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Research Article

In-silico binding approaches of β-carboline derivatives towards the possible antitumor targets

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ABSTRACT

β-Carboline moieties are important structural subunits which occur as components of many biologically interesting molecules for antitumor activity. The field of computer aided drug design and discovery (CADD) is a rapidly growing area that has seen many successes in the last few years. Through molecular docking, the binding mode and affinity of the protein-inhibitor complex formed is estimated which in turn helps in the discovery of new drug "Leads". The anticancer potential of β-Carboline analogues was proven by various targeted mechanisms. In this review, we summarise the binding mode and interactions of β-Carboline derivatives towards the various anticancer targets which advantages the discovery of this scaffold into antitumor therapy.

Keywords: β-Carboline; Antitumor; *In silico;* HTS; Hydrogen bonding; Hydrophobic.

INTRODUCTION

Carbolines are identified as most important heterocycle which own a common tricyclic pyrido[3,4-b]indole (Figure.1.) scaffold. Natural compounds and small molecule derivatives comprising carboline skeleton are of great Pharmaceutical interest due to their potent pharmacological activities such as neuroleptic, antihistaminic, antimuscarinic, antimalarial, anti-HIV, antibacterial, antiviral and antitumor (Ashok et al., 2014; Cao et al., 2007; Gao et al., 2014; Mele et al., 1988; Wang et al., 2007; Xiao et al., 2001; Yu et al., 2005). β–Carbolines were initially investigated for their effects on CNS. However, interests in these analogues were stimulated by their promising antitumor activities in the last decades.

β-Carbolines are initially discovered from the plant Pegnaum harmala, to exert their antitumor effects by intercalating into DNA. Subsequently, anticancer mode of action investigated by multiple mechanisms through several studies. Topoisomerase (Topo) I and II (Deveau et al., 2001), cyclin-dependent kinase (Li et al., 2007), mitogen activated protein kinase-activated protein kinase 2 (Nayana et al., 2009; Wu et al., 2007), polo-like kinase (Zhang et al., 2009), PIM kinases (Huber et al., 2012), Check point kinase-1 (Del Nagro et al., 2014), Haspin kinase (Cuny et al., 2012), kinesin-like protein Eg5 (Sunder-Plassmann et al., 2005) and I-Kappa-B kinase (Castro et al., 2003; Dung-Fang Lee and Mien-Chie Hung, 2008) were found to be the pharmacological targets of this class of compounds. A number of carboline derivatives have been designed and developed to target the ATP-binding domain of these proteins.

Herein, we summarize the current progress in understanding the *in silico* approach of carboline structure and its interactions into different protein targets which are involved in the cancer pathology. Our insights into the inhibitor-bound structures may be a valuable tool for emerging a new generation of carboline derivatives as an anticancer agent.s

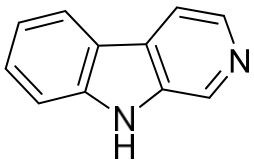

Figure 1: Structure of β–Carboline nucleus

DNA Intercalators

Most of the carboline analogues are reported as DNA intercalators due to the planar polyaromatic structure. It is easily inserted into the DNA base pairs and act through the inhibition of topoisomerase. Deveau group were synthesised amino acids functionalizing β-carboline derivatives which were structurally related with Azatoxin and Tryptostatins, the known Topo-II

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inhibitors. The compounds with tryptophan and phenylalanine exhibited significant growth inhibitory activity in lung (H520) and prostate (PC3) cancer cell lines and inhibited the topo-II mediated DNA relaxation (Deveau et al., 2001). In another study, the same group also reported that the diketopiperazine based carboline homodimers exhibited the anticancer potential in H520 and PC3 cell lines comparable to clinically approved etoposide. They concluded that the stereochemistry imparted from L-tryptophan and the hydroxyl substituents at 4 and 4' position are necessary for the anticancer potential in the homodimer class (Deveau et al., 2008).

NAD(P)H:quinone oxidoreductase (NQO1)

NQO1 is an obligate two-electron donating enzyme that reduces a number of quinones either in bioactivation or bioprotection. It contains 2 closely related monomers of 273 aminoacid residues, each containing FAD cofactor which required for NQO1 enzymatic activity. High levels of NQO1 activity and mRNA content was observed in primary solid tumors suggested that antitumor compounds that are bioactivated by NQO1 may be selectively toxic to those tumors (Gutierrez, 2000). The human NQO1 crystal structure has revealed that, each monomer is composed of a major catalytic (1-220 residues) and a small C-terminal (221-273 residues) domain. The larger number of quinone structures were accommodated and bound in the hydrophobic and plastic pocket of the active site through three H-bonding residues namely Tyr126, Tyr128 & His161. NQO1 promotes a ping-pong mechanism, (two-electron reduction) by transferring a hydride ion from NAD(P)H to the N5 of FAD which followed by the release of NAD(P)+ in the first half and the remaining half of the reaction, the hydride donation was done from the N5 of FAD to the hydride-acceptor substrate followed by hydroquinone release. The lasting proton was delivered by Tyr126, Tyr128, or His161 (Asher et al., 2006; Gutierrez, 2000).

Hassani group reported some novel Lavendamycin analogues which have carboline nucleus with quinione ring structure as potential NQO1-directed antitumor agents. The $-NH_2$ and CH_2OH substitution enhances the substrate specificity. Stearic effects of these compounds played an important role in the NQO1 active site rather than the electronic effects. The best substrate model (compound 37) was capable of producing efficient H-bond interactions with His161, Tyr126 & Tyr128 of the active site along with hydride ion reception of NQO1 (Hassani et al., 2005) (Figure 2).

Pim kinase

Pim kinases (oncogenes) are the attractive drug targets and mainly expressed in hematological and solid cancers. It regulates the signalling pathways that are essential for tumorigenesis. Pim kinases are auto-activated and do not depend on post-translational modifications (Bachmann and Möröy, 2005). It has unique structural feature by the presence of Pro123 in its hinge region. Pim kinase activity involved in the growth and survival of tumor cells through interaction and regulation of c-Myc, Histone H3, 4E-BP1 and Bad protein. Currently, two approaches have been mainly employed in designing Pim kinase inhibitors: ATP-mimetics and non-ATP mimetics; however, most of the inhibitors targets ATP-binding pocket in a competitive manner (Ogawa et al., 2012; Tursynbay et al., 2015).

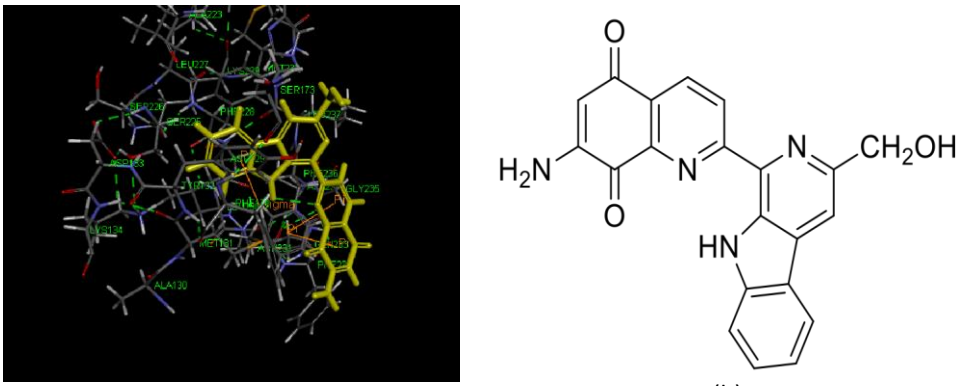
Kilian Huber group developed a series of substituted 7,8-dichloro-1-oxo-β-carbolines as a novel class of potent and selective Pim kinase inhibitors. These compounds do not rely on canonical ATP-mimetic hinge interactions. Interestingly, co-crystal structures (3CXW and 3CY2) revealed that the compound bound to the ATP binding pocket with an unusual binding mode and did not form direct H-bond interactions with hinge. But the hydrophobic dichlorobenzene ring is oriented and interacted with the kinase hinge backbone residues. Spiropiperidine nitrogen atom formed bidentate hydrogen bond interaction with Asn172 and Asp186 of the protein structure (Figure 3a.). The cross reactivities of the screened inhibitors were limited over the large kinase panel due to the distinct binding nature (Huber et al., 2012).

Kinesin Spindle Protein (KSP) Eg5

KSP is a member of the Kinesin family which play crucial role in cell cycle and apoptosis induction. KSP mainly involved in the early stage of mitosis and mediates centrosome separation. It has main role in the formation of bipolar spindle. KSP inhibition leads to mitotic arrest with monoastral microtubule array which cause cell death (Zhang and Xu, 2008). Barsanti group discovered some tetrahydro-β-carboline analogs as KSP inhibitors which bound to Eg5 in motor domain of an allosteric L5 binding pocket (Barsanti et al., 2010). A strong hydrogen bond interaction was observed between the phenolic –OH and Glu118 backbone. Additional hydrogen bond was found between the carboline –NH and amide carbonyl of Glu116 has shown in the Figure 3b. Based on this investigation, Fei Liu group developed series of tetrahydro-β-carboline analogs as mitotic KSP inhibitors with an IC50 >1 μM (Liu et al., 2010).

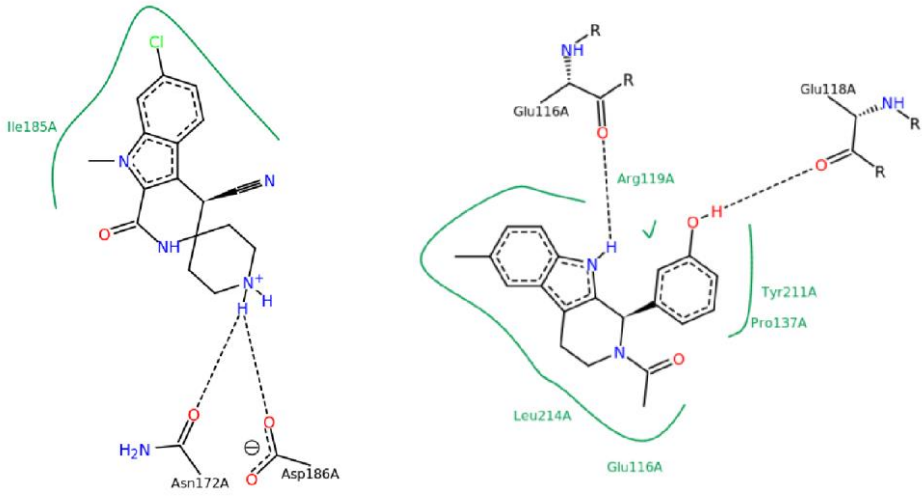
Polo-like kinases-1 (PLK-1)

PLKs, are belongs to serine/threonine kinase class. PLK1 is considered as attractive mitotic target for anticancer drugs and its expression was mainly found during late G2 and M phases. PLK-1 plays important role in the cyclin B1 degradation and proper assembly of mitotic spindle (Llamazares et al., 1991; Takai et al., 2005). Zhang group reported DH166, a β-carboline derivative competitively inhibited the PLK1 kinase activity at sub micromolar concentration in an ATP-binding domain. The docking studies have shown the deep penetration of DH166 into the kinase domain. The methoxy group of DH166 formed hydrogen bond to the nitrogen atom of



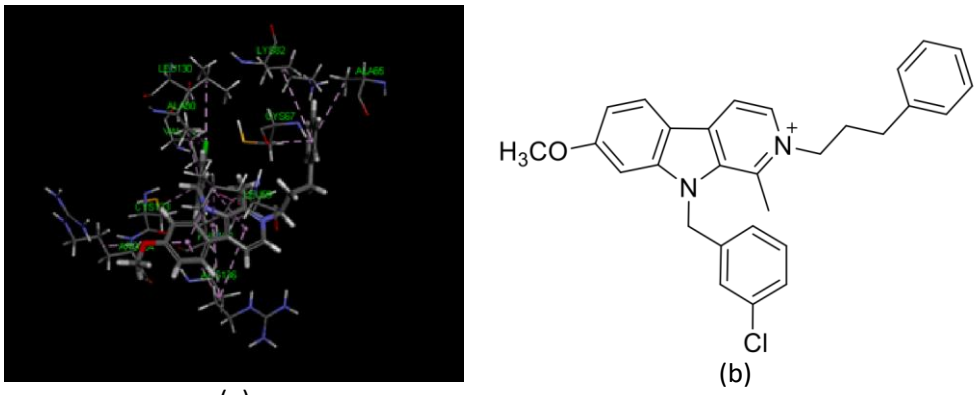
(a) (b)

Figure 2: a) Interactions between the inhibitor (Compound 37) and target protein NQO1 (PDB id-1H69); b) Structure of the β–carboline derivative (Compound 37).



(a) (b)

Figure 3: a) Ligand (7,8-dichloro-1-oxo-β-carboline) interacted into the ATP binding pocket of Pim kinase. PDB id: 3CY2); b) Ligand (3-[(1R)-2-acetyl-6-methyl-2,3,4,9-tetrahydro-1H-β-carbolin-1-yl]phenol) interacted into an allosteric binding pocket of KSP-Eg5.



(a) (b)

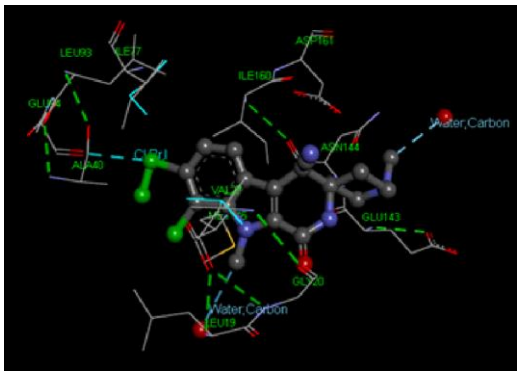
Figure 4: a) Interactions between the inhibitor (DH116) and target protein PLK-1 (PDB id-2OWB); b) Structure of the β–carboline derivative DH116.

Lys82. The carboline nucleus interacted with the Phe183 of the PLK1 through π-π

stacking (Zhang et al., 2009) (Figure 4).

Haspin kinase

Haspin kinase belongs to Serine/Threonine kinase family considered as a possible anticancer target. It has involved in mitotic function in cell cycle where it phosphorylated the Thr-3 of histone H3 protein thereby



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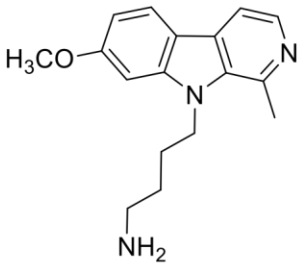
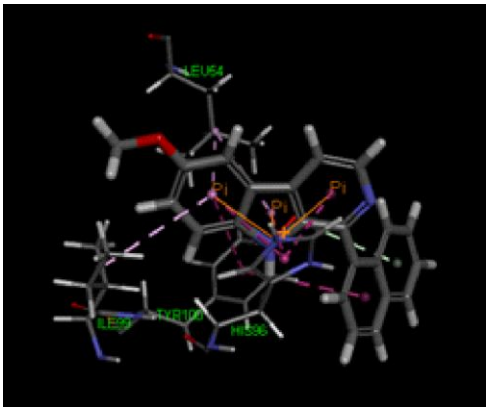


(b)

Figure 5: a) Interactions between the inhibitor and target protein haspin (PDB id-3DLZ); b) Structure of the β–carboline derivative (Compound 9a).



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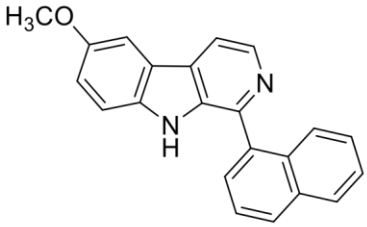

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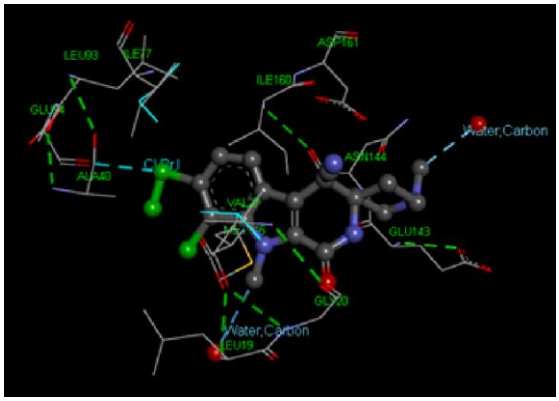
Figure 6: a) Interactions between the inhibitor SP-141 and target protein haspin (PDB id-4ERE); b) Structure of the SP-141



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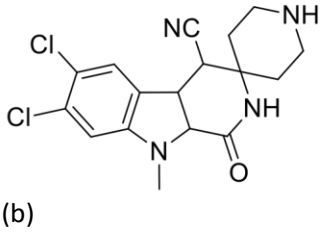

(b)

Figure 7: a) Ligand (7,8-dichloro-1-oxo-β-carboline) interacted into the ATP binding pocket of DAPK3 kinase. PDB id: 3BHY); b) Structure of 7,8-dichloro-1-oxo-β-carboline

regulated the chromosome segregation. Depletion of haspin caused the alignment defects and mitosis failure (Dai et al., 2009, 2005). Human haspin has similar bilobate structure like other eukaryotic protein kinase family members with some exceptions. A conserved glutamate which is important for catalysis was present in the alpha C helix, adopts final active conformation within the small kinase domain. It is packed in between an alpha helical insertion (kinase domain), and the activation segment, which adopts an unprecedented conformation. The activation segment does not contain any phosphorylatable residues and significantly extruded from the core of the fold, it forms an extensive plateau, hosting several residues implicated in substrate binding. Haspin kinase structure reveals an active conformation that is controlled by substrate recognition and phosphorylation in the absence of external regulators (Eswaran et al., 2009; Villa et al., 2009)

Cuny group has performed HTS of 140000 compounds and identified harmine and harmalol, the β-carboline alkaloids have moderate inhibitory activity on haspin

kinase. Then they designed a series of β-carboline analogues based on structure-activity relationship study of an acridine series reported as haspin inhibitors and did their docking studies. The compounds (9a and 9b) that substituted with alkylamine at N-9 position of harmine formed hydrogen bond with Asp687 and Gly608 (Cuny et al., 2012) (Figure 5).

Mouse Double Minute 2 (MDM2)

MDM2 is an oncogene, overexpressed in a number of human malignancies, including Triple negative breast cancer (Zhang and Wang, 2000). MDM2 protein overexpression is well correlated with decreased survival in cancer patients. It is a negative regulator of the tumour suppressor p53 and also affecting both pro- and anti-apoptotic proteins, leads to apoptosis inhibition. In addition to this, MDM2 alters cell cycle regulation, DNA replication and DNA repair (Rayburn et al., 2009; Shangary and Wang, 2008).

Wei Wang group identified SP-141 is a specific inhibitor of MDM2, by performing HTS. Further, they have carried out the molecular modelling study of SP-141 using crystal structure of MDM2. SP-141 occupied the Leu26 binding pocket and formed a H-bond with Tyr67. The naphthyl group substituted at C-1 position of SP-141 bound in the hydrophobic pocket which was formed by Leu54, Ile99, Tyr100 and Ile103 of MDM2 (Wang et al., 2014) (Figure 6).

Death associated protein kinase-3 (DAPK3)

DAPK3 belongs to CAMK family and that have been involved in variation of cell death signalling pathways. Huber group reported that the 7,8-dichloro-1-oxo-β-carboline derivative bound with DAPK3 in a different approach when compared to other kinase. In the DAPK3 – carboline derivative (compound 17) complex, the lactam carbonyl group established a hydrogen bond interaction with a water molecule in the active site. The spiropiperidine ring was little more twisted and not participated in any polar interactions. The complex ligand also benefited some hydrophobic interactions with the gatekeeper (Leu93) and an isoleucine (Ile160) residue. The halogen bonds between the 7,8-dichloro substituents in this structure was established interaction with the backbone carbonyl of Glu94 and Val96 (Huber et al., 2012) (Figure 7).

CONCLUSION

We have enumerated the various target proteins such as DNA, NQO1, PIM, PLK, KSP, haspin kinase, MDM2 and DAPK3 which efficiently bind with β-carboline analogues. We have also specified the different binding patterns between the β-carboline analogues and these proteins. Based on this perception, it has been concluded that there is a strong opportunities for this scaffold & its analogues would emerge as lead molecules for cancer therapeutics.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding the content of this article.

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