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EDITED BY

Ghasem Sargazi,
Bam University of Medical Sciences and
Health Services, Iran

REVIEWED BY

Mohammadreza Moghaddam-manesh,
Standard research institute of iran, Iran
Daryoush,
Graduate University of Advanced
Technology, Iran
Abdolali Golpayegani,
Bam University of Medical Sciences and
Health Services, Iran

*CORRESPONDENCE

Yan Li,
Liyang6709@163.com

[†]These authors share first authorship

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Comprehensive review of α -carboline alkaloids: Natural products, updated synthesis, and biological activities

Deping Li^{1,2}, Renze Yang^{1†}, Jun Wu¹, Bin Zhong^{1,2} and Yan Li^{1*}

¹Department of Pharmacy, First Affiliated Hospital of Gannan Medical University, Ganzhou, China,

²Ganzhou Key Laboratory of Immunotherapeutic Drugs Developing for Childhood Leukemia, First Affiliated Hospital of Gannan Medical University, Ganzhou, China

α -carboline (9*H*-pyrido[2,3-*b*]indole), contains a pyridine ring fused with an indole backbone, is a promising scaffold for medicinal chemistry. In recent decades, accumulating evidence shows that α -carboline natural products and their derivatives possess diverse bioactivities. However, hitherto, there is no comprehensive review to systematically summarize this important class of alkaloids. In this perspective, this paper represents the first review to provide a comprehensive description of α -carbolines including natural products, updated literature of synthesis, and their diverse biological activities. Their biological activities including antitumor, anti-microbial, anti-Alzheimer's disease, anti-atherosclerosis, and antioxidant activities were highlighted. And the targets and the main structure activity relationships (SARs) will be presented. Finally, challenges and future directions of this class of compounds will be discussed. This review will be helpful in understanding and encouraging further exploration for this group of alkaloids.

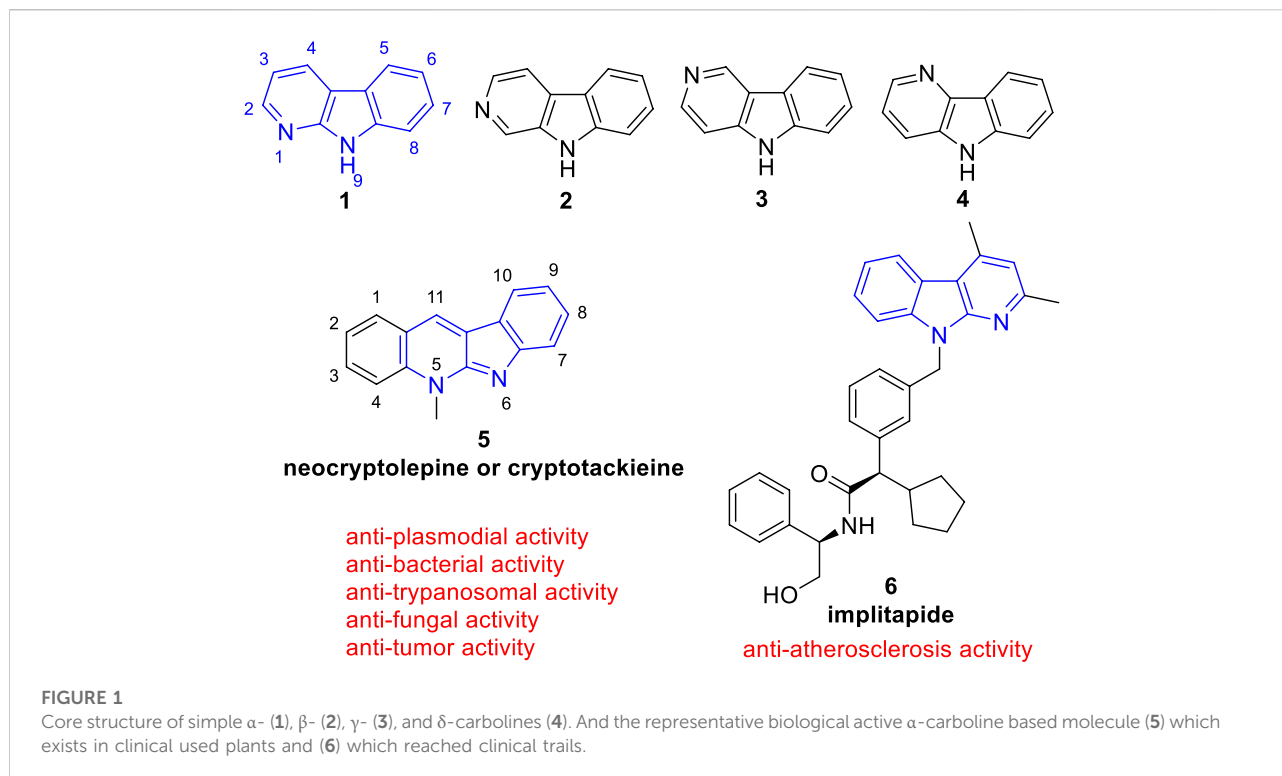
KEYWORDS

α -carboline, neocryptolepine, indolo[2,3-*b*]quinoline, biological activity, alkaloids

1 Introduction

Since the structural diversity and wide range of biological activities, carbolines are among the most attractive alkaloids. According to the position of the pyridine nitrogen atom relative to the indole ring, carbolines are classified as α - (1), β - (2), γ - (3), or δ -carbolines (4) (Figure 1) (Dai et al., 2018). Among them, α -carboline (9*H*-pyrido[2,3-*b*]indole, 1), contains a pyridine ring fused with an indole backbone, has attracted renewed

Abbreviations: A β , amyloid β -protein; AchE, acetylcholinesterase; AD, Alzheimer's disease; ALK, Anaplastic Lymphoma Kinase; BuChE, butyrylcholinesterase; ACTs, artemisinin-based combination therapies; Brk, breast tumor kinase; DiMIQ, 5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline; DPPH, 2,2-Diphenyl-1-picrylhydrazyl; ED50, 50% effective dose; IC50, 50% inhibition concentration; ID50, 50% infective dose; LDL, low-density lipoprotein; MDR, Multidrug resistance; MIC, Minimum inhibitory concentration; MTP, microsomal triglyceride transfer protein; PARP, poly ADP ribose polymerase; RaL α , ras-related protein; SAR, structure activity relationship; SI, select index; Top, topoisomerase; VLDL, very low-density lipoprotein; WHHL, Watanabe heritable hyperlipidemic.

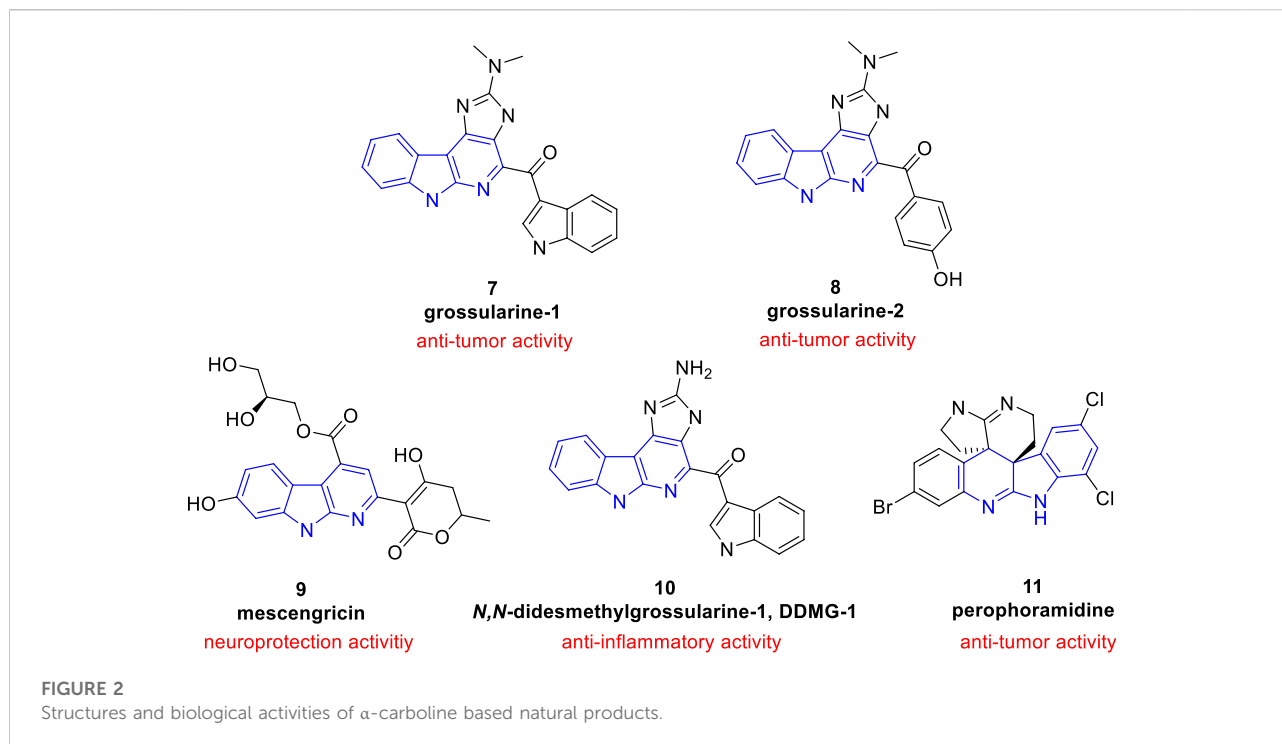


attention due to α -carboline based molecules have been successively reported with diverse biological activities including anti-tumor (Pattey and Guyot, 1989), anti-plasmodial (Sharaf et al., 1996), anti-bacterial (Cimanga et al., 1998), anti-fungal (Cimanga et al., 1998), anti-trypanosomal (Jonckers et al., 2002), anti-Alzheimer's disease (Wang et al., 2017), anti-atherosclerosis (Ueshima et al., 2005), anti-inflammatory (Oda et al., 2009), and neuroprotection activity (Kim et al., 1997).

The classical use of α -carboline alkaloids is that, the African medicinal plant *Cryptolepis sanguinolenta* (Lindl.) Schlechter (Periplocaceae), containing a biological active α -carboline based molecule (neocryptolepine or cryptotackieine, 5), has long been used in the treatment of malaria, amoebiasis, fever, and other infectious diseases (Cimanga et al., 1996; Sharaf et al., 1996) (Figure 1). Nowadays, more and more studies have been conducted to modify the structure of α -carboline natural products or the bare α -carboline scaffold to obtain derivatives with better activity. Notably, implitapide (a molecule containing α -carboline moiety, 6) has reached clinical trails as an microsomal triglyceride transfer protein (MTP) inhibitor to reduce the progression of atherosclerosis (Ueshima et al., 2005) (Figure 1). Growing bodies of evidence suggests that α -carboline is a promising scaffold in medicinal chemistry for drug discovery.

However, to the best of our knowledge, there is no review on this important class of alkaloids except Wadsworth et al.

just reviewed their synthesis in 2015 (Wadsworth et al., 2015). In this perspective, this article aims to provide a comprehensive description of α -carbolines including the natural products, the updated literature of synthesis, and the diverse biological activities of synthetic derivatives, which represents the first comprehensive review of this group of alkaloids. The main contents of this review are as follows: 1) In the first section, α -carboline natural products and their biological activities will be described. 2) Since there was a review of synthesis reported in 2015, updated literature of synthesis will be briefly given in the second section according to the reaction type and the publication date. 3) In the third section, the wide range of biological activities of synthetic α -carboline derivatives will be highlighted according to diseases, targets, research groups, and publication date. In order to better understand the context of the research, literature was first categorized by diseases/targets, then categorized by research groups. In each target/research group section, the logical sequence order was arranged by time. In case where adequate information is available, the structure activity relationships (SARs) of bioactivity will be presented. 4) Finally, challenges and future directions of this class of compounds will be discussed based on our expertise in this field (Liu et al., 2021; Li et al., 2022; Liu et al., 2022; Tian et al., 2022) and carefully analysis of related literature. This work will provide inspiration and encourage further exploration for this group of alkaloids.



2 Natural occurring α -carbolines

In comparison with other classes of carbolines (especially the renowned β -carbolines), α -carbolines are less presented in natural products. Only limited isolated natural products containing α -carboline skeleton were found (Figure 2).

Grossularine-1 (7) and grossularine-2 (8), isolated from the tunicate *sendrodoea grossularia*, were the first examples of naturally occurring α -carbolines. These two compounds were first found to exhibit striking cytotoxicity toward human and murine tumor cells (Pattey and Guyot, 1989).

Neocryptolepine (also known as Cryptotackieine, 5) possesses a linear indolo[2, 3-*b*]quinoline system or a chromophore of α -carboline fused with a benzene ring from another point of view, was isolated from the extract of root bark of African medicinal plant *Cryptolepis sanguinolenta* (Lindl.) Schlechter (Periplocaceae), which is a climbing liana from West and Central Africa used by traditional therapists in the treatment of malaria, amoebiasis, fever, and other infectious diseases (Cimanga et al., 1996; Sharaf et al., 1996). Further research showed 5 exhibited cytotoxicity and anti-plasmodial activity. Thus, as a promising natural product, literature about 5 and its derivatives is emerging (Lavrado et al., 2010; Wang et al., 2019; Nuthakki et al., 2022).

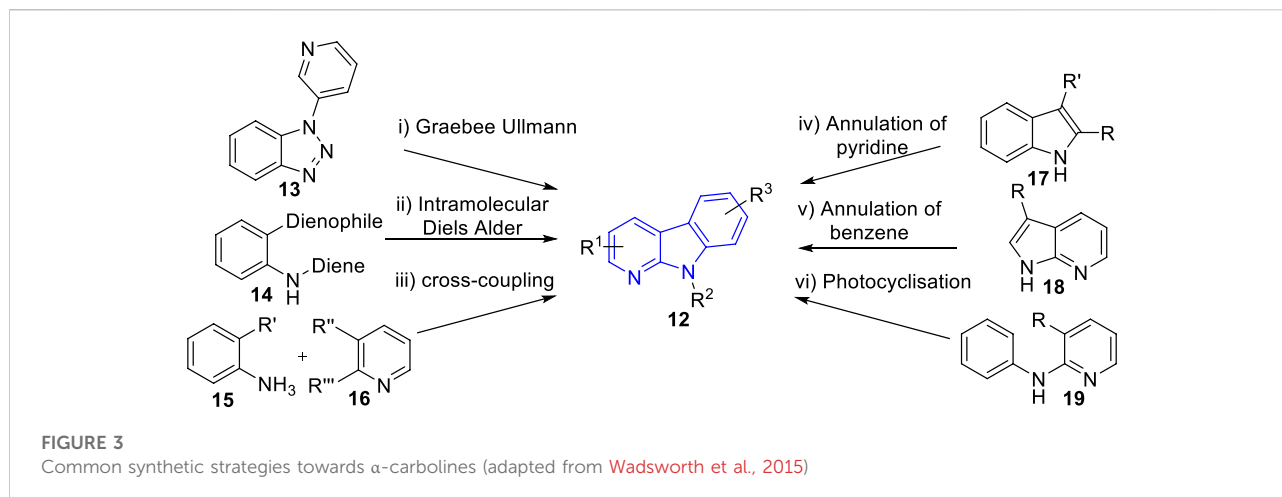
Mescengricin (9) was firstly isolated from *streptomyces griseoflavus* 2853-SVS4 as a neuronal cell protecting component (Kim et al., 1997). It possesses an α -

carboline skeleton substituted with a hydroxy, a glycerol-ester, and a hydroxydihydropyrone. In the process of screening neuronal cell protecting substances, it was found to protect chick primary mesencephalic neurons from L-glutamate toxicity with an EC_{50} value of 6.0 nM (Shin et al., 2000).

N,N-Didesmethylgrossularine-1 (DDMG-1, 10) was isolated from *Polycarpa aurata* (an Indonesian ascidian). Pharmacological experiment showed that it inhibited the mRNA of TNF- α and I κ B- α degradation and inhibited NF- κ B binding to DNA site in LPS-stimulated RAW 264.7 cells. Moreover, it also inhibited the production of IL-8. These research suggested that 10 was a promising lead compound to treat chronic inflammatory diseases (Oda et al., 2009).

Perophoramidine (11), a polycyclic alkaloid containing an α -carboline moiety, was isolated from *Perophora namei* (a Philippine ascidian). It showed cytotoxicity against HCT116 cell line with an IC_{50} value of 60 μ M and induced cells apoptosis via poly ADP ribose polymerase (PARP) cleavage within 24 h (Verbitski et al., 2002).

Kapakahines (structures not shown), a large family of cyclic peptides containing an α -carboline skeleton, were isolated from *Cribrochalina olemda* (marine sponge) (Yeung et al., 1996; Nakao et al., 2003). They were often studied as fluorescently labeled chemical probes (Rocha et al., 2015; Kamihira and Nakao, 2021) or anti-malarial agents (Goto et al., 2021).



3 General synthetic strategies and advanced synthetic literature of α -carbolines

Due to the wide range of biological activities presented by α -carboline natural products and their derivatives, interest in their synthesis has arisen. In 2015, Wadsworth et al. (Wadsworth et al., 2015) summarized the synthetic strategies towards α -carbolines, which including modified Graebbe Ullmann method, Diels Alder method, transition metal catalysed of cross-coupling method, annulation of pyridine to indole derivatives method, annulation of benzene ring method, and photocyclisation of anilinopyridines method (Figure 3). As far as we know, there has been no novel strategy for α -carbolines since then on. Here, we just summarized the representative literature on their synthesis since 2015.

3.1 Cross-coupling strategy

Using a palladium-catalyzed Ullmann cross-coupling protocol, Yan *et al.* reported a unified approach to obtain the four isomeric carbolines **1**, **2**, **3**, **4** (Yan et al., 2017) (Supplementary Scheme S1). The pivotal steps associated with the unified approach were the palladium-catalyzed Ullmann cross-coupling of 2-iodocyclohex-2-en-1-one (**20**) with the pertinent halogenated nitropyridine (**21**, **24**, **27**, **30**) and the reductive cyclization of the consequential 2-pyridylcyclohex-2-en-1-one (**22**, **25**, **28**, **31**) to give the corresponding 6,7,8,9-tetrahydrocarboline (**23**, **26**, **29**, **32**). Oxidation of these tetrahydro compounds to their fully aromatic analogues (*viz.*, the carbolines **1**, **2**, **3**, **4**) was easily achieved using 10 wt % palladium on carbon. And this unified approach not only could be used to synthesis core structures of **1**, **2**, **3**, **4**, but also their substituted derivatives, such as harman. While, this protocol was

limited by metal catalysis strategy and inflexibility with regard to substituents.

3.2 Annulation strategy

Using a transition metal catalysis strategy, Medas and co-workers reported two new methods to afford annulated 2-aryl- α -carboline heterocycles (Medas et al., 2020). The first linear method was described that Rh(I) catalysis was used to form the α -carboline skeleton by [2 + 2 + 2] cyclotrimerization. The second tandem catalytic method stated that using Pd(II) catalyst and mediating a Sonogashira reaction with a [2 + 2 + 2] cyclotrimerization in the same reaction flask to afford the same target molecules (Supplementary Scheme S2).

Through annulation of pyridine ring strategy, Debnath *et al.* reported an α -carbolines synthesis method (Debnath et al., 2021) (Supplementary Scheme S3). Using 2-sulfonamidoindoles (**42**) reaction with acetoxy allenates (**43**) under phosphine catalysis to afford dihydro- α -carboline and α -carboline scaffolds. At 25°C (room temperature), dihydro- α -carboline structures were achieved exclusively through key reactions of Michael addition, 1,4-proton shift, isomerization, 1,2-proton transfer, phosphine elimination, and aza-Michael addition. At 80°C (higher temperature), α -carboline motifs were achieved *via* key steps of addition-elimination, aza-Claisen rearrangement, tosyl migration, and aromatization.

Although a broad array of strategies for the synthesis of α -carbolines were described, many of them are limited by low yields, expensive reagents (such as metal catalysis strategy), starting materials which are difficult to obtain, or inflexibility with regard to substituents. Therefore, novel synthetic strategies of this class of compounds still needs to be explored.

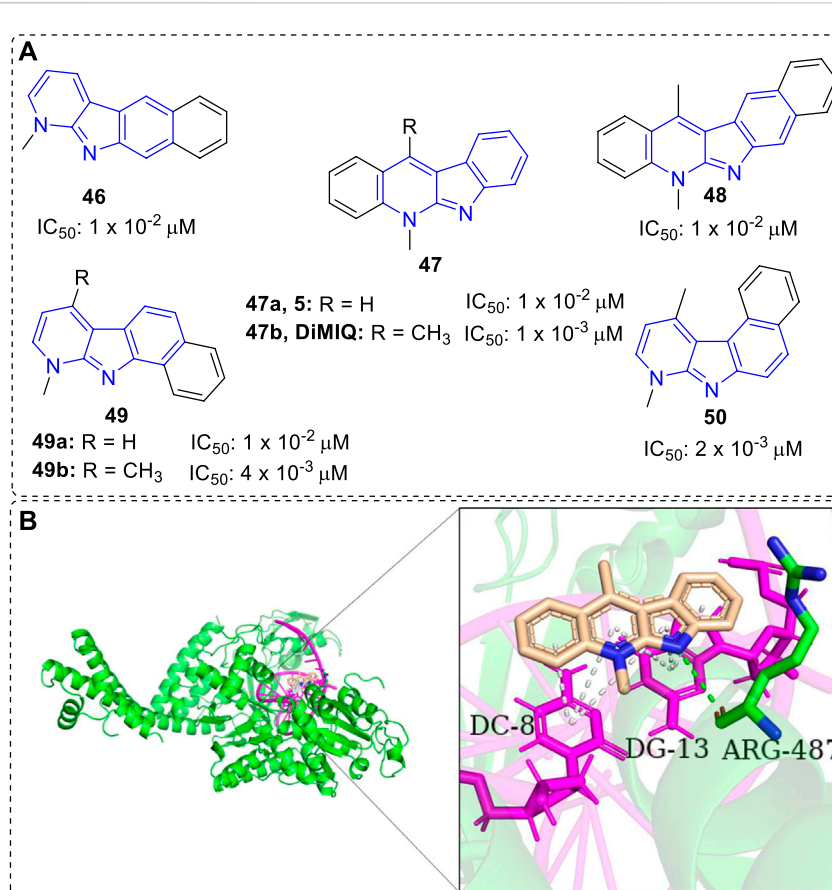


FIGURE 4

(A) Structures and bioactivity of compounds 46–50 with various shapes and sizes. IC_{50} values were tested *in vitro* against KB cells. (B) DiMIQ (47b) in the active site of Top II α complexed with DNA (PDB code: 5GWK). 47b is represented in stick model, carbons in 47b are colored wheat, DNA is colored magenta, ARG-487 residue of Top II α is colored green and labeled. Hydrogen bond is presented as green dash line. π - π interactions are presented as white dash lines.

4 Biological activities

4.1 Antitumor activity

According to the Global Cancer Statistics 2020, cancer is a leading cause of death and an big impediment to increase life expectancy in each country of the world. Worldwide, a predicted 19.3 million new cancer cases and approximated 10.0 million cancer deaths occurred in 2020 (Sung et al., 2021). Undoubtedly, it is imperative to design efficient drugs for the treatment of this disease. Based on its pathogenesis, many targets have been shown to be useful for tumor therapy, which include topoisomerase (Top) (Liang et al., 2019), aurora kinases (Pradhan et al., 2021), breast tumor kinase (Brk) (Tsui and Miller, 2015), microtubule (Kaur et al., 2014) and ras-related protein (RalA) (Fan et al., 2021), etc. Different structures of α -carboline derivatives have been designed and synthesized to regulate these targets.

4.1.1 DNA intercalators/top II inhibitors

Kaczmarek and co-workers have devoted themselves to the research of α -carbolines since 1870s, but until 1992, they demonstrated 5,11-dimethy-5*H*-indolo[2,3-*b*]quinoline (DiMIQ, 47b), a synthetic analog of 5, was a DNA intercalator and Top II inhibitor (Figure 4). It was able to stabilize the Top II-DNA cleavable complex *in vitro* (Pognan et al., 1992). In addition, docking study vividly illustrated that 47b was intercalated between the base pairs of DNA. There were hydrogen-bonding interaction formed between ARG-487 residue of Top II and indolic N-H of DiMIQ, and π - π interactions formed between DC-8/DG-13 of DNA and aromatic rings of 47b (Figure 4B). Therefore, indolo[2,3-*b*]quinolines, containing an α -carboline moiety from another point of view, had been proved as a new family of the DNA intercalators and Top II inhibitors. In this regard, the studies of indolo[2,3-*b*]quinolines with anti-tumor activity before and after 1992 would be displayed in this section.

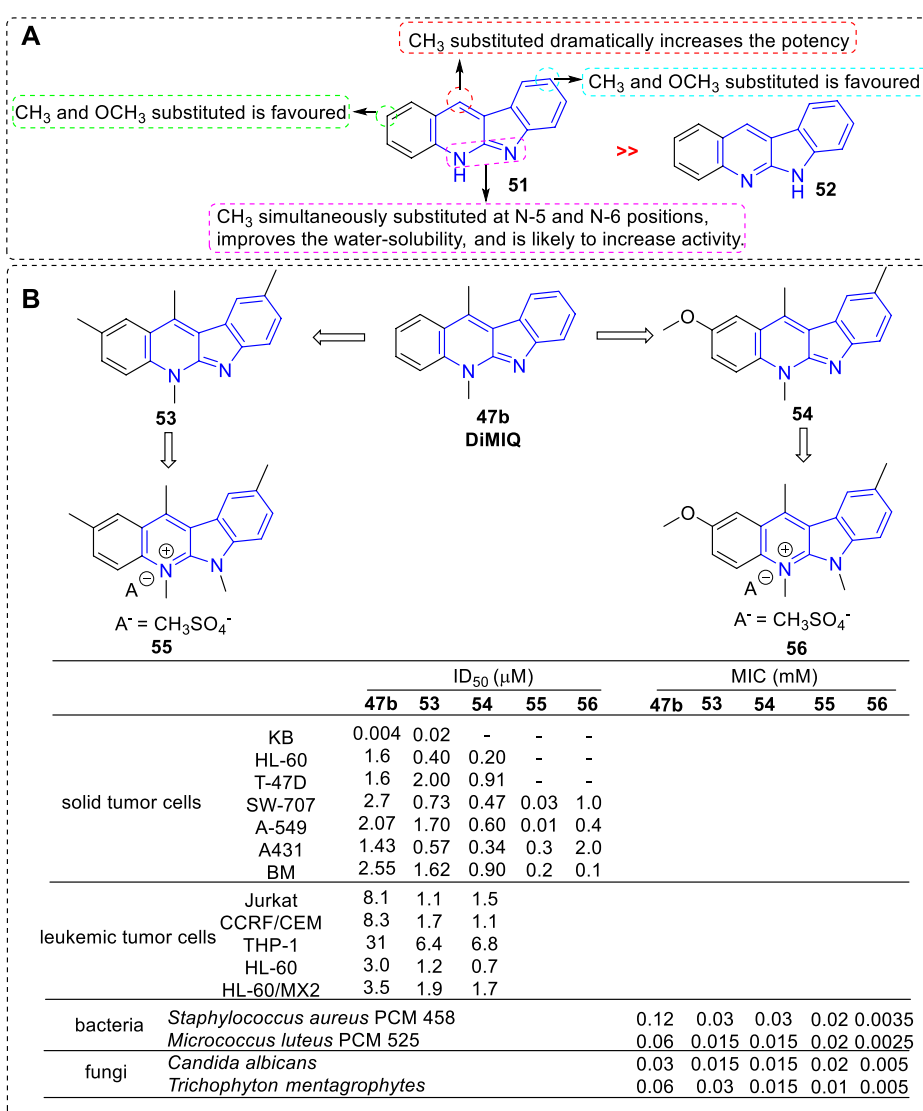


FIGURE 5

(A) SARs of 5*H*- and 6*H*-indolo[2,3-*b*]quinolines; (B) Structures and bioactivity of the representative compounds 53–56.

Early in 1988, certain tetra- or pentacyclic benzo-iso- α -carboline system of compounds were synthesized and their anti-tumor properties were evaluated by the research team of Kaczmarek (Kaczmarek et al., 1988a). The results clearly showed that the size and shape of the molecules (46–50) considerably influenced their bioactivity (Figure 4A). Among them, 47b, an analog of neocryptolepine (5), with a linear, tetracyclic moiety simultaneously bearing two methyl groups at N-5 and C-11 positions was the highest cytotoxicity compound. Further investigations showed it could significantly inhibit tumor growth *in vivo* against mice leukemias P388 and mice melanoma B16. Thus, modification of 47b has been a hot topic of research due to its anti-tumor activity.

In 1994, the biological activity of 5*H*- and 6*H*-indolo[2,3-*b*]quinolines were compared in the furtherance of SAR study (Czoch et al., 1994) (Figure 5). The results showed that all compounds belonging to the 5*H* series (e.g., 51), i.e., bearing a methyl on the pyridine nitrogen atom, displayed marked cytotoxicity against KB cells with IC₅₀ values in the range of 2×10^{-3} to 9×10^{-3} μ M. They stimulated the formation of Top II mediated DNA cleavage at concentration of 0.4–10 μ M. While, the compounds belonging to the 6*H* series (e.g., 52), i.e., lacking a methyl on the pyridine nitrogen atom, were less active in analogous tests compared with the 5*H* series. The reason may be that 5*H* series were partially protonated at pH value of 7.4 (physiological condition) and at low pH values these compounds

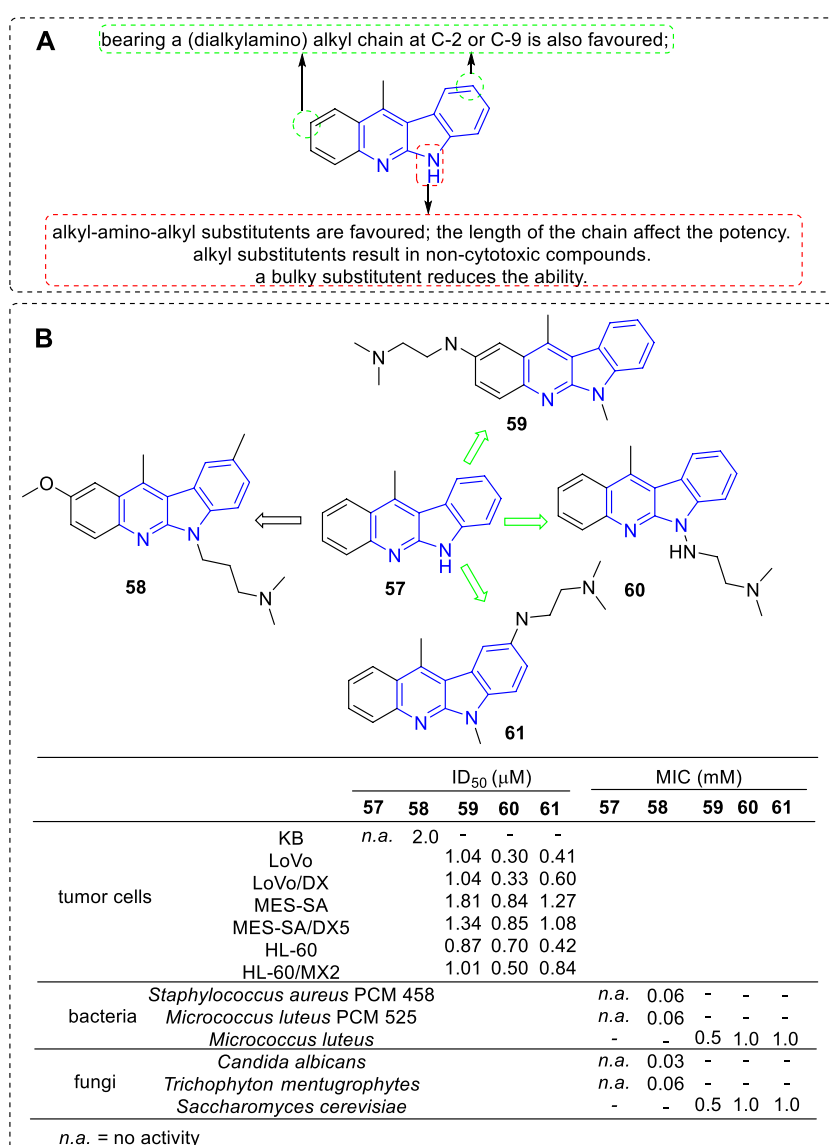
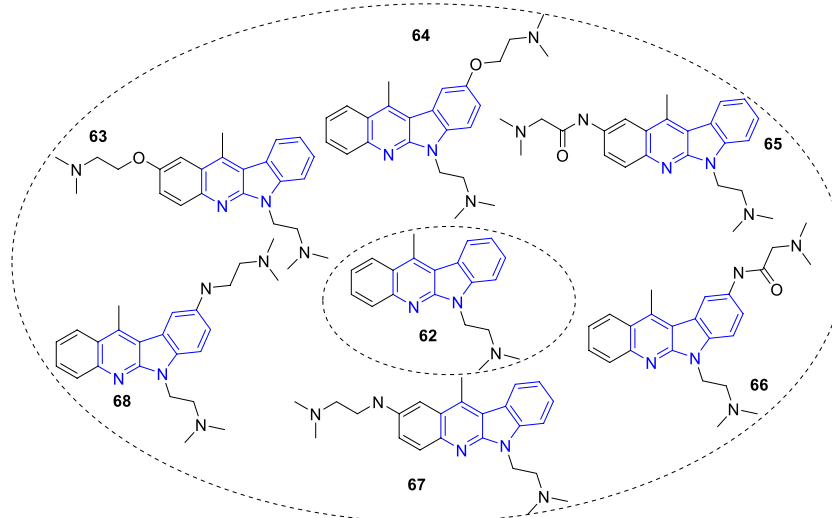


FIGURE 6

(A) SARs of 11-methylated 6H series compounds; (B) Structures and bioactivity of the representative compounds 57–61.

occurred in the form of salts, which result in a better water solubility. Among them, the most potent compound was 53 with two methyl groups substituted at C-2 and C-9 positions. Further, other analogs bearing methoxy groups at C-2 and/or C-9 positions were synthesized (Kaczmarek et al., 1999). The cytotoxicity were slightly improved in the compounds which bearing a methoxy group, or two methoxy groups at C-2 and C-9 positions compared with that of 47b. The most potent compound was 54 bearing a methoxy substituted at C-2 position and a methyl substituted at C-9 position. Later, these compounds were tested for their cytotoxicity against a panel of leukemic cell lines, and a subline HL-60/MX2 with reduced expression of Top II

(Humeniuk et al., 2002). The results illustrated that all tested compounds possessed cytotoxicity toward these leukemic cell lines and their cytotoxicity relied on the substituents introduced to the indolo[2,3-*b*]quinoline core. Interestingly, THP-1 and HL-60/MX2 cell lines, resistant to etoposide (a reference Top II inhibitor), were susceptible to methoxy- and methyl-substituted derivatives, which suggested that Top II may not be the only target for this class of analogs. In 1998, in order to increase the water solubility, new members of indolo[2,3-*b*]quinoline simultaneously bearing methyl groups at N-5 and N-6 positions were prepared and their cytotoxicity were evaluated (Kaczmarek et al., 1998b). As a result, all obtained derivatives



		IC ₅₀ (μM)						
		62	63	64	65	66	67	68
parent tumor cells	KB	6.0	0.08	0.31	0.15	0.15	0.64	0.36
	A549	-	0.19	0.32	0.24	0.81	0.17	0.29
	MCF-7	-	0.66	0.81	0.38	0.79	0.47	0.99
	Hs294T	-	0.76	0.91	0.62	0.64	0.35	0.72
	LoVo	-	0.64	0.64	0.33	0.60	0.12	0.27
	MES-SA	-	0.08	0.13	0.10	0.09	0.05	0.10
multidrug resistant tumor cells	HL-60	-	0.04	0.13	0.06	0.22	0.09	0.13
	LoVo/DX	-	0.15	0.21	0.11	0.14	0.10	0.39
	MES-SA/DX5	-	0.07	0.08	0.07	0.09	0.08	0.09
normal cell	HL-60/MX2	-	0.32	0.51	0.57	0.47	0.05	0.61
	BALB/3T3	-	0.57	0.74	0.31	0.67	0.34	0.60

FIGURE 7

Structure and bioactivity of derivatives (62–68) which N-6 fixed an (dimethylamino) ethyl chain, C-2 or C-9 linked another (dimethylamino) ethyl chain by amide, ether or amine bond.

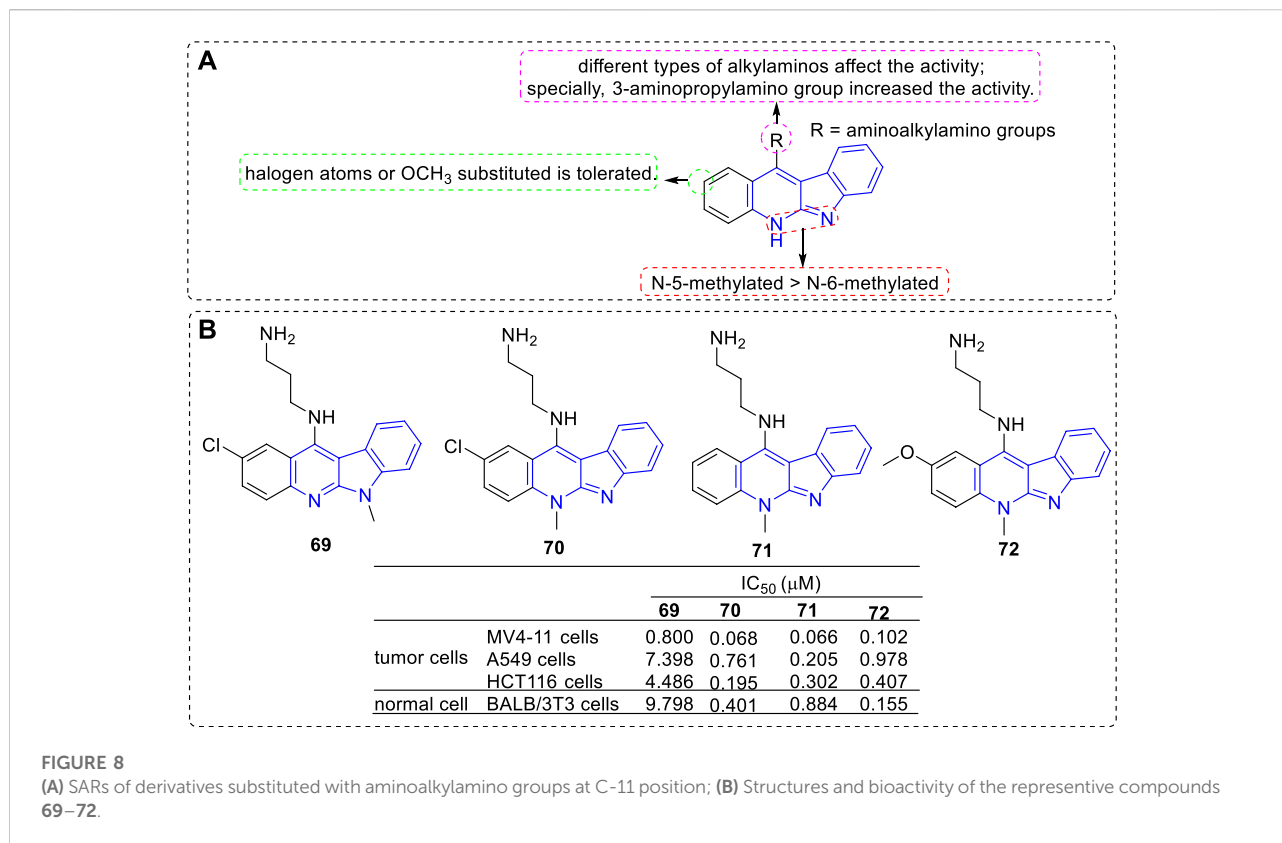
were easily soluble in water with a non-PH-dependent manner, and exhibited cytotoxicity against a panel of tumor cell lines with IC₅₀ values range from 0.01 to 0.3 μM. They also stimulated the formation of Top II mediated DNA cleavage at concentration of 0.4–0.5 μM. Compound 55, bearing a methoxy group at C-2 position and a methyl group at C-9 position, showed the most potent activity against A549 cell line.

Although 6H series (52) were less active than 5H series (51), further SAR study of 11-methylated 6H series (57) were still carried out and a panel of derivatives were synthesized in 2002 (Kaczmarek et al., 2002) (Figure 6). The substituents included alkyl-, (alkylamino) alkyl-, and 4-(3-chlorophenyl) piperazi-1-yl-propyl. According to the biological assay, only the introduction of an (alkylamino) alkyl chain into the core structure would be an advisable choice for Top II inhibition, cytotoxic and antimicrobial activity (e.g., 58). To further explore the effect of the introduction of (alkylamino) alkyl chains, novel derivatives bearing them at C-2 (e.g., 59), C-9 (e.g., 60) or N-6 (e.g., 61) position were synthesized (Godlewska et al., 2005). Their cytotoxic activity against a series of cancer cell lines as well as their drug-resistant sublines were evaluated. All the analogs exhibited DNA binding and Top II inhibiting activity *in vitro*, as

a result, showed cytotoxicity against the tested cancer cell lines and constrained the growth of Gram-positive bacteria and fungi. Notably, the results indicated a positive relationship between Top II inhibition and cytotoxicity. Certain compounds possess the ability to inhibit the growth of HL-60/MX2 cell line also suggested that Top II may not be the only target for 6H series, which was similar to that of 5H series mentioned above.

Then, novel derivatives which N-6 fixed an (dimethylamino) ethyl chain (62), C-2 or C-9 linked another (dimethylamino) ethyl chain by amide, amine or ether bond were synthesized and tested for their cytotoxic activity against a panel of cancer cell lines and multidrug resistant sublines (Luniewski et al., 2012) (Figure 7). Interestingly, all compounds (63–68) showed cytotoxic activity against the tested cell lines at a similar level.

Further, new derivatives substituted with aminoalkylamino groups at C-11 position were investigated (Wang et al., 2012; Shaban et al., 2017) (Figure 8). Their cytotoxic activity against a panel of cell lines and normal cells were evaluated. The main SARs could be summarized according to the antiproliferative assay: 1) 5-methylated derivatives were more potent than their related 6-methylated derivatives (69 vs. 70); 2) A halogen substituent at the 2-position influenced the antiproliferative



activity (70 vs. 71); 3) An electron-donating group-OMe substituted at C-2 position is tolerated (71 vs. 72). 3) Proper alkylamino substituted at C-11 could favourably influence their activities and selectivities, especially the 3-aminopropylamino group (69–72).

To increase selectivity and solubility in water, a series of new analogues of 47b containing an amino acid or a dipeptide chain at C-2 or C-9 position were synthesized respectively (Sidoryk et al., 2012; Sidoryk et al., 2014) (Figure 9). As a result, all amino acid and peptide derivatives displayed moderate to good antiproliferative activity against A549, KB, MCF-7, and LoVo cell lines. The derivatives attaching a hydrophilic amino acid or a peptide chain to the hydrophobic core of 47b increased their hydrophilic properties and decreased their hemolytic activity compared to 47b itself, which was considered to correlate with the low toxicity *in vivo*. Although the author claimed that there were no significant cytotoxic differences between C-2 and C-9 substituted derivatives, we could obtain some key messages by a careful comparison: 1) The toxicity levels of C-2 substituted derivatives was higher than that of C-9 substituted derivatives, especially against A549, MCF-7, and LoVo cell lines (73 vs. 74); 2) C-9 substituted derivatives exhibited no significant differences in antiproliferative activity against cancer and normal cell lines; 3) C-2 substituted derivatives showed marked alterations in antiproliferative activity against cancer and normal cell lines,

which indicated the presence of a distinct mechanism of action towards these two types of cell lines.

In the continued efforts to improve their solubility properties and selectivity, derivatives containing guanidine or guanylamino acid substituents were manufactured and evaluated for their cytotoxic and anti-fungal activity (Sidoryk et al., 2015; Sidoryk et al., 2017) (Figure 10). As results, most of the tested compounds exhibited cytotoxic activity and compounds 75 and 77, which guanidine group directly linked to the core of 47b, exhibited a high selectivity between cancer and normal cells. Although cytotoxic activity was also observed in the *N*-guanylamino acid substituted derivatives (76 and 78), no significant selectivity of action was identified. On the contrary, 75 and 77 were inactive against *C. albicans* biofilms, while 76 possessed a potent anti-fungal activity against *C. albicans* biofilms with an IC₅₀ value of 4.2 μM. The results indicated that the existence and position of the guanyl moiety in the molecule was essential for cytotoxic activity and selectivity.

Artemisinin, a sesquiterpene lactone from *Artemisia annua*, is famous for its use in the treatment of malaria. Besides its anti-malarial activity, artemisinin and its derivatives are identified with anti-tumor potency (Efferth, 2006; Morrissey et al., 2010). With the aim to develop potent and selective antitumor agents, a series of artemisinin-47b hybrids were designed and synthesized (Wang et al., 2014). The hybrids 79 and 80 showed an increased

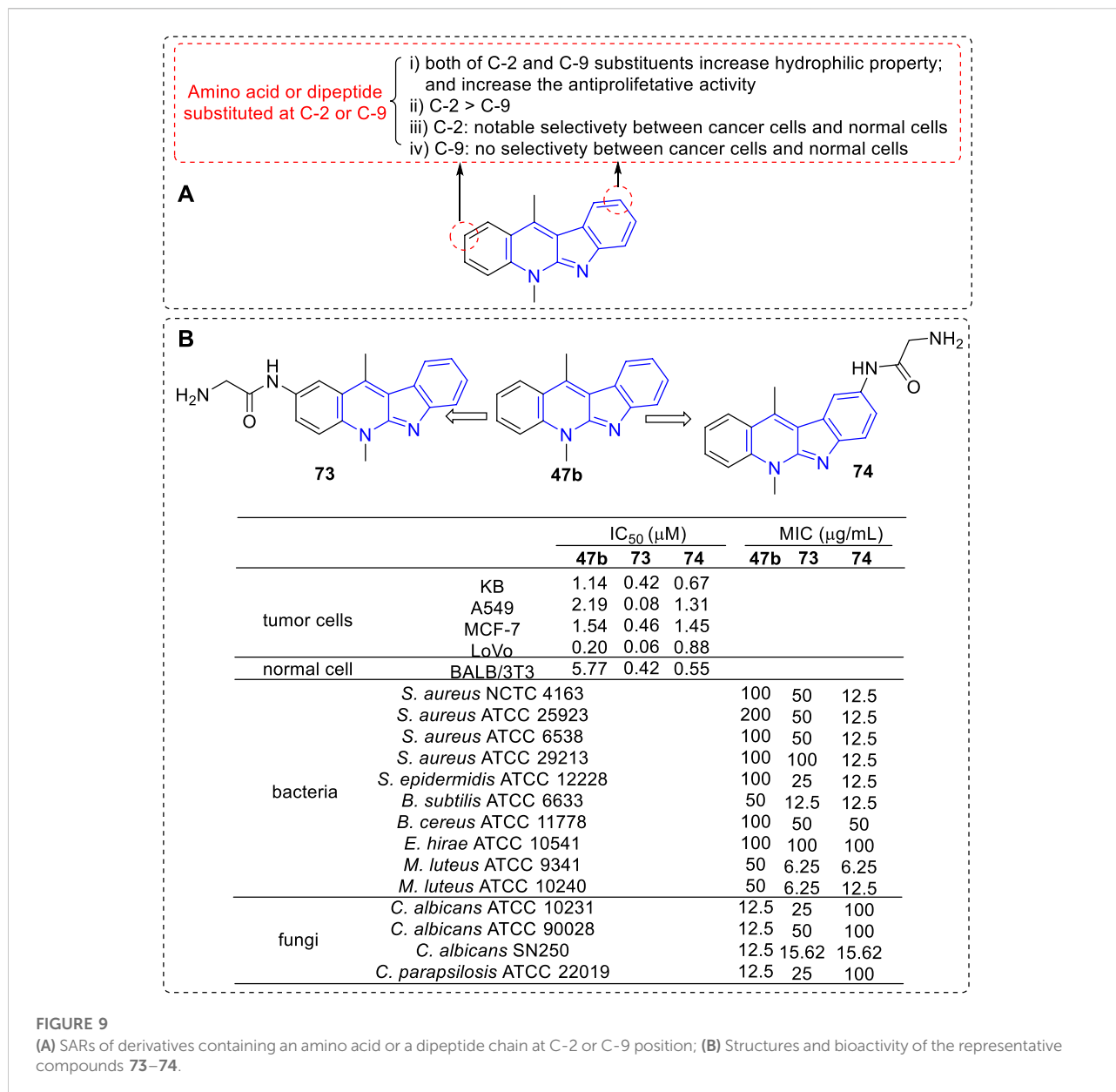


FIGURE 9

(A) SARs of derivatives containing an amino acid or a dipeptide chain at C-2 or C-9 position; (B) Structures and bioactivity of the representative compounds 73–74.

antiproliferative activity against A549 and HCT-116 cell lines compared with dihydroartemisinin (DHA) (Figure 11).

Recently, novel *O*-aminoglycosides-47b hybrids were synthesized and evaluated against A549, MCF-7, Hs294T, HL-60, MES-SA, and LoVo cell lines (Figure 12). Hybrids of acosaminy and 47b (81) showed no selectivity between cancer and normal cells, while hybrids of daunosaminy and 47b (82) showed good selectivity between cancer and normal cells. Unexpectedly, certain MDR tumor cell lines including LoVo/DX, MES-SA/DX5 were also resistant to these analogs (Bednarek et al., 2006; Roslonek et al., 2016). This was surprising because the parent analogue 47b displayed antiproliferative activity against all MDR cell lines examined.

Besides the group of Kaczmarek, there were other teams also focused on the research of 47b. In the screening of novel compounds containing quinoline core as anti-tumor and anti-malarial agents, Akkachairin et al. inadvertently found a novel 47b derivative 83 with moderate antiproliferative ability against a panel of cancer cell lines but alongside high selectivity toward normal cells (Akkachairin et al., 2020) (Supplementary Figure S1).

Altwayjry et al. synthesized four derivatives of 47b (84–87) and evaluated their *in vitro* and *in vivo* effect versus Ehrlich ascites carcinoma (EAC). In addition, their antioxidant activity was also tested using the DPPH method. The results indicated that these naturally-based alkaloids

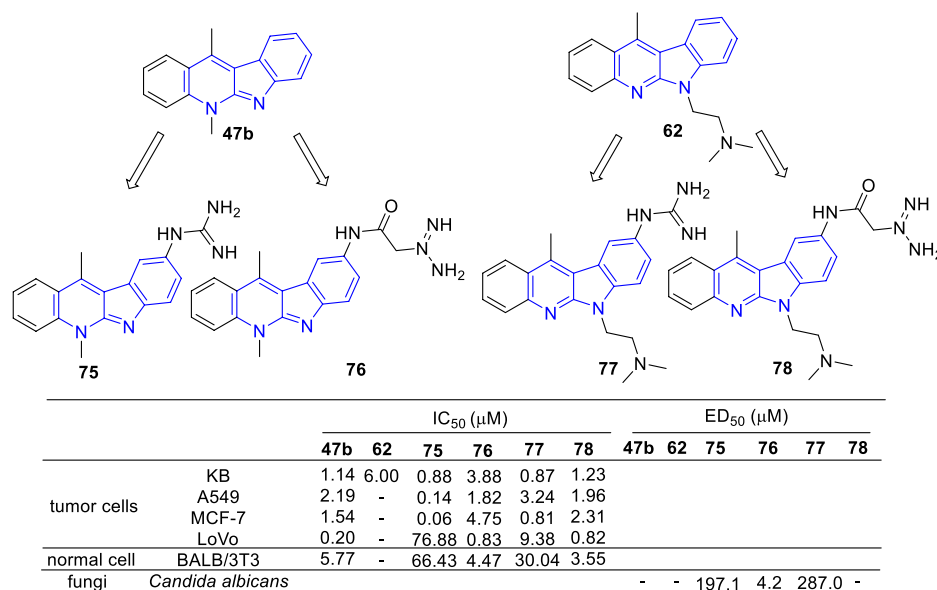


FIGURE 10

Structures and bioactivity of the representative derivatives (75–78) which C-9 substituted with guanidine, amino acid or guanylamine acid.

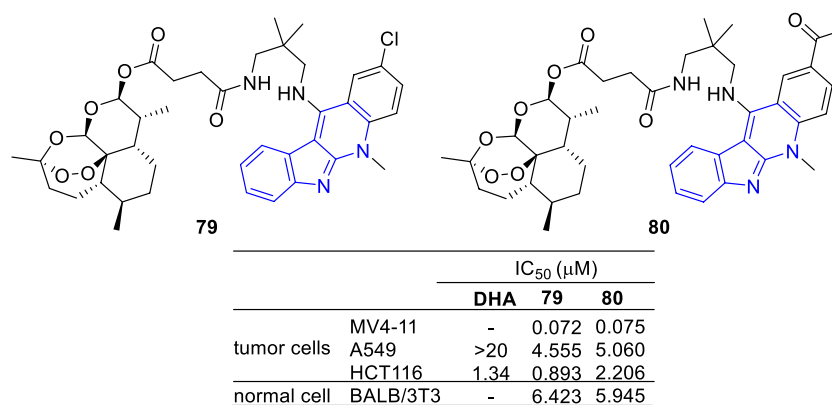


FIGURE 11

Structures and bioactivity of the representative artemisinin-indoloquinoline hybrids 79 and 80.

exhibited antioxidant activity, notable anti-tumor activity and represented an important class of leads as natural-based antitumor drugs (Altwaijry et al., 2021) (Supplementary Figure S2).

4.1.2 Aurora B kinase inhibitors

Aurora kinases are essential mitotic cell-cycle regulators and play key roles in cell mitosis and division. Among them, Aurora B is a chromosome passenger protein essential for phosphorylation of histone H3, chromosome segregation, and cytokinesis. Aurora B is frequently elevated in cancer, and represents an attractive

target for cancer therapy (Carmena and Earnshaw, 2003; Fu et al., 2007; Carmena et al., 2009).

Farrell et al. reported an Aurora B kinase inhibitor TAK-901 (88) (Farrell et al., 2013), which inhibited AurB/INCENP with an IC₅₀ value of 15 nM and inhibited various human cancer cell lines with IC₅₀ values ranging from 40 to 500 nM. Docking study illustrated that 88 occupied the ATP-binding pocket. Hydrogen-bonding interactions formed between LYS-87, LYS-106 as well as ASN-205 residues and 88, and π - π interactions formed between PHE-88 residue and α -carboline ring of 88. Since synthetic difficulty hampered its further clinical evaluation. The team

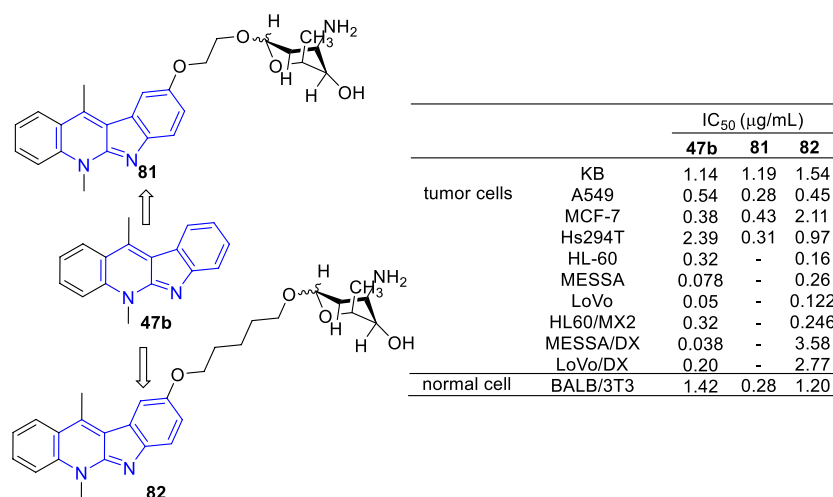


FIGURE 12
Structures and bioactivity of the representative *O*-aminoglycosides-47b hybrids **81** and **82**.

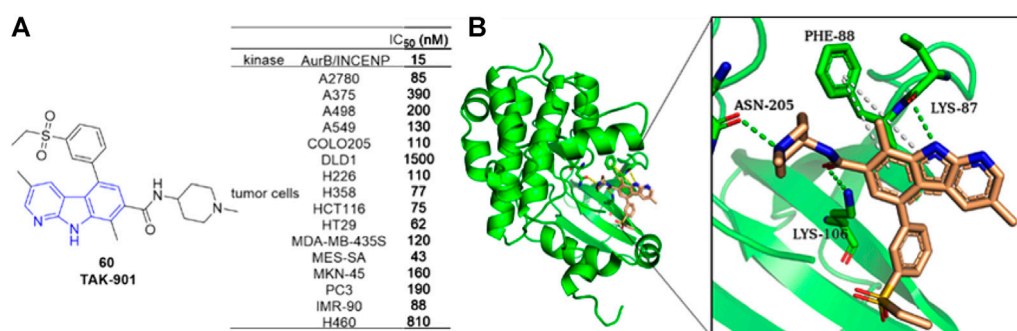


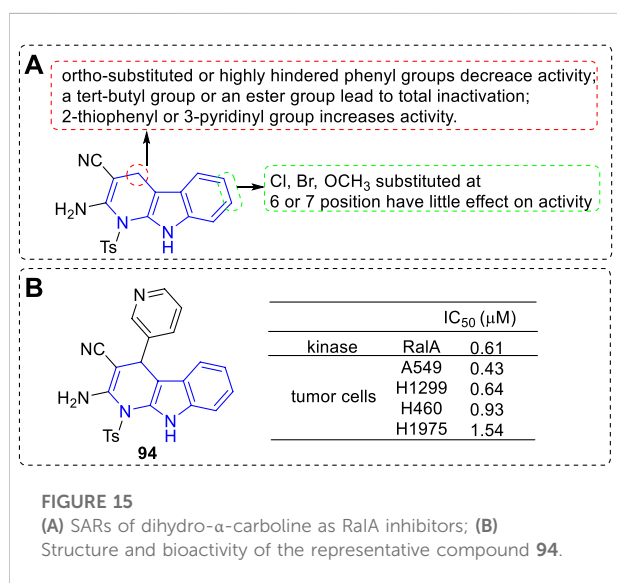
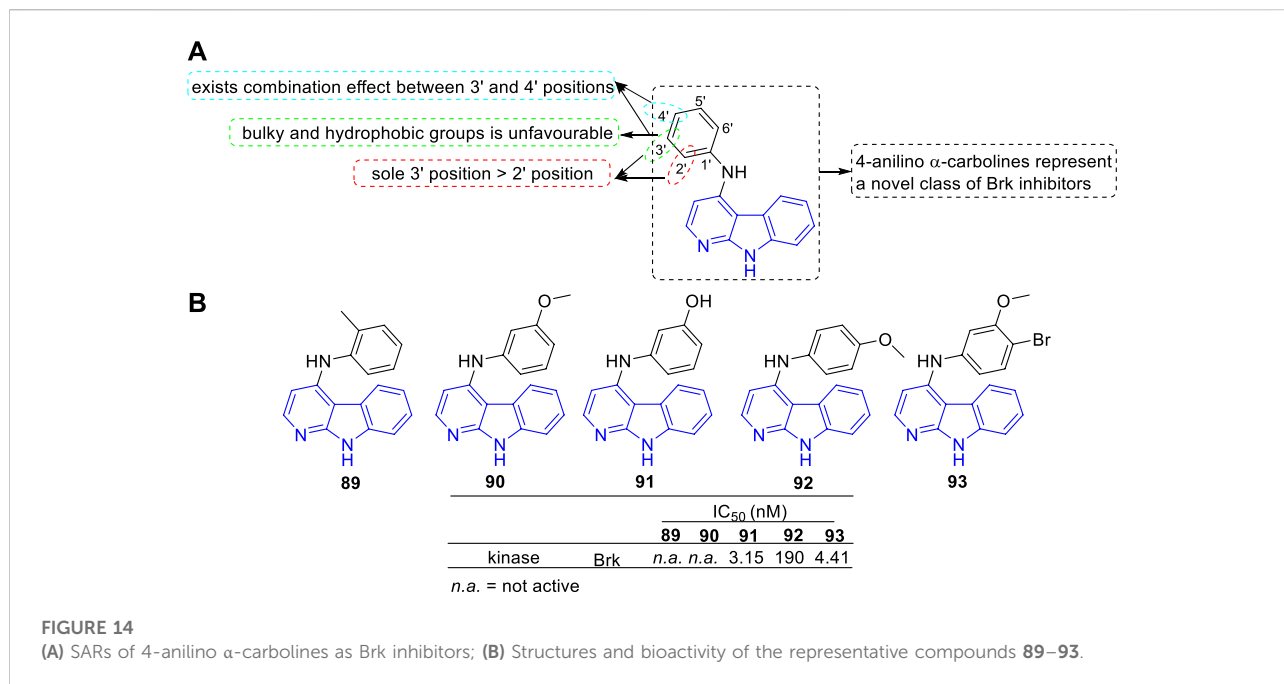
FIGURE 13
(A) Structure and bioactivity of **88** as an Aurora B inhibitor; (B) Binding mode of **88** docked into Aurora B kinase (green ribbon representation, PDB code: 4AF3). **88** is represented in stick model, carbons in ligand are colored wheat. Hydrogen bond is presented as green dash lines. π - π interactions are presented as white dash lines.

later reported a practical and efficient synthetic process for **88** using an integrated Pd-catalyzed crosscoupling strategy (Mineno et al., 2015) (Figure 13).

4.1.3 Brk inhibitors

Breast tumor kinase (Brk), which was originally found expressed in a metastatic breast tumor, plays an essential role in both cell dysregulation and metastasis. Brk has become an ideal cellular target for tumor therapy because it occurs in a majority of breast tumors but low or undetectable amounts of Brk occurs in normal tissues (Mitchell et al., 1994; Barker et al., 1997; Brauer and Tyner, 2010).

Mahmoud et al. discovered a series of 4-anilino α -carboline as a new class of potent Brk inhibitors (Mahmoud et al., 2014). The type and position of the aniline substituents determined the Brk inhibitory activity, which led to IC₅₀ values varying from nanomolar to inactive. The main SARs were summarized (Figure 14A): 1) Substituents introduced at 3'-position of the aniline residue seemed more promising compared with substituents introduced at sole 2'-position; 2) At the 3'-position of the aniline residue: A lipophilic thioether function was unfavourable; The bulky and hydrophobic trifluoromethyl substituent showed a slight decrease in Brk inhibition; A chloro substituent and hydroxy substituent with less space showed a strong increase for Brk inhibition; 3) Combined substituent



effects showed that 3'-methoxy and 4'-bromo substituents increased the activity compared to sole 3'-methoxy substituent which was found to be inactive (93 vs. 90). Structures and bioactivity of the representative compounds (89–93) were shown in Figure 14B. Later, the team reported two 4-anilino α -carboline derivatives (structures not shown) possessed the ability to induce nonadhesive breast cancer cells death through inhibiting Brk activity (Oelze et al., 2015).

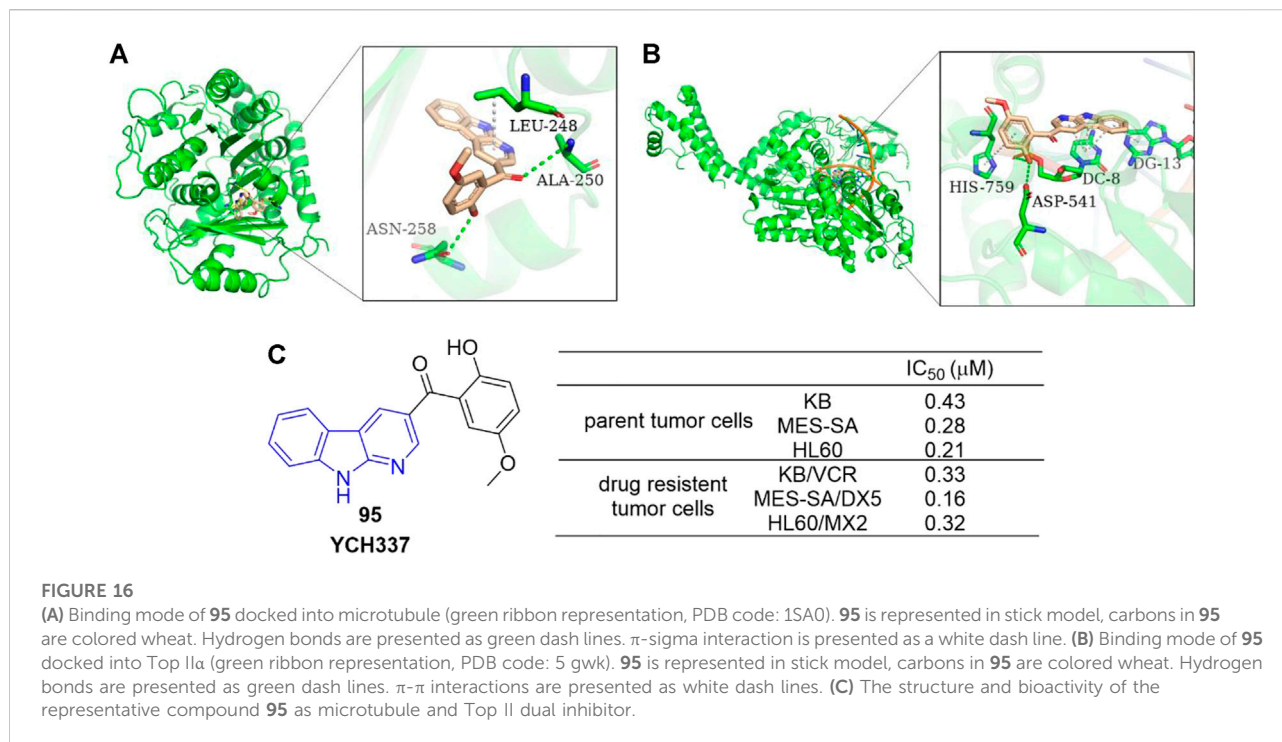
4.1.4 RalA inhibitors

RalA, a member of the Ras small GTPases superfamily, is critical for Ras-mediated human cancer cells proliferation (Hunter et al., 2015; Yan and Theodorescu, 2018). It has been proved that RalA plays an essential role in regulating cancer initiation, invasion, migration, and metastasis, which makes it an interesting tumor therapeutic target (Bum-Erdene et al., 2020; Chen et al., 2020).

Leng et al. designed and synthesized a series of dihydro- α -carboline derivatives and some of them could inhibit RalA and proliferative of a panel of cancer cell lines (Leng et al., 2020). The main SARs could be summarized (Figure 15A): 1) C-4 position: 1) The ortho-substituted or highly hindered phenyl residue would lead to lower activity; 2) Introduction of a tert-butyl or an ester group to the phenyl residue would result in total inactivation; 3) 2-thiophenyl or 3-pyridinyl moiety exhibited higher activity; 2) C-6 or C-7 position: The kind and position of the substituents had little effect on the bioactivity. The most potent derivative (94) inhibited RalA with an IC₅₀ value of 0.61 μ M and proliferative of A549 cell lines with an IC₅₀ value of 0.43 μ M (Figure 15B).

4.1.5 Microtubule and Top II dual inhibitors

Microtubule consists of microtubulins, participates in the mitotic spindle assembly (Kavallaris, 2010). Top II, a nuclear enzyme, is essential for resolving DNA entanglement and for segregating chromosomes in mitosis (Chen et al., 2013). Both of them are standout anti-tumor targets and their related inhibitors



have been extensively used in the treatment of cancer therapy (Jackson et al., 2007; Nitiss, 2009).

Yi et al. reported an α -carboline derivative YCH337 (**95**), which targeted both microtubule and Top II (Yi et al., 2015). It suppressed microtubule polymerization *via* binding to the colchicine site and subsequently resulted in mitotic arrest. Docking study showed that there were hydrogen-bonding interactions formed between ALA-250 as well as ASN-258 residues of microtubule and **95**, and π -sigma interaction formed between LEU-248 residue and aromatic rings of **95** (Figure 16A). It also inhibited Top II and caused DNA double-strand breaks. Docking study illustrated that there were hydrogen-bonding interactions formed between ASP-541 as well as HIS-759 residues of Top II and **95**, and π - π interactions formed between DC-8/DG-13 of DNA and aromatic rings of **95** (Figure 16B). Its disruption of microtubule was more potent than Top II. Notably, **95** nearly equally inhibited proliferation of MDR tumor cells and their corresponding parent cells (Figure 16C).

4.1.6 ALK inhibitor

The Anaplastic Lymphoma Kinase (ALK) is aberrantly rearranged or mutated in several tumors including inflammatory myofibroblastic tumor (IMT), anaplastic large-cell lymphoma (ALCL), neuroblastoma, inflammatory myofibroblastic tumor and nonsmall cell lung cancer (NSCLC) patients. (Mologni et al., 2022a). Thus, ALK has become a therapeutic target for personalized medicine in some selected cancers.

Mologni and coworkers designed and developed some novel ALK inhibitors based on a 4,6-substituted α -carboline scaffold. Compound **96** showed potent non-ATP-competitive inhibition of wild-type and mutant ALK in biochemical and cellular assays, as well as in xenograft mouse models (Mologni et al., 2022b). Compound **97** showed selective inhibition of native and mutant drug-refractory ALK kinase *in vitro* as well as in human ALK⁺ lymphoma and in a Ba/F3 model cells (Mologni et al., 2022a; Mologni et al., 2022b) (Figure 17).

4.1.7 Targets indetermination

Early in 1978, Namirski synthesized some 2-position substituted α -carbolines. Among them, compound **98** showed cytostatic activity (Nantka and Kaczmarek, 1978). At 50 mg/kg dose level, it inhibited tumor growth of transplanted Ehrlich ascites carcinoma and Nemeth-Kellner lymphoma with inhibition of 59 and 66% respectively. Later in 1986, the team synthesized a series of new α -carbolines and evaluated their anti-tumor activity against L1210 (lymphoid leukemia), P388 (lymphocytic leukemia), and Sarcoma180 (Wieczorek et al., 1986). The results showed that α -carboline derivatives substituted at C-4 position with a methyl group (**99**) or C-6 position with a fluorine (**100**) or chlorine (**101**) atoms caused moderate inhibition of the Sarcoma 180 growth but not other kinds of tumor (Supplementary Figure S3).

In 2010 and 2016, the team of Li successively reported a series of 3, 6, 8, or 9-substituted α -carbolines and tested their

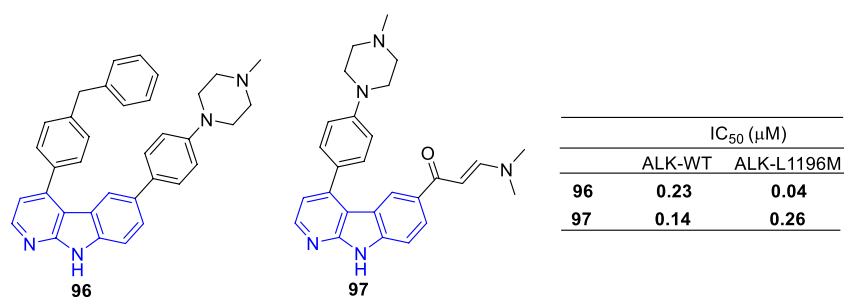


FIGURE 17

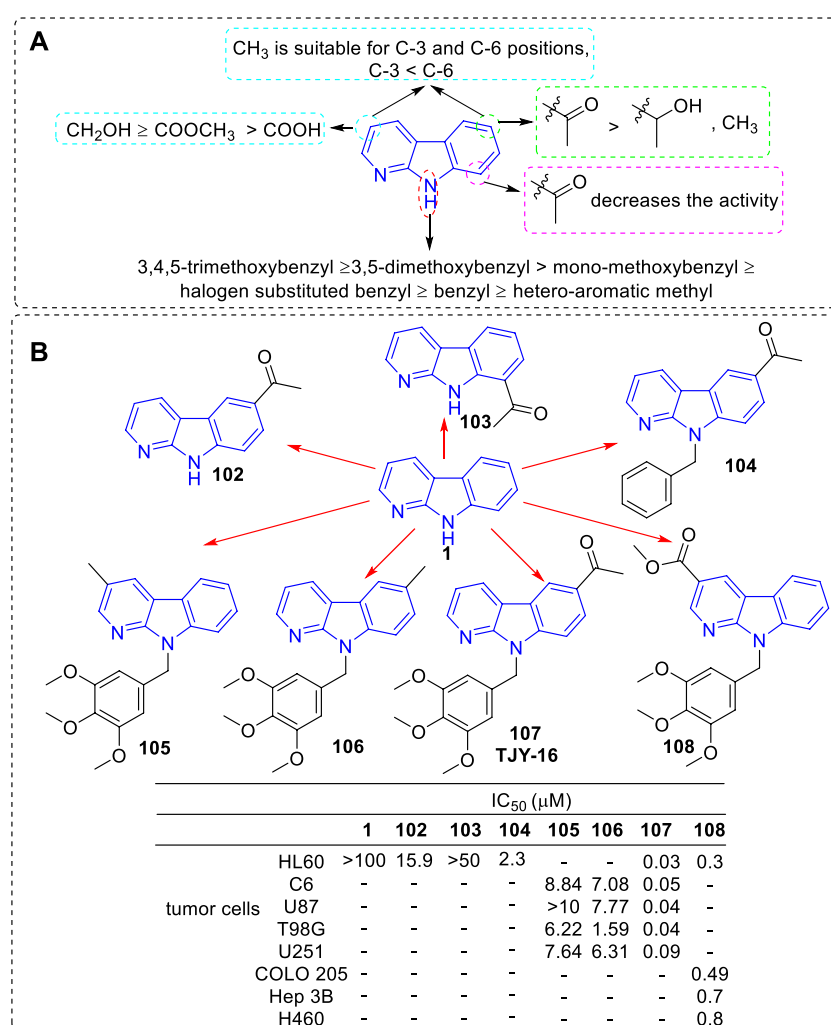
Structure and bioactivity of the representative compounds **96** and **97**.

FIGURE 18

(A) SARs of 3, 6, 8, or 9-substituted α -carbolines for their antitumor activity; (B) Structures and bioactivity of the representative compounds **102–108**.

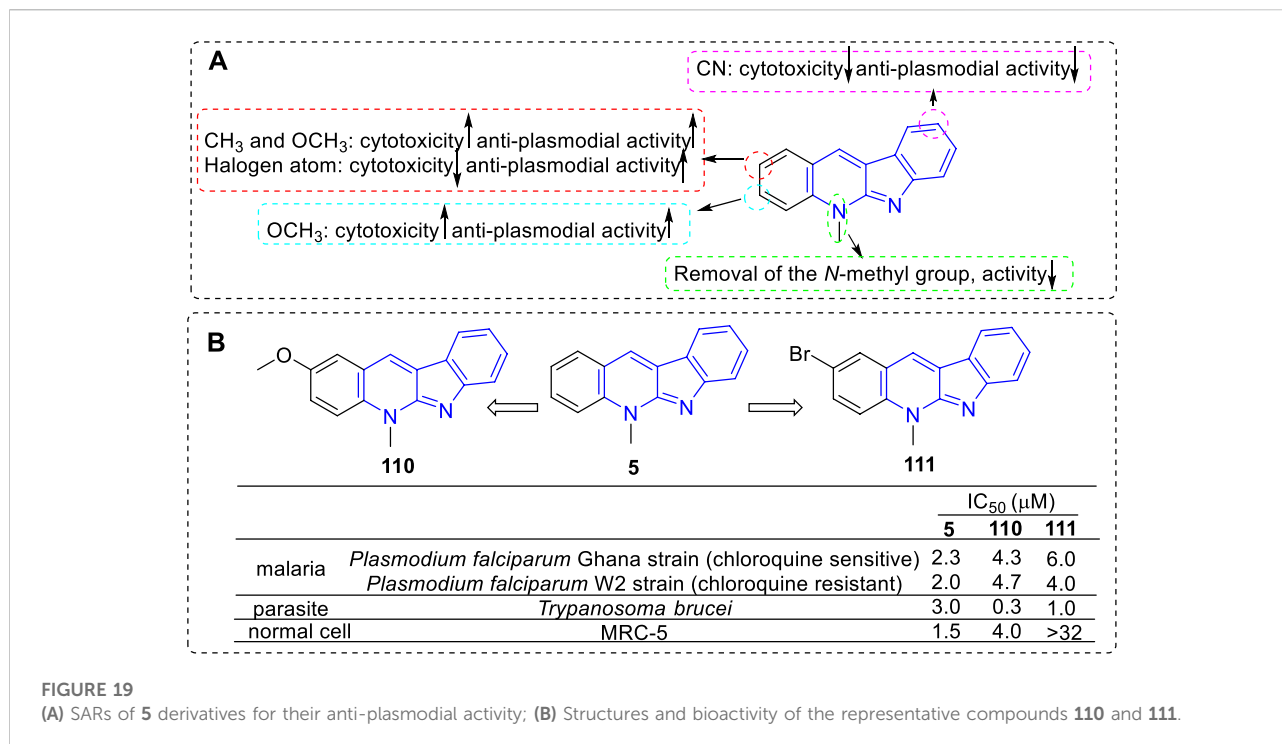


FIGURE 19
 (A) SARs of 5 derivatives for their anti-plasmodial activity; (B) Structures and bioactivity of the representative compounds 110 and 111.

antitumor activity (Tsai et al., 2010; Huang et al., 2016; Lin et al., 2016). Based on the results of activity, the main SARs could be summarized (Figure 18A): 1) The unsubstituted α -carboline (**1**) had almost no cytotoxicity; 2) An N-9 methylaryl moiety was a critical functional moiety for maintaining the potency. The following rank order was found: 3,4,5-trimethoxybenzyl \geq 3,5-dimethoxybenzyl > mono-methoxybenzyl \geq halogen substituted benzyl \geq benzyl \geq hetero-aromatic methyl. 3) Based on the C-3 substituents, the following rank order was found: CH₂OH \geq COOCH₃ \geq COOH. 4) Introduction of an acetyl group at C-6 but not C-8 position increased the inhibitory activity; 5) Substituents of C-3, C-6, and C-9 showed synergistic effects. The structures of the representative compounds **102–108** and their activity were shown in Figure 18B.

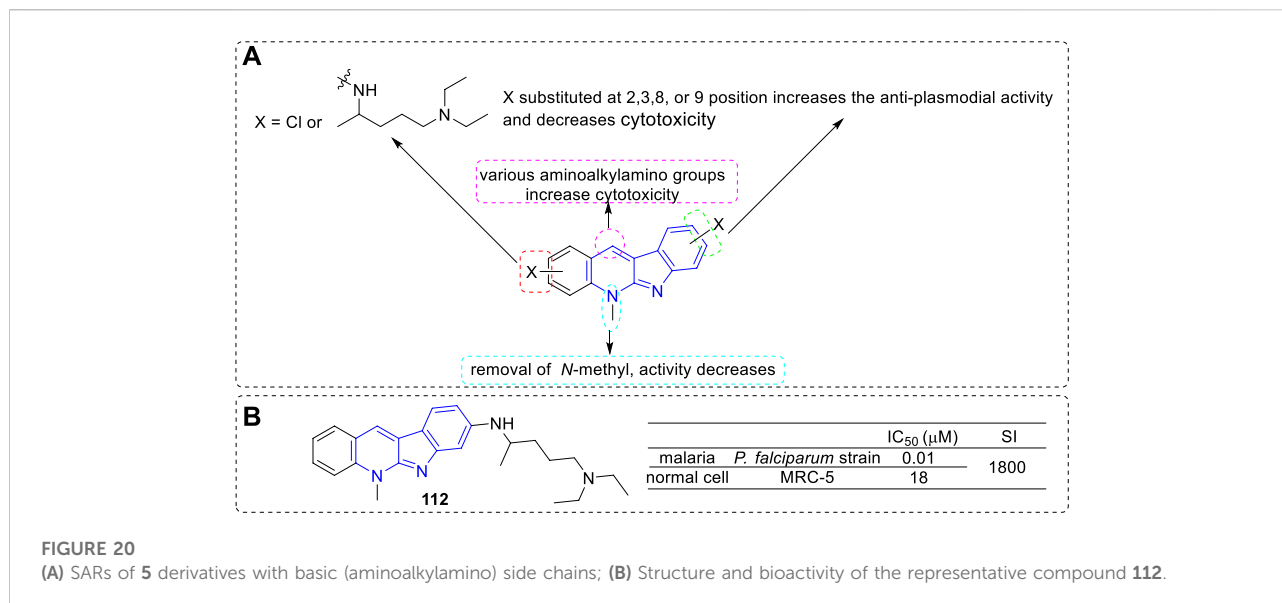
Besides, Zhang et al. achieved some 2 or 2,4-substituted α -carbolines with moderate anti-tumor activities via an effective and convenient method (Zhang et al., 2014). Since a few of these compounds were selected to determine their anti-tumor activity, the SAR could not be obtained. The most potent compound **109** exhibited antiproliferative of BEL-7402 cells with an IC₅₀ value of 0.58 μ M (Supplementary Figure S4). Emam et al. obtained several Copper (II) complexes with aminoalkylaminoneocryptolepine as anticancer agents (Emam et al., 2015). The most potent compound (structures not shown) exhibited antiproliferative activity of HT-29 cells with an IC₅₀ value of 0.58 μ M.

4.2 Anti-microbial activity

4.2.1 Anti-plasmodial activity

Due to the introduction of the artemisinin-based combination therapies (ACTs), a great success has been achieved globally in the treatment of malaria over the period 2000 to 2019, but there were still an estimated 229 million malaria cases in 2019 (<https://www.who.int/teams/global-malaria-programme>). Therefore, the development of novel drugs to treat malaria is still needed. Natural products isolated from plants are an important resource for the discovery of new drugs. Compound **5**, isolated from the root bark of African plants *Cryptolepis sanguinolenta*, is one of the representative natural products with anti-plasmodial activity besides artemisinin. Compound **5** and its derivatives have achieved great attention for their ability against malaria.

Pieters and coworkers have devoted themselves to the research of compound **5** and its derivatives against malaria since the 1990s (Cimanga et al., 1997; Cimanga et al., 1998). But until in 2002, they reported a set of synthetic analogs and evaluated their anti-plasmodial activity against chloroquine-sensitive and chloroquine-resistant *Plasmodium falciparum* strains (Jonckers et al., 2002; Van et al., 2004). Interestingly, for all compounds, the chloroquine-resistant strain were more sensitive than the chloroquine-sensitive strain. From the results, the main SARs could be summarized (Figure 19): 1) C-1 substitution led to a loss of anti-plasmodial activity; 2) Many of the 2-substituted derivatives displayed higher activity against

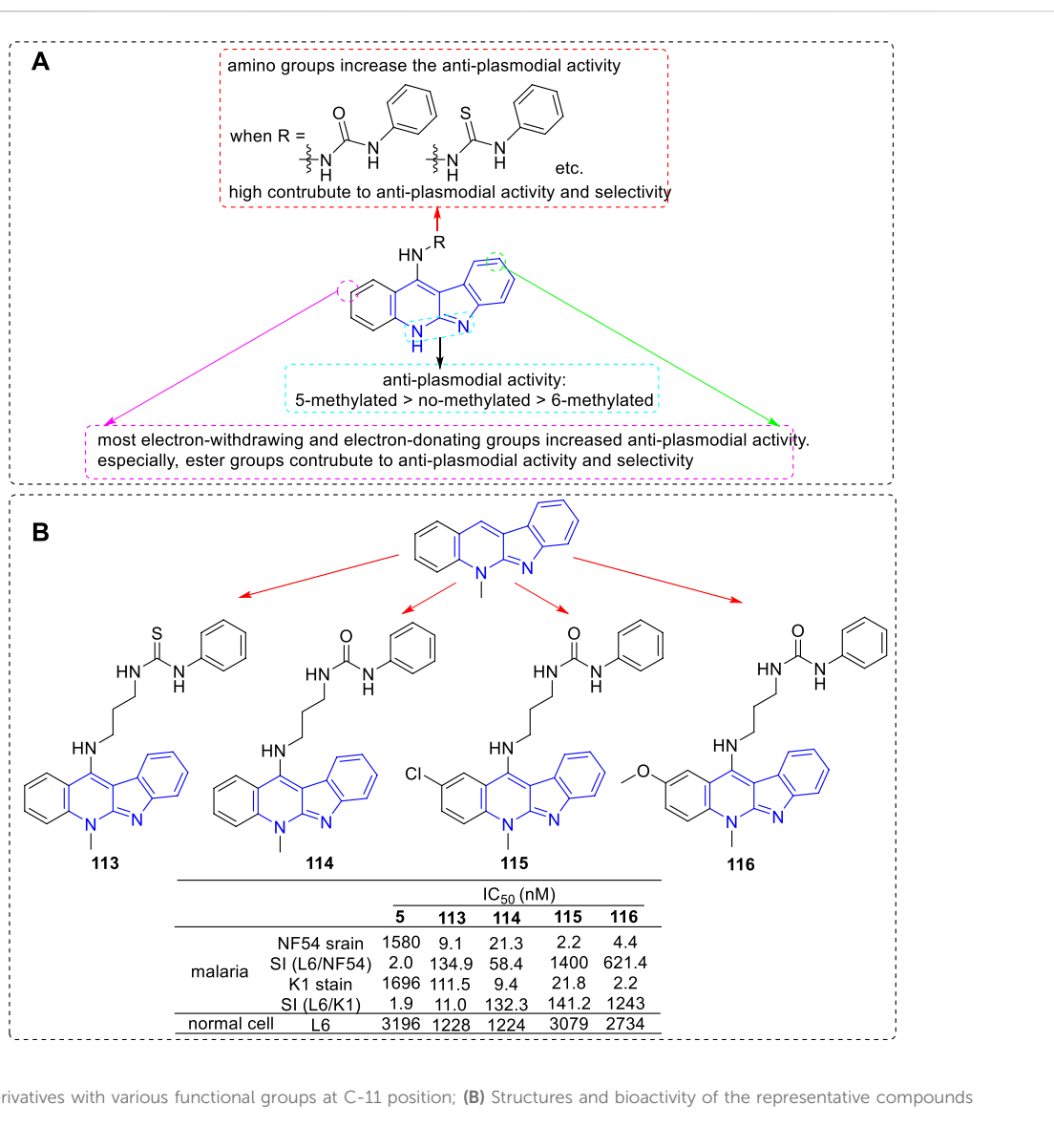


plasmodia than that of **5** itself but were also more cytotoxic (e.g., **110**). However, the 2-halo-substituted derivatives were more active against *P. falciparum* than that of **5** and less cytotoxic (e.g., **111**); 3) C-3 substituted derivatives possessed about the same or more anti-plasmodial activity against chloroquine-resistant strain, but they were more cytotoxic; 4) C-9 cyano substitution led to a reduction of cytotoxicity but also a loss of the anti-plasmodial activity. Although some **5** derivatives displayed a higher anti-plasmodial activity than **111**, these compounds also showed a more pronounced cytotoxicity. Therefore, compound **111** was considered as the most promising lead for anti-malarial agents in this regard. The mechanism research showed that **111** displayed a low affinity for DNA and no inhibition of human Top II, and this explained the reason for its low cytotoxicity. Further research illustrated this selective anti-plasmodial activity may be associated with the inhibition of β -hematin formation.

On further exploration of the anti-malarial potential of **5** derivatives, they introduced halo-substituents as in **111** to reduce the cytotoxicity of the parent compound. In addition, they introduced basic (aminoalkylamino) side chains with the aim to improve the biological activity, as a basic side chain was required for the accumulation of components into the food vacuole, and required for inhibition of hemozoin formation, which was an important character for the activity of chloroquine (El et al., 2009). Hence, a series of **5** derivatives with an *N*¹,*N*¹-diethylpentane-1,4-diamine chain (the basic side chain of chloroquine), or other aminoalkylamino chains, chloro-substituents, and a combination of both in various positions were prepared. Then, all the analogues were evaluated for their anti-plasmodial activity against a chloroquine-sensitive *P. falciparum* strain and for cytotoxicity against MRC5 cell line. Most of the compounds showed anti-plasmodial activity in the nanomolar

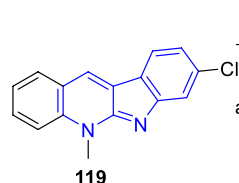
range. According to the activity data, the main SARs were summarized (Figure 20): 1) Most halo-substituted analogs were indeed less cytotoxic than their parent compounds, but also showed lower anti-plasmodial activity; 2) Substituted with the basic *N*¹,*N*¹-diethylpentane-1,4-diamine side chain led to a substantial increase of the anti-plasmodial activity, and the compound with basic chain substituted at C-8 position (**112**) appeared the most potent; 3) Compounds removal of the 5-methyl group only resulted in a 1–3 fold loss in potency (still potency), which indicated not the *N*-methyl moiety, but rather the existence of a basic nitrogen atom, was critical for biological activity; 4) Compounds substituted other various aminoalkylaminogroups at C-11 position led to a remarkable increase in cytotoxicity.

Another research group, the team of Inokuchi, has also been committed to modifying **5** in order to improve its anti-plasmodial activity. In 2012, they obtained a series of derivatives by introducing various functional groups at C-11 position (Mei et al., 2013). These functional groups included thiazolidin-4-one (a biologically privileged skeleton which is well tolerated in human subjects), sulfonamide, thiophene-2-carboxamide, and urea/thiourea (aim to improve the solubility properties and the anti-parasitic activity *in vitro*). All of the derivatives were tested for their anti-plasmodial activities toward CQS (NF54) and CQR (K1) of *Plasmodium falciparum* and for cytotoxicity against mammalian L6 cells. The results revealed that urea derivatives highly contributed to anti-plasmodial activity and selectivity. In 2013, the research group continually carried out modifications by fixing a urea/thiourea unit at C-11 position and introducing ester groups at the C2 and/or C9 positions on the core structure of **5** (Lu et al., 2013; Wang et al., 2013). The results illustrated that the ester substituted



derivatives not only possessed higher anti-plasmodial activity against both strains, but also a low cytotoxicity against L6 cells. In the same year, they reported a set of 6-methyl-5*H*-indolo[2,3-*b*]quinoline (congener of **5**) derivatives. These derivatives also were substituted with various alkylamino or ω -aminoalkylamino groups at C-11 position. The results suggested that the activity of 6-methylated derivatives were less potent than that of the corresponding 5-methylated derivatives. Based on the sequential reports, the main SARs could be summarized (Figure 21A): 1) The introduction of an amino group at the C-11 position could significantly increase the anti-plasmodial activity compared with the nonsubstituted analogs; 2) Protected nonbasic nitrogen at the terminal of amino group substantially affected the anti-plasmodial

activity. These derivatives with nonbasic groups possessed higher select index (SI) data compared with that of the derivatives with free terminal amine substituents. Especially, a urea/thiourea unit highly contributed to anti-plasmodial activity and selectivity; 3) Both electron-withdrawing and electron-donating groups introduced at C-2 and/or C-9 positions increased anti-plasmodial activity. But some of them also increased cytotoxicity. Especially, ester groups were favourable for anti-plasmodial activity and selectivity; 4) The anti-plasmodial activity with or without N-methyl group was assigned in the order of 5-methylated > no-methylated > 6-methylated. Several representative compounds (**113–116**) and their activity are shown in Figure 21B. Among these compounds, **113–115** were selected for further study against *Plasmodium*



	EC ₅₀ (μg/ml)
<i>Sclerotinia sclerotiorum</i>	2.80
<i>Rhizoctonia solani</i>	4.93
<i>Botrytis cinerea</i>	0.07
<i>Fusarium graminearum</i>	1.92
<i>Magnaporthe oryzae</i>	2.82
<i>Mycosphaerella melonis</i>	0.11

FIGURE 22
Structure and anti-fungal activity of the representative compound **119**.

berghei in Swiss mice. After intraperitoneal for four consecutive days at the dose of 50 mg/kg, compounds **113** and **114** showed some reduction of 15.4 and 22.1% in parasitaemia on day 4, respectively. Unfortunately, compound **115** showed no activity and all mice lost weight.

In the discovery of novel compounds containing quinoline core fused five-membered ring structures as anti-tumor and anti-plasmodial agents, Akkachairin *et al.* inadvertently found a novel derivative of compound **5** (**117**) with moderate anti-plasmodial activity but high selectivity (Akkachairin *et al.*, 2020) (Supplementary Figure S5).

4.2.2 Anti-bacterial activity

The team of Kaczmarek not only explored the anti-tumor activity but also the anti-microbial activity of α -carbolines. Early in 1986, they reported certain iso- α -carbolines (e.g., **118**) exhibited anti-bacterial (Gram-positive *Micrococcus luteus* and *Kitasatosporia setae* strains) in the concentration of 0.5 μ M/ml (Czoch *et al.*, 1986) (Supplementary Figure S6).

Other α -carbolines derivatives with anti-bacterial activity were seen in Section 4.1.1 (Figures 5, 6, 9).

4.2.3 Anti-fungal activity

Certain α -carbolines derivatives with anti-fungal activity were seen in Section 4.1.1 and Section 4.2.2 (Figures 5, 6, 9, 10; Supplementary Figure S6).

Besides the anti-pathogenic fungi of α -carbolines derivatives mentioned above, the anti-agriculturally fungi activity was also reported by Zhu *et al.* (Zhu *et al.*, 2020). They designed and synthesized a series of 5 derivatives and screened their anti-fungal activity against six agriculturally important fungi, including *Rhizoctonia solani*, *Botrytis cinerea* (*B. cinerea*), *Fusarium graminearum*, *Mycosphaerella melonis*, *Sclerotinia sclerotiorum*, and *Magnaporthe oryzae*. Many of these analogs presented remarkable anti-fungal activity with EC₅₀ values lower than 1 μ g/ml. Notably, compound **119** exhibited the most effective inhibitory potency against *B. cinerea* with an EC₅₀ value of 0.07 μ g/ml (Figure 22). Subsequently, they carried out its mechanism research through integrating proteomics and transcriptomics (Shang *et al.*, 2021). And the results indicated

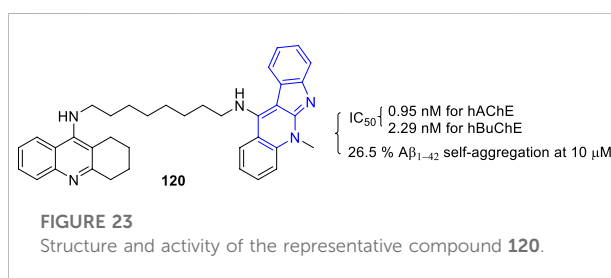


FIGURE 23
Structure and activity of the representative compound **120**.

that it caused the death of *R. solani* mycelia by binding UQCRFS1 and blocking the ion transfer.

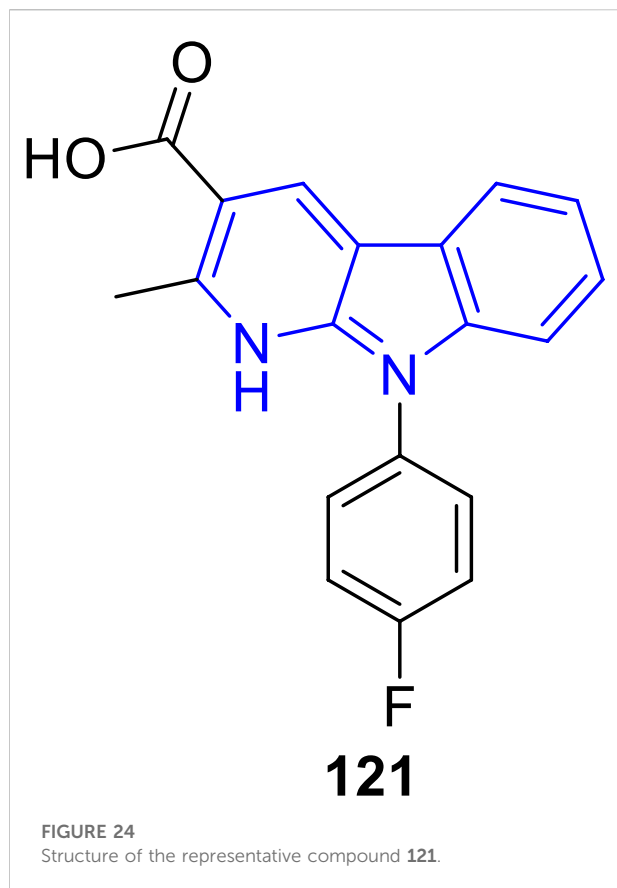
4.2.4 Anti-trypanosomal activity

Some indolo[2,3-*b*]quinoline analogs prepared by the research team of Pieters also exhibited anti-trypanosomal activity against *T. cruzi* and *Trypanosoma brucei* in the micromolar range and no obvious cytotoxicity was observed (Jonckers *et al.*, 2002) (Section 4.2.1; Figure 19).

4.3 Anti-alzheimer's disease activity

Alzheimer's disease (AD) is a progressive neurodegenerative disease resulting in memory loss, disorientation, speech failure and behavioral changes (Selkoe, 2001; Querfurth and LaFerla, 2010), leading to a significant burden to public health systems worldwide (Bosboom *et al.*, 2012). Amyloid β -protein (A β) as well as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) enzymes are associated with pathology of AD (Adlard *et al.*, 2009; Craig *et al.*, 2011).

The team of Inokuchi synthesized novel tacrine-5 heterodimers and evaluated their activity towards A β as well as AChE and BuChE (Wang *et al.*, 2017). The most potent compound **120** showing a moderate inhibition of the A β ₁₋₄₂ self-aggregation (26.5% at 10 μ M), and a high inhibition of AChE and BuChE with IC₅₀ values of 0.95 and 2.29 nM, respectively (Figure 23).

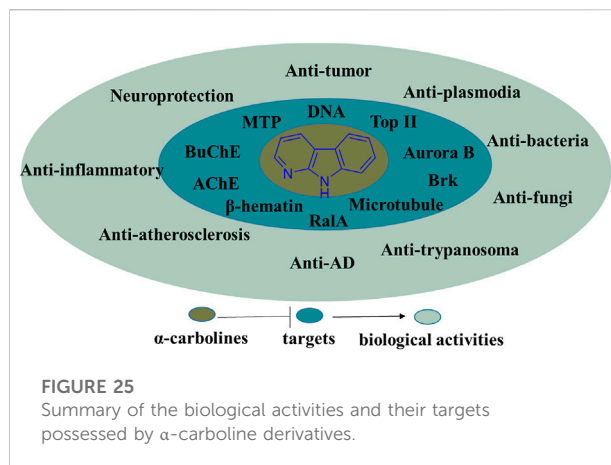


4.4 Anti-atherosclerosis activity

Implitapide (**6**), a microsomal triglyceride transfer protein (MTP) inhibitor, had been shown to reduce progression of atherosclerosis (MartinL et al., 2000; Ueshima et al., 2005). At the dose of 12 mg/kg to low-density lipoprotein (LDL)-receptor-deficient Watanabe heritable hyperlipidemic (WHHL) rabbits, the plasma cholesterol level, triglyceride level, and the very low-density lipoprotein VLDL secretion rate were decreased by 70, 45, and 80%, respectively.

4.5 Antioxidant activity

Recently, Zhang and coworkers (Zhang et al., 2022) designed and synthesized a series of α -carboline derivatives to improve the damage of cardiomyocyte caused by oxidative stress. The biological studies showed that most of the α -carbolines exhibited obvious protective activities against H_2O_2 -induced cardiomyocyte injury. Particularly, compound **121** significantly increased the cell viability in H_2O_2 -induced oxidative stress in H9c2 cardiomyoblasts with a concentration-dependent manner. Other biological results including measurement of the activities of MDA, SOD, and GSH-Px, flow cytometry analysis, and



Western blot analysis also revealed the potential of **121** as a promising cardioprotective agent against H_2O_2 -induced oxidative injury (Figure 24).

Therefore, these analogs may be used to treat many oxidation related diseases such as cancer, cardiovascular, and inflammation caused by oxidative stress (Altwaijry et al., 2021).

4.6 Miscellaneous

Besides the activities mentioned above, α -carboline derivatives also showed other biological activities. Amino- α -carboline, which was formed during the cooking of meat or fish, could be used as mutagens due to its genotoxicity (Yoshida et al., 1979; Zhang et al., 1996). Mescengricin (**9**), was first found in the process of screening for neuronal cell protecting components, showed protection of chick primary mesencephalic neurons from L-glutamatic toxicity, suggesting this class of α -carbolines possess a potential of neuroprotective activity (Shin et al., 2000). DDMG-1 (**10**) could inhibit the mRNA degradation of $I\kappa B-\alpha$, mTNF- α , and influence other inflammation related factors including NF- κB , IL-8, etc., indicating this class of analogs should be further researched for the treatment of chronic inflammatory diseases (Oda et al., 2009). Some α -carbolines were used to develop organic semiconductors (Han et al., 2015) and host materials (Hwang et al., 2020) due to their highly planar, rigid, polycyclic chromophore structure and sufficiently large triplet energy.

5 Conclusion and future directions

In summary, the α -carboline natural products, recent literature of synthesis and information of the biological activities possessed by α -carboline alkaloids have been presented in the review. In the section of biological activities, some SARs and activity mechanisms had been described.

Undoubtedly, α -carboline derivatives exert diverse biological activities, suggesting this class of alkaloids have great potential in medicinal chemistry (Figure 25). Although there are no α -carboline-based drugs on the market currently, some α -carboline-based compounds have reached clinical trials (implitapide, **85** for example). The research of α -carbolines as drugs should be going.

Still, there will be a long way to go before α -cabolines become drugs, and incontrovertibly many challenges will be faced. The first challenge is their synthesis. Although a broad array of strategies have been reported for their synthesis, it is surprising that few literature reported the total synthesis of α -carboline natural products. Many of the synthetic methods of α -carbolines described are limited by low yields, starting materials difficult to obtain, expensive reagents, or inflexibility with regard to substituents and substitution patterns. The second challenge is their activity. It can be found from literature that many novel α -cabolines have been synthesized, but their activity is poor or mediocre. The third challenge is their clinical research. Although some teams have studied α -cabolines for decades, and some compounds possessed good activity, there are still no compounds reached clinical trials.

Nevertheless, some future directions of α -carboline-based medicinal chemistry could be summarized as follows: 1) Efficient and facile synthesis methods still need to develop; 2) The structural modification of active α -carbolines still needs to be carried out. On the one hand, to improve their physicochemical properties or selectivity, on the other hand, to broaden the scope of compounds for diverse biological activity; 3) Recent biological activity research of α -carbolines mainly focuses on anti-tumor activity, research on other biological activities should be reinforced; 4) The mechanisms of their biological activities should be elucidated, especially their target should be clear; 5) Due to their polycyclic chromophore structure, making α -carbolines into medical materials is also an important direction.

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Author contributions

All authors contributed to the review concept, design, and bibliographic research. DL, RY, JW, and YL prepared the first version of the manuscript. DL, RY, and BZ prepared the schemes and figures. DL, RY, and YL critically reviewed the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2022.988327/full#supplementary-material>

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