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Review Article

Indole Based Alkaloid in Cancer: An Overview

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ABSTRACT

Indole alkaloids are well characterized for diverse activities. Meanwhile, the present scenario of disease depicting a different story, urge a call for novel scaffolds and pharmacophores. In recent years, indole based alkaloids gain significant importance in cancer chemotherapy and used as an adjuvant especially in case of Vinca alkaloids. These reports encourage the researchers for new finding related to indole based alkaloids to retrieve better scaffold for designing and synthesis of anticancer agents. However we tried to compile the literatures which cover the recent reports and updates of indole based alkaloids targeting in cancer. Moreover this review paper brings new dimension and interface between the indole based alkaloids and their valuable commitment towards cancer targeting.

Keywords: Indole alkaloids, Anticancer Agents, Indole-Based Natural Products

INTRODUCTION

Cancer cells are quite similar to the normal cells, expect the advancement in the signaling which makes them immortal. They readily adapt to starvation microenvironments, and modify their protein-nucleic acid machinery to assure their continued survival so that they can able to utilize the altered mechanisms to promote cellular immortality. All these hallmarks of cancer make challenging task to target the cancerous cells.

Moreover modern cancer chemotherapy utilizes following strategies to target the cancer as follows:

- Combined modality chemotherapy which uses the drugs together with radiation therapy or surgery.
- Neoadjuvant chemotherapy (preoperative treatment)
- Adjuvant chemotherapy (postoperative treatment) is used where there is a risk of recurrence after the surgery.
- Palliative chemotherapy is implicated to increase the life expectancy.

These chemotherapeutic drugs can be majorly classified as:

- Alkylating agents
- Antimetabolites
- Anthracyclines
- Plant alkaloids
- Topoisomerase inhibitors

Natural products, especially those ones which are extracted\obtained from plant origin, have been used for the treatment of various diseases since ancient times and can be witnessed in the numerous ancient\traditional medicinal plant books. In present circumstances where diseases modulated themselves to a new level of adaptation (resistance) and modifies. Therefore new scaffolds or pharmacophore are much needed to overcome these issues. Moreover cancer is one such disease and therefore alternatively plant derived agents are being employed for the treatment of cancer. Several

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PHARMATUTOR
PHARMACY INFOPEDIA
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natural derived anticancer agents including Taxol, Vinblastine, Vincristine, Camptothecin derivatives, Topotecan and Irinotecan, and Etoposide are in clinical use. Even a number of promising agents such as flavopiridol, roscovitine, combretastatin A-4, betulinic acid and silvestrol are in clinical or preclinical development.

The Indole alkaloids are the major class of alkaloids which turn out into different anti-cancerous scaffolds, enlisted as:

- Non-isoprenoid tryptamine
- Piperazinedione
- Indoloiminoquinolines
- β-Carbolines
- Bisindole
- Cytochalasins
- Elliptinium
- Vinblastine and vincristine

Indole is a basic heterocyclic scaffold which was originated with the study of a dye, indigo. This scaffold is composed of a benzopyrrole, in which the benzene and pyrrole rings are fused *via* *C*2 and *C*3 positions of the pyrrole nucleus (see in Fig.1.). Its presence in the nature is highly versatile even it is found endogenously in human e.g. tryptophan amino acid. Moreover natural secondary metabolite (alkaloids) contain indole nucleus which is ubiquitously present in nature including plants like (vincristine), marine creatures (manzamines), insects, fungal metabolites (cytochalasins), mammalian as well as human tissues, and body fluids.

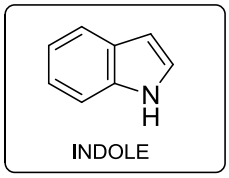
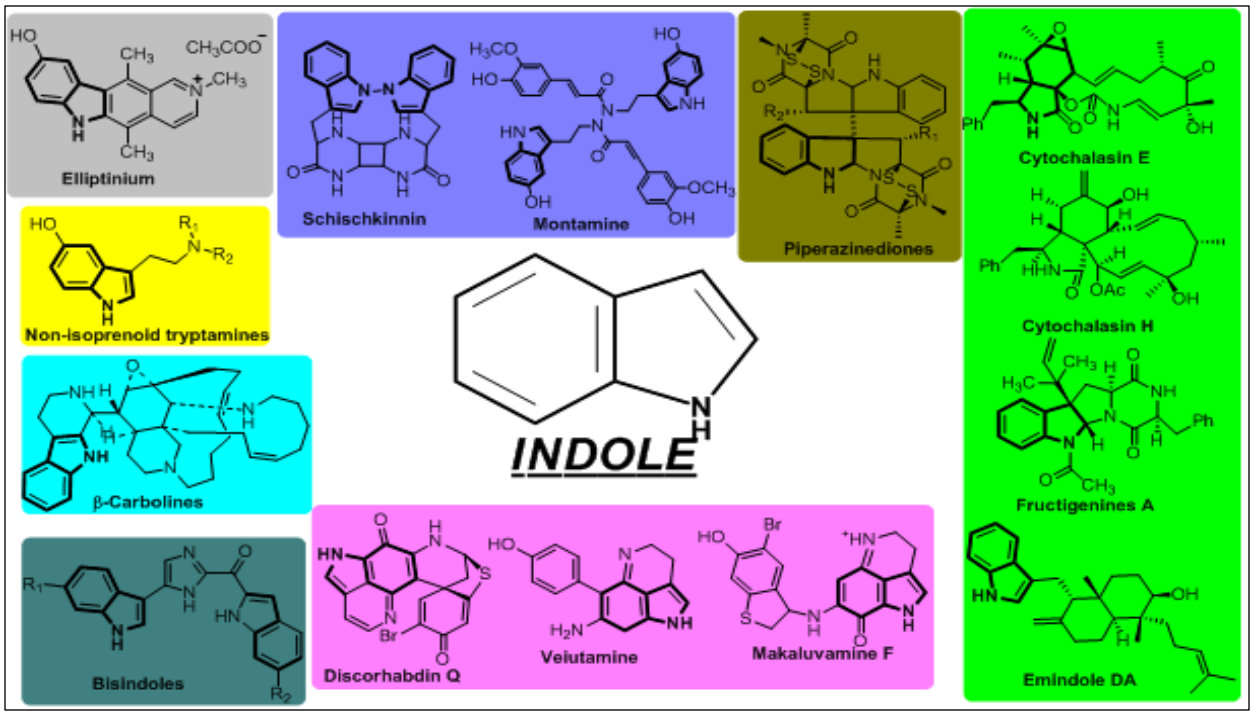


Fig. 1. Structure of indole.

This review covers some of the active indole derivatives which have shown anticancer activity. These includes Non-isoprenoid tryptamine, Piperazinedione, Indolo-iminoquinolines, β-Carbolines, Bisindole, Cytochalasins, Elliptinium, Vinblastine and Vincristine.



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INDOLE-BASED NATURAL PRODUCTS AS ANTICANCER AGENTS

Non-isoprenoid tryptamines

Two new bioactive indole alkaloids, Bufobutanoic acid (**2**) and Bufopyramide (**3**) were isolated from the skin secretions of the local toads *Bufo bufo garigarizans* or *Bufo melanostrictus*. Both compounds exhibited cytotoxicity against murine P388 lymphocytic leukemia cells with IC_{50} values of 22 µg mL^{-1} and 26 µg mL^{-1}, respectively [1-4] see in fig.3.

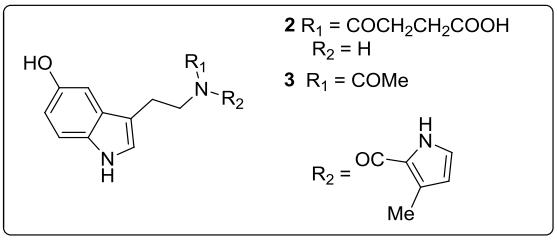

Fig. 3. Structure of anti-cancerous Non-isoprenoid tryptamines.

Piperazinediones

Two cytotoxic epidithiodioxopiperadine dimers, 11,11'-dideoxyverticillin A (**4**) and 11' deoxyverticillin A (**5**) together with known Verticillin A, had been isolated from the mycelium of a marine-derived fungus of the genus *Penicillium.* Cytotoxicity against HCT-116 human colon carcinoma of compounds (**4**) and (**5**) have been described (IC_{50} = 30 ng ML^{-1}) [4] see in fig.4.

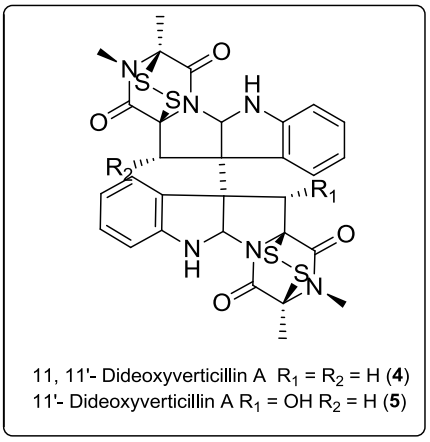

Fig. 4. Structure of piperazinediones alkaloids

Indoloiminoquinolines

A new discorhabdin, Discorhabdin Q (**6**) (16,17-dehydro-discorhabdin B), had been isolated from cytotoxic extracts of the sponge *Latrunculiapurpurea* and *Zyzzyamassalis*, Z. *fuligi-nosa*, and Z. spp. Discorhabdin Q **(6)** exhibited moderate cytotoxic activity (GI_{50} = 0.5 µg ML^{-1}) possessing essentially a differential cytotoxic profile in a NCI 60 cell line antitumor screen [4] see in fig.5.

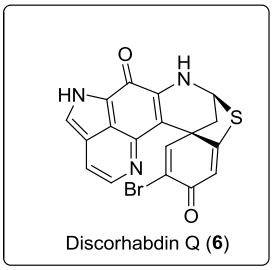

Fig. 5. Structure of anti-cancerous indolo iminoquinolines (Discorhabdin Q).

The first complete synthesis of pyrrolo-iminoquinone marine alkaloid Veiutamine (**7**), isolated from the Fijian sponge *Zyzzya fuliginosa*, has been done (Scheme.1.).This alkaloid has potent anticancer activity against solid tumours versus leukaemia (IC_{50} = 0.12 µg mL^{-1} in a 25 cell line panel and IC_{50} = 0.3 µg mL^{-1} against the human colon tumor cell line HCT-116).

PHARMATUTOR
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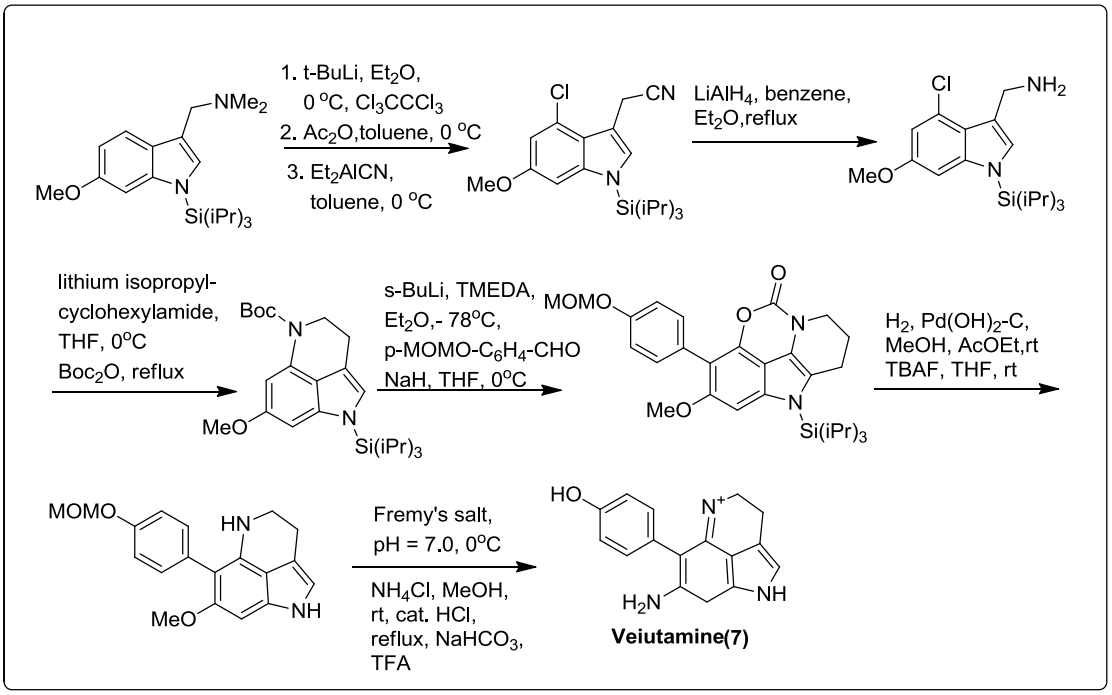
ISSN: 2347 - 7881



Scheme.1. Synthetic scheme of Indoloiminoquinolines derivative (Veiutamine).

A total synthesis of the marine alkaloid makaluvamine F (**8**) (see in fig.6.), isolated from the Fijian sponge *Zyzzya cf. marsailis* and the Indonesian sponge *Histodermella* sp. (G), has been completed. Makaluvamine F (**8**) exhibits the potent cytotoxicity towards the human colon tumor cell line HCT-116 (IC_{50} = 0.17 µM) and the inhibition of topoisomerase II.

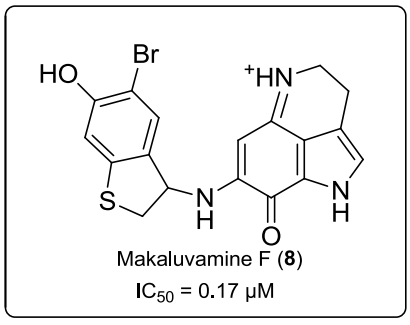


Fig. 6. Structure of Indoloiminoquinolines (Makaluvamine F).

β-Carbolines

A manzamine congenor, 1,2,3,4-tetrahydro-manzamine B (**9**) has been isolated from a Okinawan marine sponge *Amphimedon*sp. Further, its absolute stereochemistry of (**9**) has been established as (1*S*)-1,2,3,4-tetrahydromanzamine B (1) by circular dichroism spectroscopy. This compound (**9**) exhibits cytotoxicity against L1210 murine leukaemia cells and KB human epidermoid carcinoma cells (IC_{50} = 0.3 and 1.2 µg mL^{-1}, respectively) [5] (see in fig.7.).

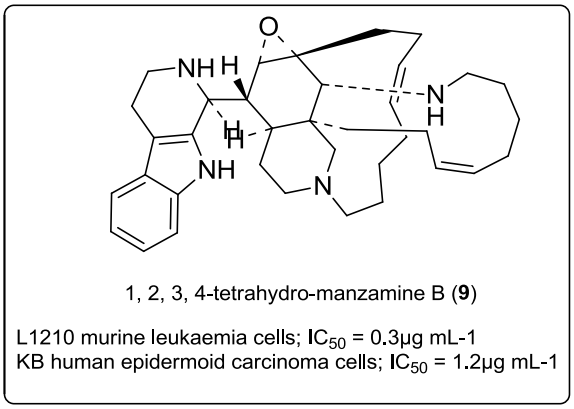


Fig.7. Structure of manzamine cogenor.

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Bisindole

Two bisindole alkaloids Bromodeoxytopsentin (**10**) and Isobromodeoxytopsentin (**11**) isolated from the sponge *Spongosoritesgenitrix* together with known deoxy-topsentin (**12**) and bromotopsentin (**13**) These compounds displayed moderate cytotoxicity against human leukemia cell-line K-562 (IC_{50}= 0.6 and 2.1 µg ML^{-1}, for (**10**) and (**11**), respectively).

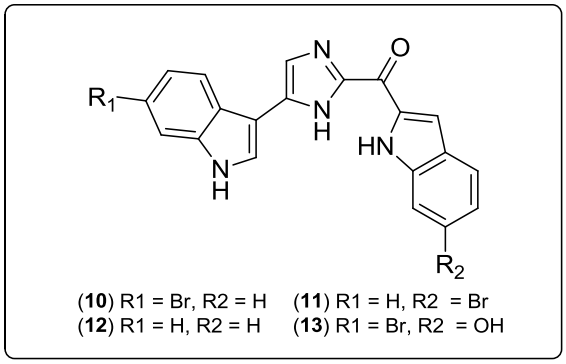

Fig.8. Structure of Bisindole alkaloid derivatives.

Cytochalasins

Fungal endophytes comprises of about 60% of alkaloids with known anti-tumour activity. Among these cytochalasins are interesting because of their broad spectrum anti-tumour activity. Among various metabolites obtained from fungi *Rhinocladiella* residing on plant *Tripterygium wilfordii,* cytochalasin E (**14**) (see in fig.9.) shown significant activity against three human tumour cell lines 2780S (IC_{100}<0.0153µg/mL), SW-620 (colon tumour cell lines IC_{100}=0.244µg/mL) and HCT-116 (IC_{100}=0.977µg/mL) respectively.

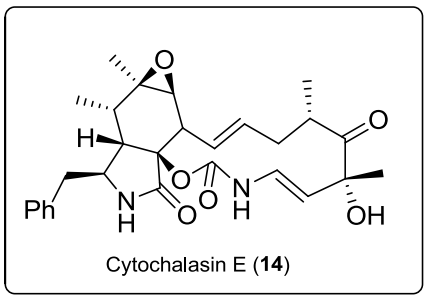

Fig.9. Structure of Cytochalasin.

Cytochalasin H (**15**) (see in fig.10.), another metabolite isolated from mangrove fungal endophyte*Phomopsis*sp. (ZZF08) in South China Sea coast. It has shown potent cytotoxicity against towards KB and KBv 200 cells with IC_{50} less than 1.25µg/mL.

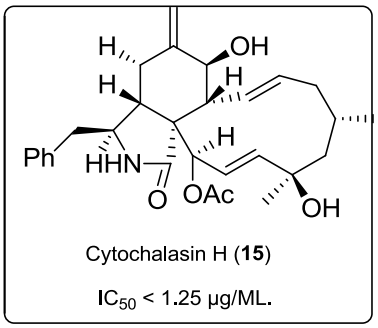

Fig.10. Structrue of Cytochalasin.

Fructigenines A (**16**) (see in fig.11.), a diketopiperazine alkaloid separated from the endophytic *Penicillium auratiogriseum* derived from sponge *Mycale plumose* by bioassay oriented fractionation showed potent cytotoxic activity against tsFT210 (mouse cdc2 mutant cells) with maximum inhibitory effect at 22µg/mL.

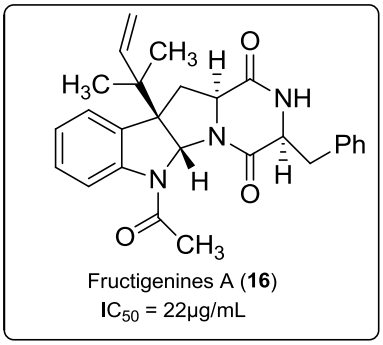

Fig.11. Structure of Fructigenines A.

Emindole DA (**17**) (see in fig.12.) an indole alkaloid derived from marine fungus *Emericella nidulans* var. *acristata* (a green alga of Mediterranean sea around Sardinia). This alkaloid had exhibited anti-tumour activity on a panel of 36 human tumour cell lines, with IC_{50}=

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ISSN: 2347 - 7881

5.5µg/mL *in vitro* survival and proliferation assay.

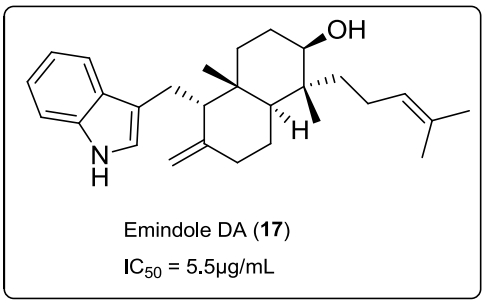

Fig.12. Structure of Emidole.

Elliptinium

A derivative of ellipticine (**18**) (see in fig.13.), isolated from a Fijian medicinal plant *Bleekeri avitensis* A.C. Sm., is marketed in France for the treatment of breast cancer.

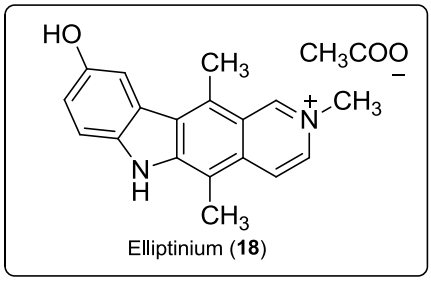

Fig.13. Structure of elliptinum.

Vinblastine and vincristine

Vinblastine and vincristine are alkaloids isolated from Periwinkle. Their solution route of administered majorly *via* intravenously in sulphate form. Although if their solutions can be fatal if administered by any other route and can also cause an allergic reactions or irritation if they leak out of the blood vessels. Vinca alkaloids are useful in the treatment of both malignant and non-malignant diseases (especially in hodgkins lymphoma) [6].

The major mechanism of cytotoxicity of all the vinca alkaloids state to their relations with tubulin and disruption of microtubule function. It leads to metaphasic arrest. They are also able to effect many other accessory downstream intracellular signalling proteins. Also they possess broad spectrum anticancer activity *via*-inhibiting synthesis of proteins and nucleic acids, elevating oxidized glutathione, altering lipid metabolism and membrane lipids, elevating cyclic adenosine monophosphate (cAMP), and inhibiting calcium-calmodulin-regulated cAMP phosphodiesterase [7,8].

Schischkinnin and Montamine

Two novel alkaloids, schischkinnin (**19**) and montamine (**20**) (see in fig.14.) were isolated from the seeds of *Centaurea schischkinii* and *Centaurea montana*. Both of these alkaloids have shown significant cytotoxicity against human colon cancer cell lines [9,10].

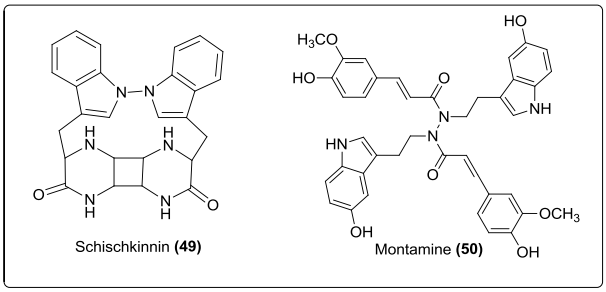

Fig.14. Structure of Schischkinnin and Montamine.

CONCLUSION

Recent reports disclosed numerous naturally occurring indole alkaloids were isolated and evaluated against different cancer cell lines where they revealed commendable\appreciable anticancer activity. Therefore it is evident about their potential, to overcome the concerning issues related to the present cancer chemotherapy. The indole scaffold is so versatile that it has shown diverse activities against the different targets in cancer. This special attribute of indole alkaloids can be utilized in rational drug design against the cancer in the near future.

PHARMATUTOR
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