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Design, synthesis and *in vitro* cytotoxicity studies of novel *β*-carbolinium bromides

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ABSTRACT

A series of novel *β*-carbolinium bromides has been synthesized from easily accessible *β*-carbolines and 1-aryl-2-bromoethanones. The newly synthesized compounds were evaluated for their *in vitro* anticancer activity. Among the synthesized derivatives, compounds **16l**, **16o** and **16s** exhibited potent anticancer activity with IC_{50} values < 10 μM against tested cancer cell lines. The most potent analogue **16l** was broadly active against all the tested cancer cell lines (IC_{50} = 3.16-7.93 μM). In order to test the mechanism of cell death, we exposed castration resistant prostate cancer cell line (C4-2) to compounds **16l** and **16s**, which resulted in increased levels of cleaved PARP1 and AO/EB staining, indicating that *β*-carbolinium salts induce apoptosis in these cells. Additionally, the most potent *β*-carbolines **16l** and **16s** were found to inhibit tubulin polymerization.

β-Carboline unit containing natural products and synthetic molecules often exhibit a broad spectrum of pharmacological properties including sedative, anxiolytic, hypnotic, antioxidant, anticonvulsant, antitumor, antiviral, antiparasitic and antimicrobial.[1] Particularly, *β*-carboline analogues have been reported to exhibit significant antitumor activities against several human cancer cells (Fig. 1).[2-4] For example, natural *β*-carbolines Harmine (**1**) and Fascaplysin (**2**) exhibited interesting antiproliferative activity through apoptosis induction, DNA intercalation and CDK inhibition.[5-10] Cao research group identified benzyl-*β*-carbolinium bromides **3** (IC_{50} = 0.8-8 μM) and **4-5** (IC_{50} = 0.4-2.7 μM) as potent cytotoxic agents by modification of natural Harmine.[11, 12] In 2012, Frederick and co-workers prepared the trisubstituted Harmine derivative **6**, with impressive anticancer activity (IC_{50} = 0.7 μM; OE33).[13]

Among the various ways to enhance aqueous solubility, alkylation of azaheterocycles may lead to azolium salts with enhanced water solubility.[14,15] In the recent past, many cationic nitrogen heterocycles have been emerged as potent antitumor agents.[16, 17] For example, Zhang group reported imidazolium bromides as potent cytotoxic agents (IC_{50} < 5.0 μM).[18] Zeng *et al.* prepared 1-mesityl-3-(2-naphthoyl-methano)-1*H*-imidazo-lium bromide **7** (IC_{50} = 0.3-5 μM) with interesting anticancer activity *via* arresting cell cycle at G1 phase and induced apoptosis in K562 cells.[19]

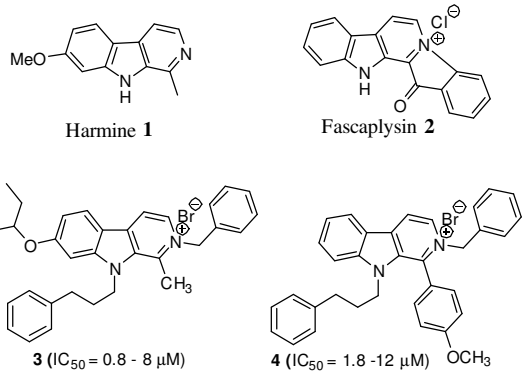

Figure 1. Representative *β*-carboline-based anticancer agents

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Recently, Xu group identified a series of novel 1-((indol-3-yl)methyl)–1*H*-imidazolium salts **8** (IC_{50} = 1.89 μM; HL60) as apoptosis inducing potent anticancer agents.[20]

In an effort to identify potent cytotoxic agents, recently, we designed and prepared synthetic indolyl heterocycles with potent anticancer activities.[21-23] Inspired by the fascinating anticancer properties of *β*-carbolines and azolium salts, in this paper we designed a diverse series of *β*-carbolinium salts by incorporating remarkable features of *β*-carboline and 1-aryl-2-bromoethanones in single molecule as depicted in Figure 2.

Substituted *β*-carboline intermediates **13** were prepared from L-tryptophan **9** as illustrated in Scheme 1.[24] Firstly, the reaction of **9** with formaldehyde solution (3.5 mL, 37%) under basic conditions produced tetrahydro *β*-carboline-3-carboxylic acid **10**. However, under similar reaction conditions substituted tetrahydro *β*-carboline-3-carboxylic acid **11** could not be prepared. Alternatively, carboxylic acid **11** was prepared from the reaction of **9** with aliphatic or aromatic aldehydes under acidic conditions. Next, iodobenzene diacetate-mediated decarboxylative aromatization of **10** or **11** led to *β*-carbolines **12** in good yields. Reaction of **12** with an appropriate alkyl halide and sodium hydride produced *N*-alkylated *β*-carbolines **13** in excellent yields. On the other hand, required 1-aryl-2-bromoethanones **15** were prepared from the reaction of arylethanones **14** with *N*-bromosuccinimide (NBS) in acetonitrile using *p*-toluenesulfonic acid (PTSA) as a catalyst in good yields (Scheme 1).[25] Finally, the reaction of *β*-carboline **13** and 1-aryl-2-bromoethanone **15** was performed in refluxing ethanol. After refluxing the reaction contents for 20 h, we isolated the *β*-carboline salt **16** only in moderate yield (55%). In an attempt to enhance the reaction efficiency and product yield, we performed the alkylation of *β*-carboline **13** in focused microwave (MW). Reaction of **13** and 1-aryl-2-bromoethanone **15** in focused MW led to *β*-carbolinium bromide **16a** with improved yield and notable reduced time (from hour to min.). MW-assisted organic synthesis received substantial attention in pharmaceutical industry due to dramatic savings of reaction times and higher product yields.[26, 27] Initially, we irradiated reaction mixture in MW oven at 50 °C for 20 min and obtained **16a** in 60% yield. Notably, by increasing reaction temperature from 50 °C to 80 °C, *β*-carbolinium bromide salt **16a** was produced in 89% yield. The generality of identified reaction conditions was demonstrated by synthesizing an array of *β*-carbolinium bromides **16a-t** in good to excellent yields (75-92%). 1-Aryl-2-bromoethanones with electron-donating (CH_3 and OCH_3) and electron-withdrawing (Br) groups smoothly delivered **16** in high yields.

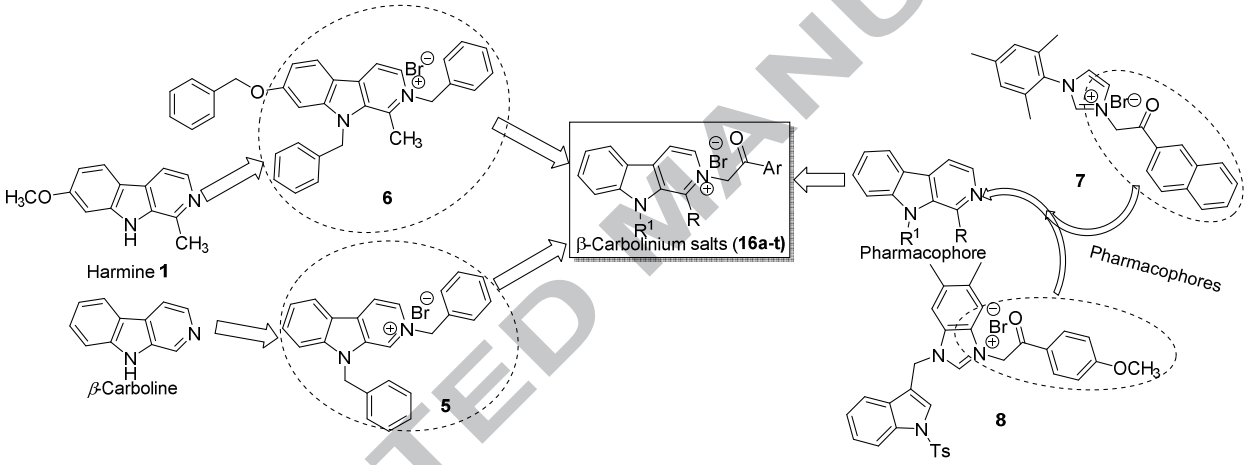
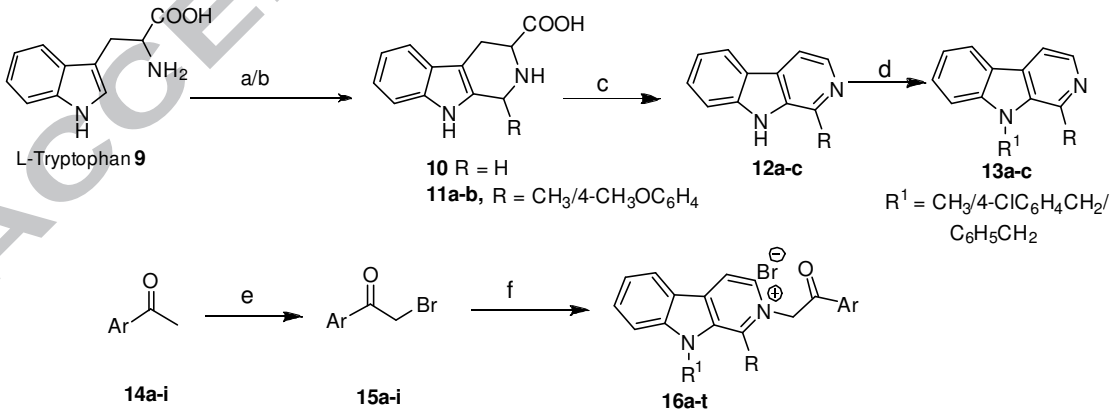


Figure 2. Rational design for *β*-carbolinium bromides

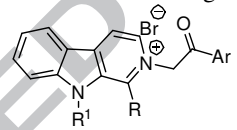


Scheme 1. Reagents and conditions: (a) 37% formaldehyde solution, 0.4N NaOH, 37 °C, 3 days, CH_3COOH, rt, 2 days; (b) RCHO, CH_3COOH, 100 °C, 12 h; (c) IBD, DMF, rt, 2 h; (d) R^1X, NaH, DMF, rt, 12 h. (e) NBS, CH_3CN, PTSA, reflux, 4-5 h; (f) **13**, EtOH, MW, 80 °C, 20 min.

Structures of all the synthesized *β*-carbolinium bromides **16a-t** were confirmed by IR, NMR (^{1}H & ^{13}C) and mass spectral data. In ^{1}H NMR spectrum, two characteristic singlets appeared at ~9.5 and ~6.6 ppm due to C-1 proton of *β*-carboline and CH_2- of arylacyl moiety at N^2, respectively. ^{13}C NMR of **16** showed a characteristic signal at ~190 ppm for the carbonyl carbon (C=O). A band at 1690 cm^{-1} in IR spectra of **16** indicated the presence of C=O functional group. The purity of carbolinium bromides **16a-t** was found to be greater than 97% by HPLC analysis.

In vitro cytotoxicity of *β*-carbolinium bromides **16a-t** was evaluated against pancreatic (BxPC-3), cervical cancer (HeLa), castration-resistant prostate (C4-2), human prostate (PC-3), human embryonic kidney 293 (HEK293T) and breast carcinoma (MDA-MB-231) cells by MTT assay. Doxorubicin was used as the reference drug. Activity results in terms of IC_{50} values are summarized in Table 1. Structure–activity relationship study was carried out by varying substituents on *β*-carboline (R and R^1) and 1-aryl-2-bromoethanone (Ar) moieties. Compound **16a** without any substituent on *β*-carboline and arylacyl moieties was found to be moderately active against a panel of cancer cell lines (IC_{50} = 21.6-74.9 μM). Replacement of phenyl with a *p*-tolyl ring in arylacyl part at N^2 led to **16b** with slightly improved cytotoxicity (IC_{50} = 18.4-31.9 μM, **16a** *vs* **16b**). Similarly, *p*-methoxyphenyl analogue **16c**, slightly augmented the growth inhibitory potency when compared to **16a** and **16b** (IC_{50} = 13.2-55.8 μM). Dimethoxyphenyl (**16d**) and trimethoxyphenyl (**16e**) derivatives were found to be weakly cytotoxic against kidney cells (IC_{50} = 67.8 and 28.6 μM; HEK293T) and inactive against other cell lines. *β*-Carboline **16f** with electron-withdrawing (*p*-bromophenyl) substituent displayed improved cytotoxicity (IC_{50} = 18.8-44.1 μM) when compared to compound **16a**. 2-Naphthyl analogue **16g** showed improved activity with IC_{50} values ranging 11.1-40.4 μM ((**16g** *vs* **16a**). Replacement of an aryl group with heteroaryl (furyl and thienyl) moiety led to compounds **16h-i** with weak cytotoxicity or inactive against the tested cell lines except **16i** with moderate cytotoxicity towards kidney (HEK293T) cells (IC_{50} = 18.2 μM). *N*-Methylated derivatives **16j-k** showed moderate cytotoxicity (IC_{50} = 14-65 μM) towards tested cancer cell lines. *N*-(4-Chlorobenzyl) unit is reported to be beneficial for the potency of various indole-based anticancer lead molecules.[28, 29] In an efforts to improve anticancer activity of the *β*-carbolinium bromides, we prepared *N*-(4-chloro-benzyl) *β*-carbolinium bromides **16l-n** with significant enhanced cytotoxicity against the tested cancer cells compared to *β*-carbolines with free *N*-H. Notably, compound **16l** found to be the most potent analogue of the series with broad cytotoxicity against all the tested cell lines (IC_{50} 3.2-7.9 μM). Incorporation of methyl and *p*-metho-xyphenyl substituents at position 1 (**16o-s**) of *β*-carboline further increased the growth inhibitory potency (IC_{50} = 8.7-49.2 μM) when compared to **16c**, **16e** and **16g** (IC_{50} = 11.1-116.3 μM). *N*-Benzylation of **16q** led to **16t** with moderate cytotoxicity (IC_{50} = 12.6-94.1 μM). Overall, most of the *β*-carbolinium bromides proved to be active against kidney cells (HEK293T, IC_{50} = 3.7-67.8 μM). Activity results suggest that substituents at positions 1, 2 and 9 of *β*-carboline and arylacyl part bearing 4-methoxyphenyl and 2-naphthyl groups are beneficial for the anticancer activity. Notably, the most potent compound **16l** with moderate water solubility (86 μg/mL) was found to be 95% stable at pH 4.5 up to 24 h.

Table 1. In vitro cytotoxicity of *β*-carbolinium bromides **16a-t** against a panel of cancer cells (IC_{50} in μM)



16a-t

Compd	R	R^1	Ar	BxPC-3	HeLa	C4-2	PC-3	HEK293T	MDA-MB-231
16a	H	H	C_6H_5	27.8±2.7	37.7±3.4	74.9±5.5	59.6±5.3	21.6±2.8	37.2±4.1
16b	H	H	4-$CH_3C_6H_4$	19.9±2.3	27.5±3.1	31.9±3.5	39.1±3.1	18.4±4.1	29.2±2.2
16c	H	H	4-$CH_3OC_6H_4$	> 100	48.7±2.9	45.7±5.4	55.8±4.9	13.2±2.6	> 100
16d	H	H	3,4-$(CH_3O)_2C_6H_3$	> 100	> 100	> 100	> 100	67.8±7.9	> 100
16e	H	H	3,4,5-$(CH_3O)_3C_6H_2$	> 100	> 100	> 100	> 100	28.6±3.8	> 100
16f	H	H	4-BrC_6H_4	24.5±3.9	44.5±5.0	33.3±2.9	43.2±5.2	18.8±3.1	44.1±5.3
16g	H	H	2-Naphthyl	15.1±2.4	35.2±2.6	40.4±3.9	35.8±3.0	11.1±2.2	25.1±3.6
16h	H	H	2-Furyl	> 100	> 100	> 100	> 100	> 100	> 100
16i	H	H	2-Thienyl	38.8±4.9	65.0±4.6	> 100	> 100	18.2±2.6	48.9±5.8
16j	H	CH_3	4-$CH_3OC_6H_4$	18.0±2.1	55.6±5.4	37.9±4.3	35.2±4.1	14.2±2.8	38.1±2.9
16k	H	CH_3	2-Naphthyl	64.9±4.3	33±3.2	25.4±2.2	43.8±3.9	17.6±3.0	54.2±5.4
16l	H	4-$ClC_6H_4CH_2$	4-$CH_3OC_6H_4$	**6.3±1.0**	**3.2±0.9**	**7.4±1.2**	**5.4±0.8**	**3.8±1.1**	**7.9±1.1**
16m	H	4-$ClC_6H_4CH_2$	3,4,5-$(CH_3O)_3C_6H_2$	35.3±2.9	13.16±2.5	41.0±3.8	36.5±3.4	11.5±3.1	37.0±4.0
16n	H	4-$ClC_6H_4CH_2$	2-Naphthyl	36.9±3.6	14.2±2.2	11.6±2.1	15.2±2.7	10.6±2.8	16.2±1.8
16o	CH_3	H	4-$CH_3OC_6H_4$	26.6±1.8	23.9±2.9	28.1±2.6	26.7±2.0	9.5±1.1	16.8±3.1
16p	CH_3	H	3,4,5-$(CH_3O)_3C_6H_2$	30.9±3.2	54±6.2	49.2±3.4	39.5±3.3	18.9±2.0	40.2±5.2
16q	CH_3	H	2-Naphthyl	12.3±2.0	13±2.6	17.7±1.9	19.5±2.1	17.7±2.8	14.1±2.1
16r	4-$CH_3OC_6H_4$	H	4-$CH_3OC_6H_4$	20.0±2.5	26.4±1.4	22.1±2.9	28.1±3.4	17.8±2.0	22.4±2.7
16s	4-$CH_3OC_6H_4$	H	2-Naphthyl	12.2±1.6	15.5±2.0	8.7±1.5	10.1±1.1	11.6±1.9	14.1±2.1
16t	CH_3	$C_6H_4CH_2$	2-Naphthyl	94.1±6.4	37.6±2.4	12.6±2.3	15.3±1.4	29.0±4.2	44.1±6.3
Doxorubicin				14.3	4.85	2.5	14.3±2.3	4.8±1.2	2.5±0.8

The activity data represent mean IC_{50} values of experiments conducted in triplicates

To determine the preliminary mechanism of action of *β*-carbolinium bromides, PARP1 cleavage assay for the active compounds **16l** and **16s** was performed. C4-2 Cells were treated with **16l** and **16s** for 48 h, and cleaved PARP1 levels was analyzed using immunoblotting. As shown in Figure 3, exposure of C4-2 cells by either 16l or 16s enhanced the levels of PARP1 cleavage as indicating apoptotic induced cell death in C4-2 cells.

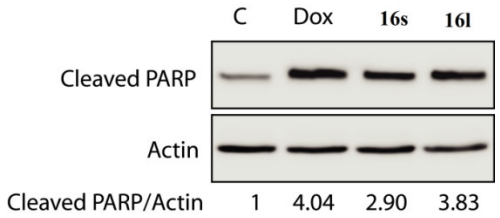


Figure 3. PARP1 cleavage (in C4-2 cells) induced by **16l** and **16s**

Furthermore, we also conducted acridine orange/ethidium bromide assay to investigate the mechanism of cell death. Acridine orange (AO) stains both live and dead cells, whereas ethidium bromide (EB) only stains dead cells.[30] Therefore, AO/EB staining is used to examine whether cell death occurred *via* apoptosis or necrosis. Effect of *β*-carbolinium salts on the morphological changes of C4-2 cells is illustrated in Figure 4. Incubation of compounds **16s** (IC_{50} = 8 μM) and **16l** with C4-2 cells (IC_{50} = 7 μM) for 24 h resulted in typical nuclear fragmentation (red), whereas no visible changes in cell nucleus and cell membrane integrity was observed for the control cells. The results of AO/EB staining revealed that compounds **16l** and **16s** trigger apoptosis in C4-2 cells, thereby confirming the PARP cleavage data.

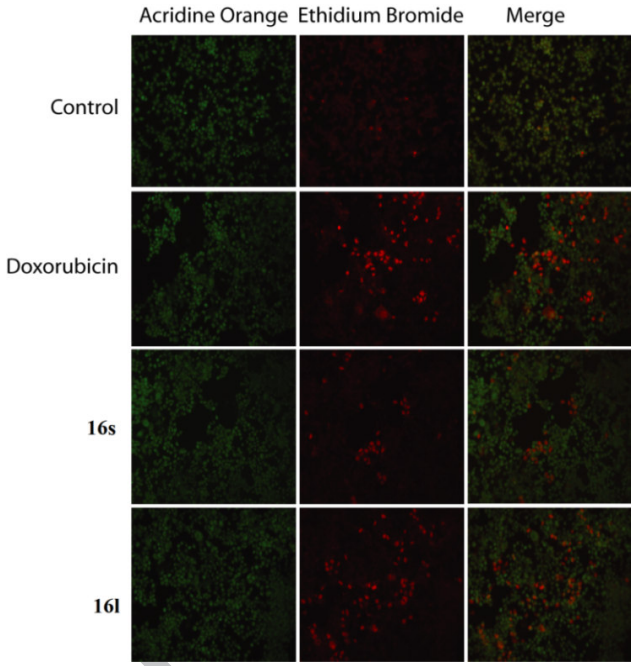


Figure 4. Apoptosis inducing effects of **16l** and **16s** in C4-2 cells.

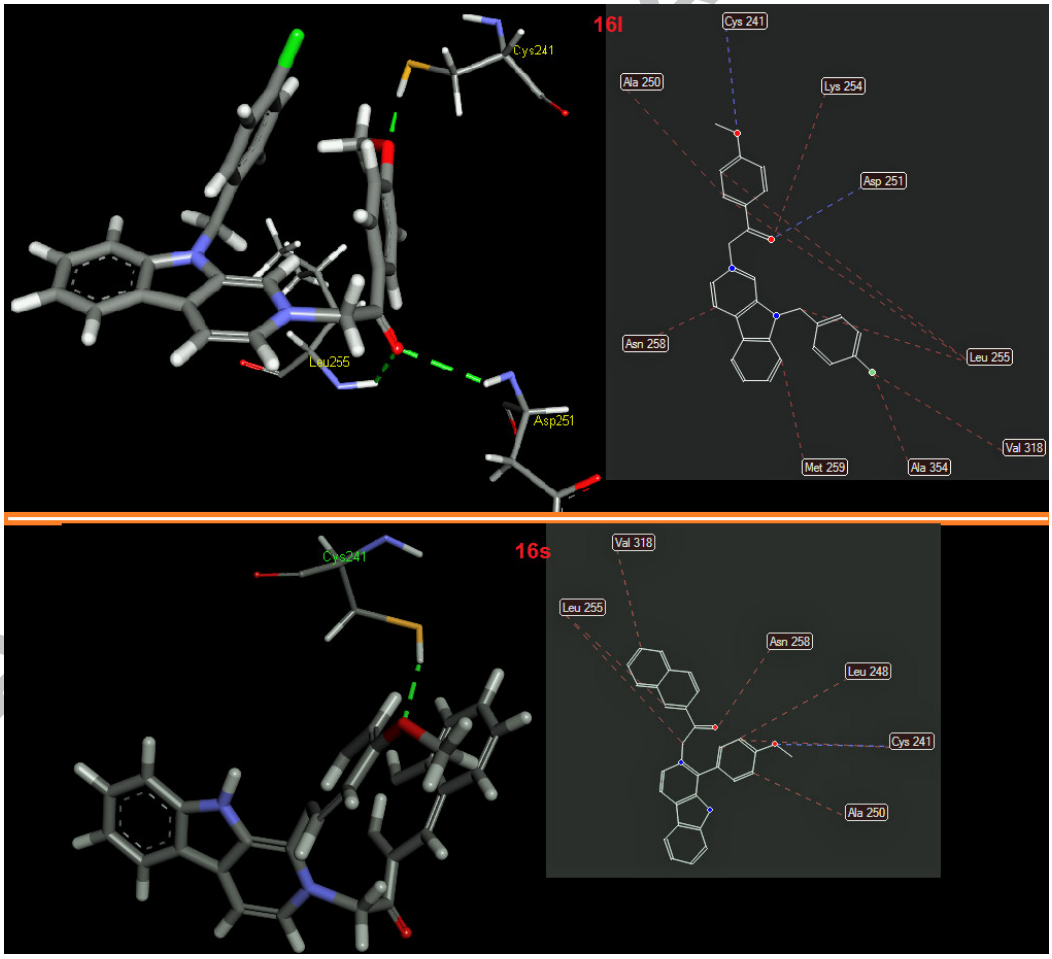


Figure 5. Binding interactions of **16l** and **16s** in the colchicine-binding site of tubulin. Hydrogen bonds (green and blue dotted lines) and steric interactions (red dotted lines) are outlined.

In the recent past, indole-based compounds have been reported for their significant anticancer activity through modulation of tubulin-heterodimer dynamics and binding at colchicine binding sites.[31] In order to find the theoretical binding sites of novel *β*-carboline bromides, a docking study for the identified potent compounds **16l** and **16s** was performed by Molegro Virtual docker program[32] according to reported high-resolution crystal structure of the tubulin-DAMA-colchicine (CN-2) complex (PDB ID: 1SA0).[33] Scoring functions and hydrogen bond formed with the surrounding amino acids predicted the binding affinities for **16l** and **16s** with MolDock Scores of -151.18 and -167.90, respectively. The docking poses of the molecule with the receptor are detailed in Figure 5. Binding interactions for **16l** are strongly stabilized by two hydrogen bonds; first interaction between C=O and Asp251 with hydrogen bond distance of 3.0616 Å; the second one between oxygen of 4-methoxyphenyl group and Cys241 with the bond length of 2.6103 Å. Similarly, compound **16s** also showed hydrogen-bonding interactions between the oxygen of 1-(4-methoxyphenyl)-*β*-carboline and Cys241 with 3.207Å distance of hydrogen bond. Apart from hydrogen bonding interactions, compounds **16l** and **16s** also strongly stabilized by steric interactions (red dotted lines) as illustrated in Figure 5. Additionally, the hydrophobic interactions in the colchicine-binding domain of the tubulin for *β*-carbolines **16l** and **16s** are shown in Figure 6.

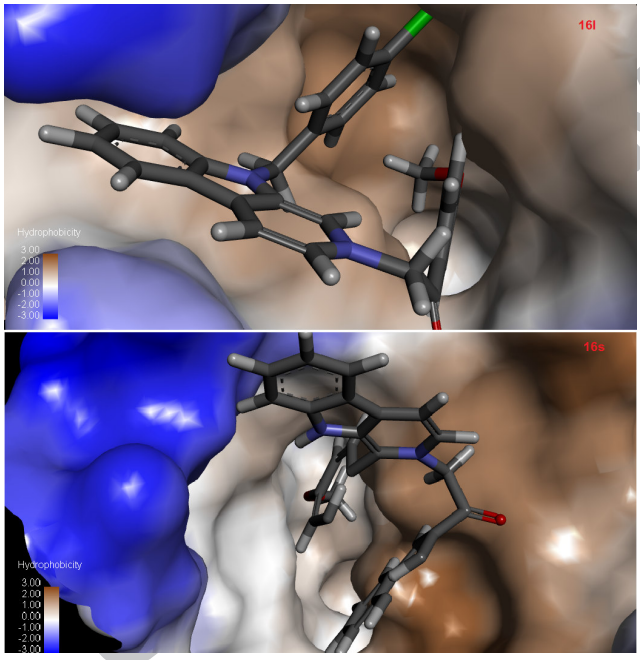


Figure 6. Hydrophobicity effect of **16l** and **16s** in the binding pocket of colchicine

To validate the theoretical molecular-docking hypothesis, we examined the tubulin polymerization activity for the identified two potent compounds **16l** and **16s** in a cell free system. *β*-Carbolinium bromides **16l** and **16s** were found to inhibit tubulin polymerization at 6 µM as shown in Figure 7.

In summary, a series of *β*-carbolinium bromides **16a-t** was prepared from easily accessible *β*-carbolines and 1-aryl-2-bromoethanones under MW irradiation. *In vitro* anticancer activity of *β*-carbolinium bromides **16a-t** was evaluated against six-human tumor cell lines. *β*-Carboline **16l** displayed most potent cytotoxicity against the tested cancer cell lines with IC_{50} values ranging 3.16-7.93 µM. The preliminary mechanism of action study revealed that compounds **16l** and **16s** induced apoptotic cell death by enhancing the level of cleaved PARP1 in C4-2 cells and exhibited their activity through the inhibition of tubulin polymerization. This class of compounds can be further exploited for obtaining highly potent cytotoxic compounds.

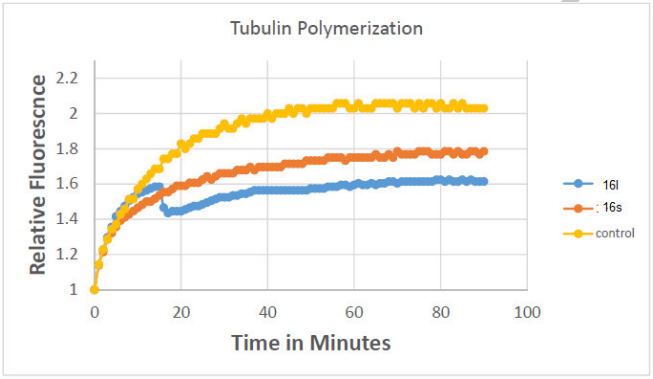


Figure 7. Effect of compounds **16l** and **16s** on *in vitro* tubulin polymerization

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures for the synthesis of compounds **10, 11, 12, 13, 15** and **16a-t**, protocol for cytotoxicity assay and analytical spectra of final compounds **16a-t)** associated with this article can be found, in the online version, at http://dx.doi.org/

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Graphical Abstract

Design, synthesis and *in vitro* cytotoxicity studies of novel *β*-carbolinium bromides

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