades. In continuation of our research, we have developed methodology for the synthesis of 1,3-benzodioxole tagged noscapine ionic liquids. In the present work, 5-(Bromomethyl)-1,3-benzodioxole was synthesized by using 1,3-Benzodioxole-5-methanol (Supporting information Scheme-1) followed by quaternization reaction on noscapine to get the desired ionic liquid, which was then reacted with various anion metathesis reactions at room temperature to replace bromide anion with the desired anion. All the salts used for the anion metathesis were KI, $NaBF_4$, CH_3COONa, $NaN(CN)_2$, $NaNO_3$, NaOTf, and NaCl. Scheme 1 shown below summarizes the quaternization and metathesis reaction routes for the synthesis of 1,3-benzodioxole tagged noscapine based ionic liquids. All the synthesized ionic liquids were obtained in excellent yield. These ionic liquids were obtained pure which were characterized by ^{1}H-, ^{13}C-NMR spectroscopy, and mass spectrometry (see supporting information).



Scheme 1: Synthesis of Noscapine based ionic liquids

Table 1. Pharmacological properties analysis of [Pip-Nos] OTf and [Pip-Nos] OAc

Drug	Water solubility (Log mol/L)	Caco-2 permeability (Log Papp in 10-6 cm/s)	Intestinal absorption (human) % Absorbed	Skin Permeability Log Kp	P-glycoprotein substrate	VDss(human) (Log L/kg)	Fraction unbound (human) (Fu)	Total Clearance (Log ml/min/kg)
[Pip-Nos] OTf	-2.972	0.077	79.62	-2.735	No	-0.818	0.391	0.759
[Pip-Nos]	-3.202	0.921	85.839	-2.735	No	-0.717	0.347	0.656

OAc

Table 2. Toxicity profile of [Pip-Nos] OTf and [Pip-Nos] OAc

Drug	AMES toxicity	Max. tolerated dose (human) (Log mg/kg/day)	hERG I inhibitor	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) Log mg/kg_bw /day)	Skin Sensitization	*T.Pyriformis* Toxicity (Log ug/L)	Minnow toxicity (Log mM)
[Pip-Nos] OTf	No	0.409	No	3.007	0.289	No	0.285	-3.973
[Pip-Nos] OAc	No	0.273	No	3.125	1.07	No	0.285	-3.607

3.2. Biology

Biological target of Noscapine retrieval and its evaluation

The 3D structure of the tubulin protein of human origin was retrieved from the protein data bank with PDB ID 1TUB. Tubulin structure was consisted of two chains (alpha and beta chains), chain **A** of length 440 amino acids and chain **B** of chain length 427 amino acids; along with conjugated co-crystal ligands Guanosine-5'-Diphosphate, Taxotere and Guanosine-5'-Triphosphate (Figure-1). Stereochemical and structural properties of tubulin protein were analyzed through the Ramachandran plot evaluation. It defines the dihedral angels and existence of amino acid residues in allowed/disallowed regions. Ramachandran plot showed that the 88.5% amino acids lie in favorable to allowed region, 6.2% amino acids in the generously allowed region and only 5.3 % amino acids lies in the disallowed region (Figure-1). Local quality assessment plot depicted the tubulin structure has high similarity (~0.1 Å to 0.8 Å deviations) with native structure reported to have high quality. Also, the Verify3D server confirmed the good qualities of the structure by demonstrating more than 80% of residues have optimal 3D/1D profiles (Figure-2). These outputs concluded the good quality of the tubulin crystal structure for further studies.

Molecular docking analyses

Molecular docking was performed to assess the interaction of noscapine and its potential IL analogs with target tubulin protein. Hex 8.0 was set to shape and 3D conformations mode to identify the binding mode in fast Fourier transformation mode, with whole protein sampling algorithms. Grid dimension for tubulin protein made to 0.6 Å (as per docking manual), translation steps, protein flip and twist range of 360° and output of 25 interacting conformations. Out of these 25 complex systems, a top-scored docked complex with minimum binding free energy score was opted. In results, among all the synthesized ionic liquid products compound 6 and compound 9 has shown the best binding score (supplementary table-S1). [Pip-Nos]OAc and [Pip-Nos]OTf scored best -336.19 kJ/mol and -326.71 kJ/mol, respectively, much higher than Noscapine (-267.06 kJ/mol) (Figure-3). [Pip-Nos]OAc was found possess the potential interaction to tubulin protein with two hydrogen bonds; one at 166th amino acid of chain **B** of bond length 3.18 Å with donor angle 152.99° and second at 407th amino acid of chain **A** of bond length 3.51 Å with donor angle 111.58°. Also, hydrophobic interactions with 165th amino acid of chain **B** and 407th amino acid of chain **A** of tubulin protein.

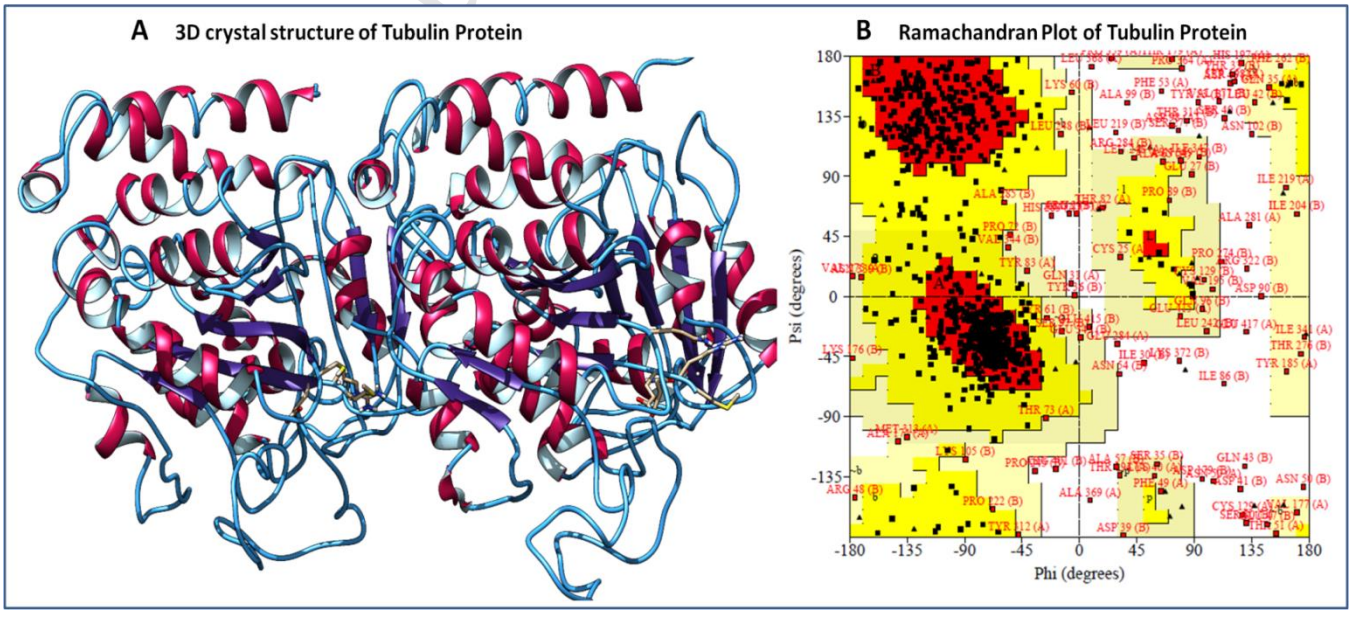


Figure-1: (A) Three-dimensional crystal structure of Tubulin protein; retrieved from protein databank with PDB ID:1TUB, (B) Ramachandran plot assessment of tubulin protein, 88.5% amino acids lie in favorable to allowed region, 6.2% amino acids in the generously allowed region and only 5.3 % amino acids lies in the disallowed region.

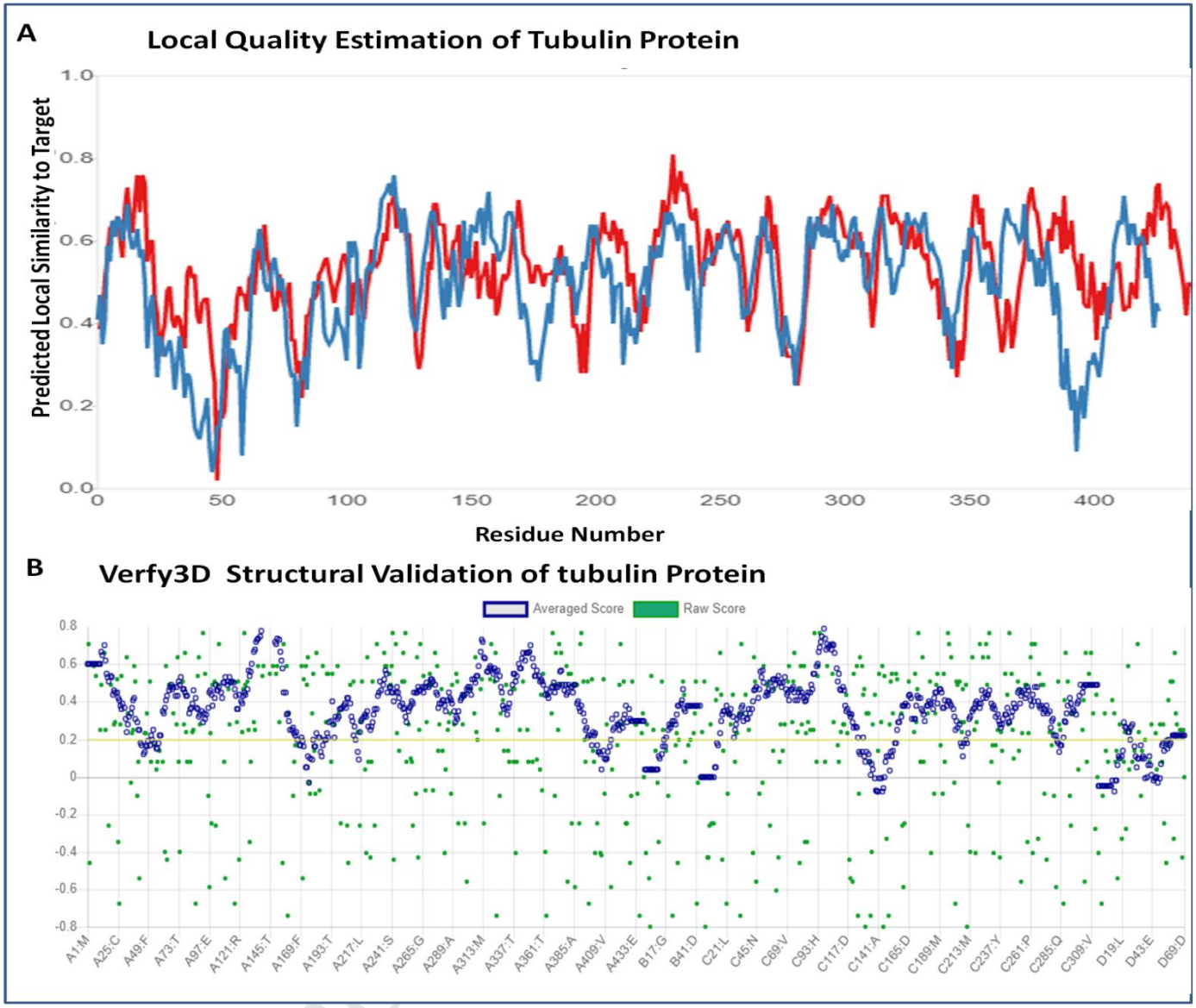


Figure-2: (A) Local quality estimation of tubulin protein residues. (B) Structural validation of tubulin protein structure by Verify3D servers. Both servers showed a good quality of protein structure.

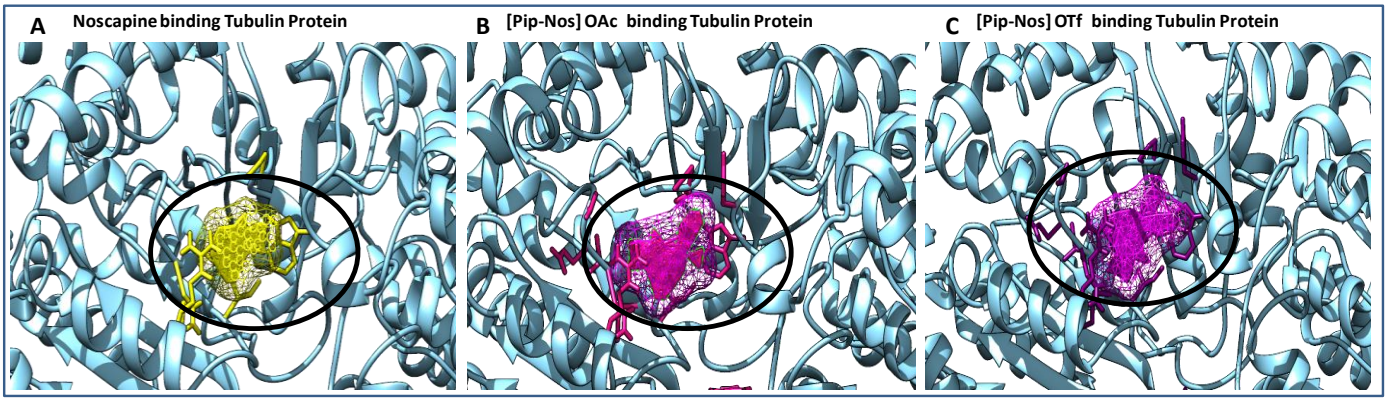


Figure-3: (A) Binding of Noscapine (encircled in yellow) to the binding groove of tubulin protein (sky blue ribbon style depiction), (B) Binding of [Pip-Nos]OAc (encircled in pink) to the binding groove of tubulin protein, (C) Binding of [Pip-Nos]OTf (encircled in purple) to the binding groove of tubulin protein.

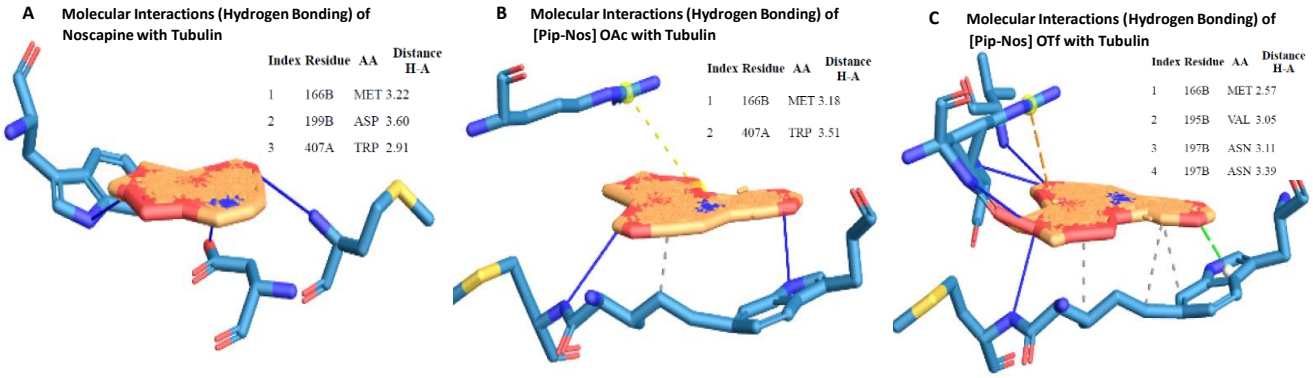


Figure-4: Depiction of Molecular interactions of; (A) Noscapine with tubulin protein, (B) [Pip-Nos]OAc with tubulin protein, (C) [Pip-Nos]OTf with tubulin protein.

[Pip-Nos]OTf compound found to possess the strong interaction majorly at chain **B** with five hydrogen bonds; one at 166th amino acid of chain **B** of bond length 2.57 Å with donor angle 159.65° and second at 195th amino acid of chain **B** of bond length 3.05 Å with donor angle 158.93°, third and fourth at 197th amino acids of chain **B** of bond lengths 3.11 Å and 3.39 Å and fifth at 407th amino acid of chain **B** of bond length 3.10 Å with donor angle 102.10°. Also, hydrophobic interaction with residues 165th of chain **B** and 407th amino acid of chain **A** of tubulin protein. Noscapine resulted in a docking score of -267.06 kJ/mol and three hydrogen bonds with 166 and 119 residues of chain **B** and 407 residues of chain **A** and hydrophobic interaction with 407 residues of chain **A** of tubulin protein (Figure-4). On comparative study with parent compound (noscapine), both [Pip-Nos]OAc and [Pip-Nos]OTf have shown the higher binding energy score and large molecular interactions. These results elucidated the potency of designed IL analogs of noscapine.

Pharmacological analyses of [Pip-Nos]OTf and [Pip-Nos]OAc

After the evaluation of lead compounds ([Pip-Nos]OAc and [Pip-Nos]OTf) with *in vitro* and *in silico* assays, pharmacological properties were analyzed based on Lipinski rule of five, which includes these assumptions: Molecular mass less than 500 Dalton, High lipophilicity (expressed as LogP less than 5), Less than 5 hydrogen bond donors, Less than 10 hydrogen bond acceptors and Molar refractivity should be between 40-130. Our results showed both compounds do not violet the Lipinski rule of five for drug development. One primary consideration for drug development is its absorption, as the intestine is the primary site of the absorption during oral administration of the drug. We studied the percentage of intestinal absorption of drugs for humans. We found [Pip-Nos]OTf and [Pip-Nos]OAc compounds have high oral absorption values 79.62% and 85.83% respectively, with same skin permeability value (log Kp) of -2.735 Compounds with less than 30% absorption considered to be poorly absorbed.[37] P-glycoprotein substrate properties analysis was studied with its important role during the glycoprotein mediated transport, which may be either exploited. Another important parameter is to assess the plasma concentration of the drug; determined by the volume of distribution (VDss). We found both the compounds are very lesser absorbed with a score of -0.818 and -0.717 and fraction unbound values of 0.391 fraction unit and 0.347 fraction unit respectively for [Pip-Nos]OTf and [Pip-Nos]OAc (Table-1).[38] Besides, maximum recommended daily dose of drugs for human were determined using the local weighed methods using the pkCSM server. In results, we found that [Pip-Nos]OTf has high tolerated daily dose with 0.409 log mg/kg/day, and [Pip-Nos]OAc has a 0.273 log mg/kg/day.

For drug design and development, one of the important aspects is side effects and toxicity. We have assessed the toxicity profiles of the drugs, which showed both compounds are non-carcinogenic with negative results to the Ames test. The relative toxicity of compounds was measured to determine the acute toxicity lethal dosage value (LD_{50}). LD_{50} illustrates the dosage concentration of the drug, which may lead to the death of 50% of animals under study. We found the LD_{50} values of 3.007 and 3.125 (mol/kg), and Oral Rat Chronic Toxicity value 0.289 log mg/kg_bw/day and 1.07 log mg/kg_bw/day for [Pip-Nos]OTf and [Pip-Nos]OAc respectively and no skin sensitivity to humans for both the drugs (Table-2).

Cytotoxicity Assay for Noscapine and lead compounds in *HeLa* cancer cells

By molecular docking analysis, we found [Pip-Nos]OAc and [Pip-Nos]OTf as potential compounds to bind strongly with tubulin protein. These compounds were studied for cytotoxicity and compared with parent compound (Noscapine) on *HeLa* cells. The cytotoxicity induced by noscapine, [Pip-Nos]OAc and [Pip-Nos]OTf in *HeLa* cells was measured by standard cell proliferation assay in terms of IC_{50} value. The IC_{50} of [Pip-Nos]OTf was estimated to be 17.2-µM significantly lower than (One way ANOVA test, $P<0.05$) 23.5-µM of noscapine acetate and 47.2-µM of noscapine (see supporting information, Table S2). The high therapeutic efficacy of [Pip-Nos]OTf as compared to [Pip-Nos]OAc and noscapine may be contributed to augmented permeation that further disrupted the cell organelles and triggered death mechanism in a lower concentration.

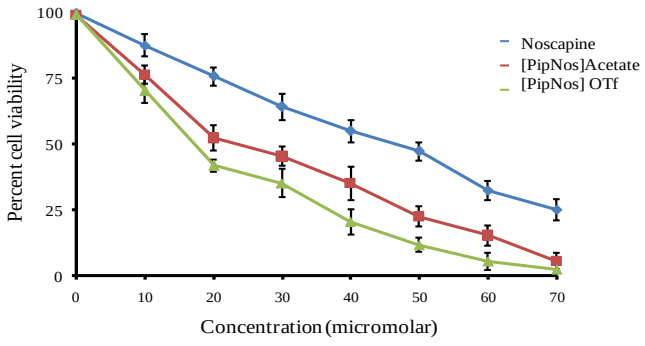


Figure-5: Depiction of cytotoxicity analysis of Noscapine, [Pip-Nos]OAc and [Pip-Nos]OTf on *HeLa* cells

3. Conclusion

The present study employs the state of art synthesis methods to design an efficient methodology and synthesis of novel 1,3-benzodioxole tagged Noscapine based ionic liquids. These ILs were characterized using various techniques such as ^{1}H,^{13}C-NMR spectroscopy, mass spectrometry, and melting point techniques. *In silico* studies were carried out, which showed [Pip-Nos]OTf and [Pip-Nos]OAc derivatives have the strongest binding with the target tubulin protein. Furthermore, these derivatives were assessed through the *in vitro* cytotoxicity analysis on *HeLa* cell lines in which we found that [Pip-Nos]OTf showed considerable toxicity in *HeLa* cancer cells. *In* vitro results confirmed the potency of [Pip-Nos]OTf and [Pip-Nos]OAc with high cytotoxicity values than parent compound noscapine. Moreover, pharmacological analysis also confirmed the potency of these derivatives to be used as an efficient anticancer drug. This study paved the way to design and development of a potential cancer-curing drug.

Conflict of interest

Authors have no conflict interest.

Acknowledgments

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Highlights

- Design and synthesis of 1,3-benzodioxole tagged Noscapine based ionic liquids
- Pharmacological analyses of Noscapine ionic liquids
- *In vitro* cytotoxicity assay for Noscapine and lead compounds in *HeLa* cancer cells
- Noscapine based ionic liquids as potential cancer curing drug