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# Therapeutic journey of synthetic betacarboline derivatives: A short review

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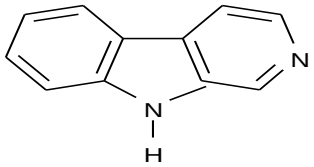
## ABSTRACT

A large number of medicinal compounds which have been discovered belong to a major class of heterocyclic compounds containing nitrogen as a hetero atom. The versatile synthetic applicability and biological activities of these heterocyclic compounds has helped the medicinal chemist to plan, organize and implement new approaches towards discovery of novel drugs. . β-carboline also known as nor-harmane is a nitrogen containing heterocyclic compound. It belongs to the group of indole alkaloids and consists of pyridine ring that is fused to an indole skeleton. The structure of β-carboline is similar to that of tryptamine, with the ethylamine chain re-connected to the indole ring via an extra carbon atom, to produce a three- ringed structure. It is a key pharmacophore present in a large number of natural tricyclic alkaloids. The natural and synthetic β-carboline derivatives are reported to have pharmacological effects in several aspects, such as the anticancer activity against colon and lung cancers, central nervous system activity in mammals and also as the biological control agent for receptor research on bio-enzyme inhibitors. Some β-carbolines are known to bind with high affinity to the central benzodiazepine receptors with anticonvulsive and anxiolytic properties. Nor-harmine also prevents bone loss by suppressing osteoclastogenesis. The Pictet-Spengler condensation is commonly used to synthesize β-carbolines, This comprehensive overview summarizes the medicinal importance of synthetic betacarboline derivatives, which may be useful for researchers to explore the hidden potential of nor-harmine.

**Keywords:** Betacarboline, Nor-Harmane, Tryptamine, Indole, Pictet-Spengler Condensation,

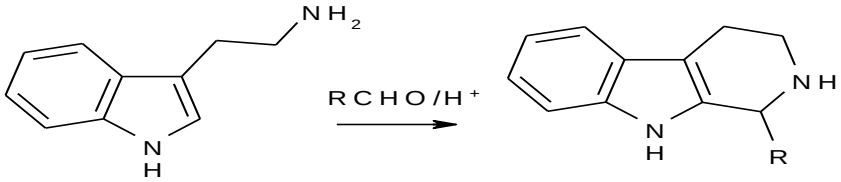
## INTRODUCTION

β-Carboline (9*H*-pyrido[3,4-*b*]indole), also known as norharmane **is** a tricyclic alkaloid that was originally isolated from seeds of *Peganum harmala* in 1847. It is nitrogen containing heterocyclic compound, belongs to the group of indole alkaloids and consists of pyridine ring that is fused to an indole skeleton. The structure of β-carboline is similar to that of tryptamine with the ethylamine chain re-connected to the indole ring via an extra carbon atom, to produce a three- ringed structure. [1- 2]

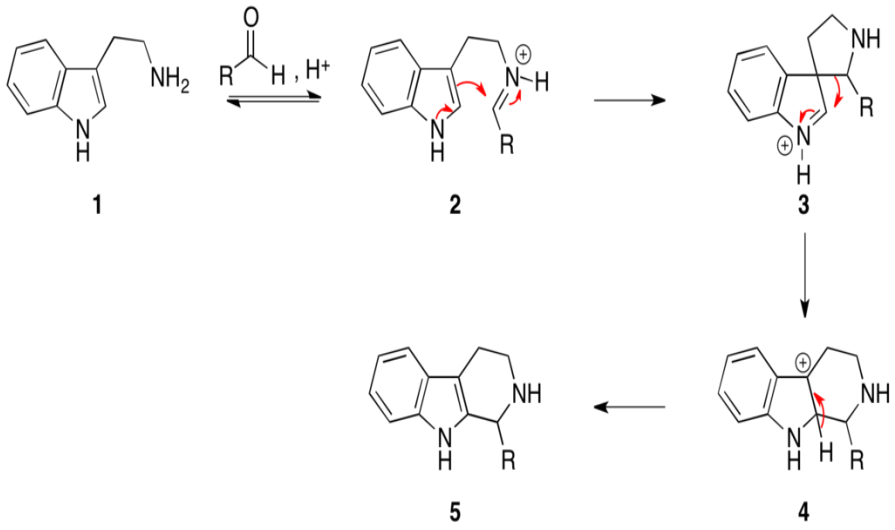


It is a key pharmacophore present in a large number of natural tricyclic alkaloids. Naturally occurring β-carboline alkaloids and synthetic analogues containing β-carboline subunit are endowed with diverse pharmacological properties including anticancer activity against colon and lung cancers, central nervous system activity in mammals and also as the biological control agent for receptor research on bio-enzyme inhibitors. Some β-carbolines are known to bind with high affinity to the central benzodiazepine receptors with anticonvulsive and anxiolytic properties. Norharmine also prevents bone loss by suppressing osteoclastogenesis. [3-12]

The Pictet-Spengler condensation is commonly used to synthesize β-carbolines, due to its analogy to the biosynthesis of these systems. This reaction needs an arylethylamine, an aldehyde and an acid catalyst. This reaction can be considered a special case of the Mannich reaction.




Some groups describe a sequence of Pictet-Spengler condensation followed by oxidation, without the isolation of the intermediate tetrahydrocarbolines (THC), to prepare the carbolines. A variety of substituted β and gama-carbolines have been prepared in good to excellent yields by the cyclization of internal acetylenes by the tert-butylimines of N- Substituted 3-iodoindole-2-carboxaldehydes and 2-Haloindole-3-carboxaldehydes, respectively, in the presence of a palladium catalyst. The reaction mechanism occurs by initial formation of an iminium ion (**2**) followed by electrophilic addition at the 3-position, in accordance with the expected nucleophilicity of indoles, to give the spirocycle **3**. After migration of the best migrating group, deprotonation gives the product (**5**) [13-17].

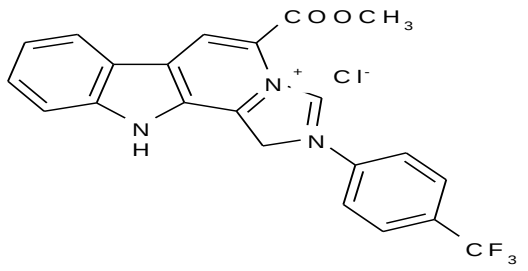


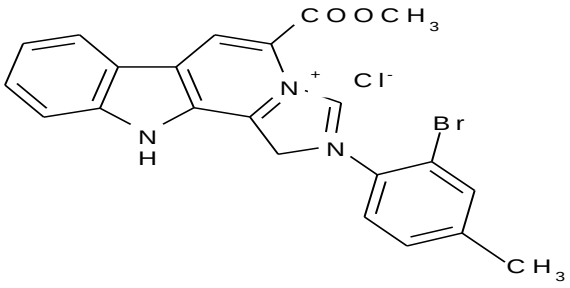
## Anti-cancer activity

Shashikant *et al*[18]. worked on Synthesis of β-Carboline-Based N-Heterocyclic Carbenes and Their Antiproliferative and Antimetastatic Activities against Human Breast Cancer Cells 1.

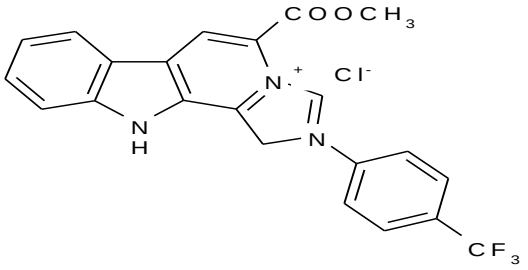
A series of novel β-carboline-based N-heterocyclic carbenes was prepared via Mannich reaction between methyl 1-(dimethoxymethyl)-9H-pyrido[3,4-b]indole-3-carboxylate, formaldehyde, and primary amines. All compounds were evaluated for their antiproliferative activity using human breast cancer and lung cancer cell lines. Three compounds, 3c, 3j, and 3h, were discovered to display IC50 less than 10 μM against human breast cancer MDA-MB-231 cells at 24 h of treatment. Pharmacologically these compounds lead to G2/M phase cell cycle arrest and induction of cellular apoptosis by triggering intrinsic apoptotic pathway through depolarization of mitochondrial membrane potential and activation of caspases. At lower concentrations, these compounds also showed antimigratory and antiinvasive effects against highly metastatic human breast cancer MDA-MB-231 cells via aberration of MAPkinase signaling and by the inhibition of matrix metalloproteinases. However, these analogues lack in vivo effect in mouse model. which may be attributed to their strong affinity to HSA that was investigated spectroscopically with compound 3h.

**3c**



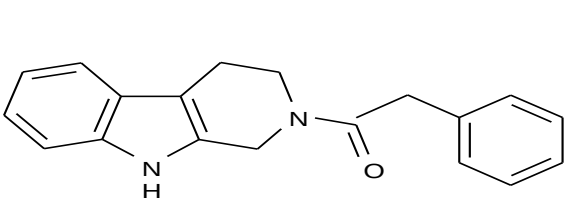

**3h**



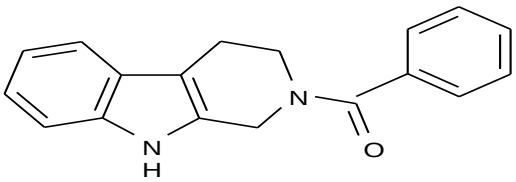

**3j**

Cong Zheng *et al*[19]. Synthesis and Biological Evaluation of Novel Tetrahydro-β-carboline Derivatives as Antitumor Growth and Metastasis Agents through Inhibiting the Transforming Growth Factor-β Signaling Pathway 0000

The transforming growth factor beta (TGFβ) signaling cascade is considered as one of the pivotal oncogenic pathways in most advanced cancers. Inhibition of the TGFβ signaling pathway by specific antagonists, neutralizing antibodies, or small molecules is considered as an effective strategy for the treatment of tumor growth and metastasis. Here we demonstrated the identification of a series of tetrahydro-β-carboline derivatives from virtual screening which potentially inhibit the TGFβ signaling pathway. Optimization of the initial hit compound 2-benzoyl-1,3,4,9-tetrahydro-β-carboline (8a) through substitution at different positions to define the structure−activity relationship resulted in the discovery of potent inhibitors of the TGFβ signaling pathway. Among them, compound 8d, one of the tested compounds, not only showed potent inhibition of lung cancer cell proliferation and migration in vitro but also strongly suppressed growth of lung cancer and breast cancer in vivo.



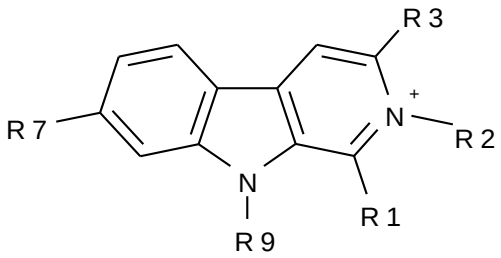
**8d**



**8a**

Jahan B. *et al*[20]. worked on 3D-QSAR and Docking Studies of a Series of β-Carboline Derivatives as Antitumor Agents of PLK1.

An alignment-free, three dimensional quantitative structure-activity relationship (3D-QSAR) analysis has been performed on a series of -carboline derivatives as potent antitumor agents toward HepG2 human tumor cell lines. A highly descriptive and predictive 3D-QSAR model was obtained through the calculation of alignment-independent descriptors (GRIND descriptors) using ALMOND software. For a training set of 30 compounds, PLS analyses result in a three-component model which displays a squared correlation coefficient () of 0.957 and a standard deviation of the error of calculation (SDEC) of 0.116. Validation of this model was performed using leave-one-out, of 0.85, and leave-multiple-out. This model gives a remarkably high (0.66) for a test set of 10 compounds. Docking studies were performed to investigate the mode of interaction between -carboline derivatives and the active site of the most probable anticancer receptor, polo-like kinase protein.




Some related compounds are:

$R_1$- H, $CH_3$; $R_2$- $CH_2$ $C_6H_5$, $CH_2)_2$ $C_6H_5$, $CH_2)_3C_6H_5$

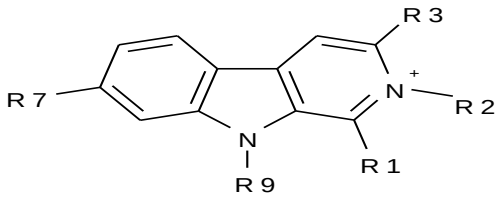
$R_3$-H, CHO, $CH_2OH$, $CONH(CH_2)_2OH$, $CONH(CH_2)_6NH_2$

$R_7$- H, OH, $OCH_3$, $OC_2H_5$

$R_9$- H, $C_2H_5$, $C_4H_9$(n), $C_4H_9$(i)

Han X *et al*[21]. Worked on A series of beta-carboline derivatives inhibit the kinase activity of PLKs.

Polo-like kinases play an essential role in the ordered execution of mitotic events and 4 mammalian PLK family members have been identified. Accumulating evidence indicates that PLK1 is an attractive target for anticancer drugs. In this paper, a series of beta-carboline derivatives were synthesized and three compounds, DH281, DH285 and DH287, were identified as potent new PLK inhibitors. We employed various biochemical and cellular approaches to determine the effects of these compounds on the activity of PLK1 and other mitotic kinases and on cell cycle progression. We found that these three compounds could selectively inhibit the kinase activity of purified PLK1, PLK2 and PLK3 *in vitro*. They show strong antitumor activity against a number of cancer cell lines with relatively low micromolar $IC_{50}$s, but are relatively less toxic to non-cancer cells (MRC5). Moreover, these compounds could induce obvious accumulation of HeLa cells in $G_2$/M and S phases and trigger apoptosis. Although MRC5 cells show clear S-phase arrest after treatment with these compounds, the G2/M arrest and apoptosis are less insignificant, indicating the distinct sensitivity between normal and cancer cells. We also found that HeLa cells treated with these drugs exhibit monopolar spindles and increased Wee1 protein levels, the characteristics of cells treated with PLK1 inhibitors. Together, these results demonstrate that DH281, DH285 and DH287 beta-carboline compounds are new PLK inhibitors with potential for cancer treatment.




DH281 DH285 DH287

| | | | |
|---|---|---|---|
| R1 | $CH_3$ | $CH_3$ | $CH_3$ |
| R2 | $CH_2C_6H_5$ | $CH_2C_6H_5$ | $CH_2C_6H_5$ |
| R3 | H | H | H |
| R7 | $OCH_2C_6H_4$ (p- F) | $OCH_2C_6H_4$ (p- F) | $OCH_2C_6H_5$ |
| R9 | CH2)3 $C_6H_6$ | n ($C_4H_9$) | $CH_2C_6H_5$ |

Ravindra Kumar*et al*[22]. worked on QSAR analysis for some β-carboline derivatives as anti-tumor.

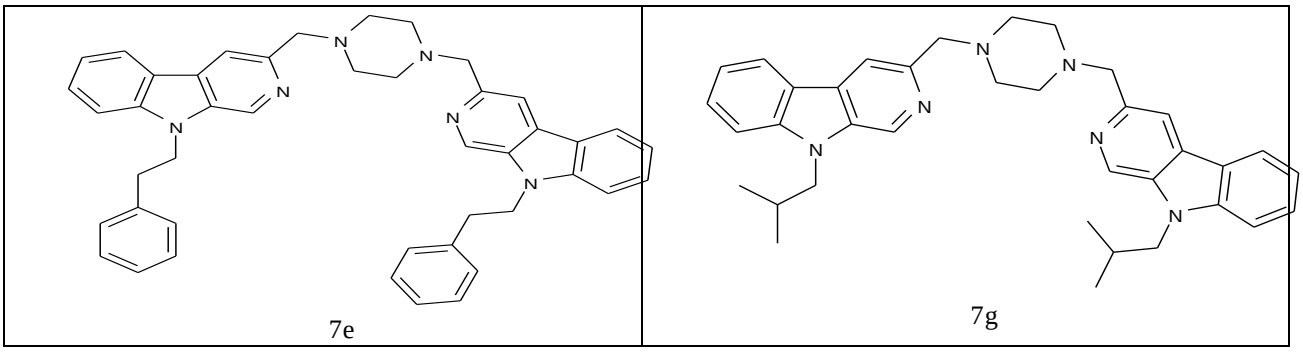
Quantitative structure–activity relationship (QSAR) studies have been performed on β-carboline derivatives to explore the structural necessities for antitumor activity. 3D QSAR studies were done using V-Life Sciences MDS 3.0 drug designing module to explain the structural requirements for the anti-tumor activity. The 3D-QSAR was performed using the Step Wise K Nearest Neighbour Molecular Field Analysis [(SW) kNN MFA] technique with the partial least-square (PLS) method on a database. Obtained best 3D-QSAR model having high predictive ability with $q^2 = 0.743$, $r^2 = 0.721$, pred_$r^2 = 0.708$ and standard error = 0.346, explaining the majority of the variance in the data with partial least square (PLS) components. The results of the present study may be useful on the designing of more potent compounds as antitumor drugs.

Li *al et al.* [23] *Worked on* Synthesis and bioactivity of beta-carboline derivatives.

A series of beta-carboline derivatives were synthesized from L-tryptophan through the Pictet-Spengler reaction and oxidation of K2Cr2O7 by a sequential one-pot synthesis method. In vitro anti-bacterial, insecticidal, and cytotoxic activities of all synthesized compounds were investigated by the tablet diffusion, leaf disc, and MTT methods, respectively. Some of the compounds (1-1, 1-2, 1-3 and 1-12) exhibited obvious anti-bacterial effects and some (1-3) had significant cytotoxic activities against tumor cells 3LL, MCF-7, BGC-823 and QGY-7701, with IC50 values of 7.79, 5.75, 3.53 and 4.02 microg/mL, respectively. No insecticidal activity against third stage instar larvae of Mythimna separata Walker were observed under the tested concentration.

Guang Shao et al [24] worked on Synthesis and biological evaluation of piperazine group-linked bivalent β-carbolines as potential antitumor agents

A series of novel bivalent β-carbolines with a piperazine group spacer between 3-methylene units were synthesized and evaluated as antitumor agents. The results demonstrated that compounds **7e** and **7g** exhibited the most potent cytotoxic activities against ten tumor cell lines. Structure–activity relationships analysis indicated that (1) the substituents in positions 1 and 9 of the β-carboline ring played a significant role in modulating the antitumor activity; (2) the introduction of alkyl groups into position-9 of the β-carboline nucleus enhanced their cytotoxic potencies and the butyl substituent was the optimal group. Investigation of the preliminary mechanism of action demonstrated that compound **7g** showed obvious anti-angiogenic activity in the *in vivo* CAM assay, and the potency was similar to that of CA4P (200 μM).

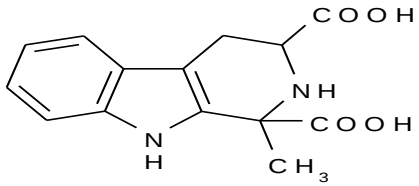


7e 7g

## Antioxidant activity

Koteppa Pari et al[25]. Worked on β-Carbolines That Accumulate in Human Tissues May Serve a Protective Role against Oxidative Stress

β-Carbolines are tricyclic nitrogen heterocycles formed in plants and animals as Maillard reaction products between amino acids and reducing sugars or aldehydes. They are being detected increasingly in human tissues, and their physiological roles need to be understood. Two β-carboline carboxylates have been reported to accumulate in the human eye lens. We report here on the identification of another β-carboline, namely 1-methyl-1-vinyl -2,3,4-trihydro-β-carboline-3-carboxylic acid, in the lenses of some cataract patients from India. Analysis of these three lenticular β-carbolines using photodynamic and antioxidant assays shows all of them to be inert as sensitizers and effective as antioxidants; they quench singlet oxygen, superoxide and hydroxyl radicals and inhibit the oxidative formation of higher molecular weight aggregates of the test protein, eye lens γ-crystallin. Such antioxidative ability of β-carbolines is of particular relevance to the lens, which faces continual photic and oxidative stress. The β-carboline diacid IV is also seen to display an unexpected ability of inhibiting the thermal coagulation of γ-crystallin and the dithiothreitol-induced precipitation of insulin. These results offer experimental support to earlier suggestions that one of the roles that the β-carbolines have is to offer protection against oxidative stress to the human tissues where they accumulate. Several reports have appeared in recent literature of the presence of β-carbolines in human tissues. It thus becomes important to understand their physiological role in human health.



## Prevents bone loss by suppressing osteoclastogenesis

Takayuki Yonezawa*et al*[26]. Worked on Harmine, a β-carboline alkaloid, inhibits osteoclast differentiation and bone resorption *in vitro* and *in vivo*. 18

Bone homeostasis is controlled by the balance between osteoblastic bone formation and osteoclastic bone resorption. Excessive bone resorption is involved in the pathogenesis of bone-related disorders such as osteoporosis, arthritis and periodontitis. To obtain new antiresorptive agents, we searched for natural compounds that can inhibit osteoclast differentiation and function. We found that harmine, a β-carboline alkaloid, inhibited multinucleated osteoclast formation induced by receptor activator of nuclear factor-κB ligand (RANKL) in RAW264.7 cells. Similar results were obtained in cultures of bone marrow macrophages supplemented with macrophage colony-stimulating factor and RANKL, as well as in cocultures of bone marrow cells and osteoblastic UAMS-32 cells in the presence of vitamin D(3) and prostaglandin E(2). Furthermore, harmine prevented RANKL-induced bone resorption in both cell and bone tissue cultures. Treatment with harmine (10

mg/kg/day) also prevented bone loss in ovariectomized osteoporosis model mice. Structure-activity relationship studies showed that the C3-C4 double bond and 7-methoxy group of harmine are important for its inhibitory activity on osteoclast differentiation. In mechanistic studies, we found that harmine inhibited the RANKL-induced expression of c-Fos and subsequent expression of nuclear factor of activated T cells (NFAT) c1, which is a master regulator of osteoclastogenesis. However, harmine did not affect early signaling molecules such as ERK, p38 MAPK and IκBα. These results indicate that harmine inhibits osteoclast formation via down regulation of c-Fos and NFATc1 induced by RANKL and represses bone resorption. These novel findings may be useful for the treatment of bone-destructive diseases.

### PDE5 Inhibitors

Ahmed Kumar *et al*[27] *Worked on a* Novel Access to Arylated and Heteroarylated Beta-Carboline Based PDE5 Inhibitors.

A series of structurally related tetrahydro-β-carboline derivatives were prepared. The tetrahydro-β-carboline skeleton was fused either to a hydantoin or to a piperazindione ring, the pendant aryl group attached to C-5 or C-6 was changed to a 3, 4-dimethoxyphenyl or a 3-pyridinyl ring; different N-substituents on the terminal ring were introduced, a straight chain ethyl group, a branched tert. butyl and P-chlorophenyl group rather than n-butyl group of the lead compound. All four possible diastereomers of target tetrahydro-β-carboline derivatives were prepared, separated by column chromatography and the significance of these stereo chemical manipulations were studied. Synthesized compounds were evaluated for their inhibitory effect versus PDE5. Seven hits were obtained with appreciable inhibitory activity versus PDE5 with $IC_{50}$s 0.14 - 4.99 µM.

## REFERENCES


[1]. Guowu Lin , Yue Wang, Qingfa Zhou , Weifang Tang , Jian Wang, Tao Lu, “A Facile Synthesis of 3-Substituted 9H-Pyrido[3,4-b]indol-1(2H)-one Derivatives from 3-Substituted β-Carbolines”, *Molecules*, 2010, 15, 5680-5691.

[2]. Ratsch, Christian, “The Encyclopedia of Psychoactive Plants, Ethnopharmacology and its Applications”, *Park Street Press*, 2005.

[3]. Arshad N, Zitterl Eglseer K, Hasnain S, Hess M, "Effect of *Peganum harmala* or its beta-carboline alkaloids on certain antibiotic resistant strains of bacteria and protozoa from poultry”, *Phytother Res,* 2008, 22, (11), 1533-38.

[4]. Klaus P.L, Walter G.S, Wolfgang W, Walter E.M, “β-Carbolines as benzodiazepine receptor ligands”, J. *Med. Chem*, 1983, *26*, 499-503.

[5]. Guan H, Chen H, Peng W, Ma Y, Cao R, Liu X, Xu A, *Eur. J. Med. Chem*, 41, 2006 1167–1179.

[6]. Funayama Y, Nishio K, Wakabayashi K, Nagao M, Shimoi K, Ohira T, Hasegawa S, Saijo N, *Mutat. Res*, 349, 1996, 183–191.

[7]. Hino T, Nakagawa M, *J. Hetercycl. chem*, 31, 1994, 625-630.

[8]. Guzman F, Cain N, Larscheid P, Hagen T, Cook J M, Sehweri M, Skolnick P, Paul S N, *J. Med.Chem*, 27, (5), 1984, 564-570.

[9]. Farzin D, Haghparast A, Motaman S, Baryar F, Mansouri N. Effects of harmane and other β-carbolines on apomorphine-induced licking behavior in rat. Pharmacol Biochem Behav.2011;98 (2):215–219. [PubMed] mao aor b

[10]. Yonezawa T, Hasegawa S, Asai M, Ninomiya T, Sasaki T, Cha BY, et al. et al. Harmine, a β-carboline alkaloid, inhibits osteoclast differentiation and bone resorption *in vitro* and *in vivo*. Eur J Pharmacol. 2011;650(2-3):511–518

[11]. Boger D L, Yasuda L, Mitseher, Drake S D, Ketos P A, *J. Med.Chem*, 30, (10), 1987, 1918-1928.

[12]. Fariza Hadjaz, Soizic Besret, Francoise Martin –Nizard, Said Vous, Sebastien Dilly, Nicolas Lebegue, Philippe Cgavatte, Patrick Duriez, Pascal Berthelot, Pascal Carato, *European j. med.chem,* 46, 2011, 2575-2585.

[13]. *Pictet, A.; Spengler, T. (1911). "Über die Bildung von Isochinolin-derivaten durch Einwirkung von Methylal auf Phenyl-äthylamin, Phenyl-alanin und Tyrosin". Berichte der deutschen chemischen Gesellschaft 44 (3): 2030–2036. doi:10.1002/cber.19110440309.*

[14]. Jump up^ *Whaley, W. M.; Govindachari, T. R. (1951). "The Pictet-Spengler synthesis of tetrahydroisoquinolines and related compounds".Org. React. 6: 74.*

[15]. Jump up^ *Hahn G., Ludewig H. (1934). "Synthese von Tetrahydro-harman-Derivaten unter physiologischen Bedingungen". Chemische Berichte 67 (12): 2033. doi:10.1002/cber.19340671221.*

[16]. Jump up^ *Nielsen, T. E.; Diness, F.; Meldal, M. (2003). "Solid-Phase Synthesis of Pyrroloisoquinolines via the Intramolecular N-Acyliminium Pictet-Spengler Reaction". Curr. Opin. Drug Discov. Devel. 6 (6): 801–814. PMID 14758752.*

[17]. Jump up^ *Nielsen, T. E.; Meldal, M. (2005). "Solid-Phase Synthesis of Pyrroloisoquinolines via the Intramolecular N-Acyliminium Pictet-Spengler Reaction". J. Comb. Chem. 7 (4): 599–610. doi:10.1021/cc050008a*

[18]. 13.Shashikant, Dighe, Sajid Khan, Isha Soni, Preeti Jain, Samriddhi Shukla, Rajeev Yadav, PratikSen, Sy ed M. Meeran, and Sanjay Batra, Synthesis of β-Carboline-Based N-Heterocyclic Carbenes and Their Antiproliferative and Antimetastatic Activities against Human Breast Cancer Cells . *Journal of Medicinal Chemistry,* 2015: *58* (8), 3485-3499

[19]. Cong Zheng, Yuanzhang Fang, Weiguang Tong, Synthesis and Biological Evaluation of Novel Tetrahydro-β-carboline Derivatives as Antitumor Growth and Metastasis Agents through Inhibiting the Transforming Growth Factor-β Signaling Pathway. *J. Med. Chem.*, 2014: *57* (3), pp 600–612.

[20]. Jahan B. Ghasemi and Valentin Davoudian, 3D-QSAR and Docking Studies of a Series of β-Carboline Derivatives as Antitumor Agents of PLK1. *Journal of Chemistry,* 2014.

[21]. . Han X, Zhang J, Guo L, Cao R, Li Y, Li N, Ma Q, Wu J, Wang Y, Si S , A series of beta-carboline derivatives inhibit the kinase activity of PLKs . Epub. 2012:7(10).

[22]. 17. Ravindra Kumar Chourasiya[a], Vishnukanth Mourya[b], Ram Kishore Agrawal, QSAR analysis for some β-carboline derivatives as anti-tumor. *Journal of Saudi Chemical Society,* 2012.

[23]. Li S, Yang B, Zhang Q, Zhang J, Wang J, Wu W, Synthesis and bioactivity of beta-carboline derivatives. *Nat Prod Commun*. 2010: 5(10), 1591-6.

[24]. Rongqin Sun,[a] Rui Liu,[a] Chi Zhou,[a] Zhenghua Ren,[b] Liang Guo,[c] Qin Ma,[c] Wenxi Fan,[c] Liqin Qiu,[a] Huijuan Yu,[a] Guang Shao*[a] and Rihui Cao* Synthesis and biological evaluation of piperazine group-linked bivalent β-carbolines as potential antitumor agents. *Med. Chem. Commun.*, 2015,6, 2170-2174

[25]. Koteppa Pari‡§, C. Sivakama Sundari‡, Sushil Chandani¶ and Dorairajan Balasubramanian¶ β-Carbolines That Accumulate in Human Tissues May Serve a Protective Role against Oxidative Stress. *The Journal of Biological Chemistry, 2000* , 275, *2455-2462.*

[26]. Takayuki Yonezawa Shin-ichi Hasegawa, Midori Asai,Tadashi Ninomiya,Toshinori Sasaki[c], Byung-Yoon Cha[b], Toshiaki Teruya, Harmine, a β-carboline alkaloid, inhibits osteoclast differentiation and bone resorption *in vitro* and *in vivo*. *European Journal of Pharmacology*, 2011: 650, ( 2–3), Pages 511–518.

[27]. Ahmed, Nermin S. . Gary, Bernard D, Piazza Gary A, Tinsley N, Heather, Laufer, Stefan, Abadi, Ashraf H, A Novel Access to Arylated and Heteroarylated Beta-Carboline Based PDE5 Inhibitors. *Medicinal Chemistry*, 2010: 6, pp.374-387.