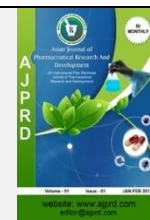


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Review Article

## Indole-3-Glyoxylamide- An Important Scaffold for Anticancer Activity

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## ABSTRACT

Synthetic indolylglyoxyl amides were identified as a new group of microtubule destabilizing anticancer agents, with the most active derivative N-(pyridine-4-yl)-[1-(4-chlorobenzyl)indol-3-yl]glyoxylamide (Indibulin, D-24851, ) possessing the promising in vitro activity against SKOV3 ovarian cancer, U87 glioblastoma and ASPC-1 pancreatic cancer cells. Indole-3-glyoxylamides are an attractive lead series for continuing development as potential therapeutic agents. A number of Indole-3-glyoxylamides have previously been reported as tubulin polymerization inhibitors; exert a cytotoxic effect against multiple cancer cell lines. Recently, substituted indolylglyoxylamides were found to exhibit anticancer, antiprion and anti HIV activity. This developed an interest in reviewing lead based on indole-3-glyoxylamide. This review focused on overview of drug molecule of indole-3-glyoxylamide. We hope that the review could give a guide to develop newer anti-cancer agents with greater potency against drug-sensitive and drug-resistant cancers in the future.

**Key words:** Indole-3-glyoxylamide, Anticancer activity, Indibulin (D-24851)**ARTICLE INFO:** Received 05 June 2020; Review Completed 05 August 2020; Accepted 09 August 2020; Available online 15 August 2020

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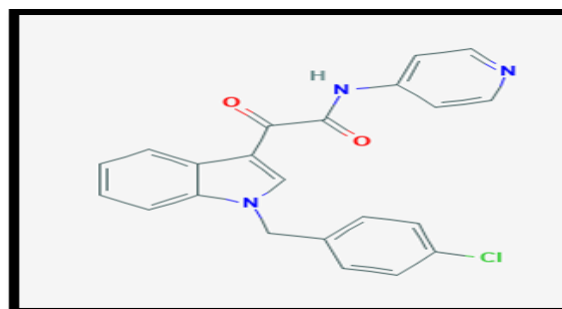
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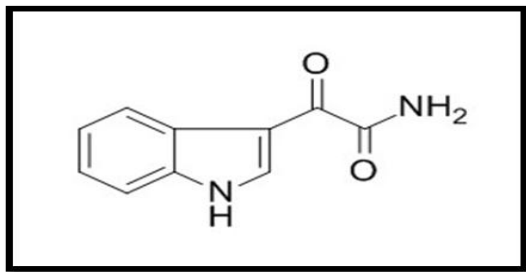
## INTRODUCTION

INDIBULIN (D-24851)<sup>1-2</sup>

Indibulin (N-(pyridine-4-yl)-[1-(4-chlorobenzyl)-indol-3-yl]-glyoxylamide; ZIO-301 or D-24851) is a novel synthetic, orally active anti-mitotic agent that binds tubulin, destabilizes microtubulin polymerization, and arrests tumor cell growth at the G2/M phase. Its tubulin binding site is distinct from that of other microtubulin inhibitors such as taxanes, colchicines, and vinca alkaloids. Indibulin does not bind acetylated (neuronal) tubulins and, in contrast to all other microtubulin inhibitors, has not caused neurotoxicity in animal models or in patients enrolled in ongoing Phase I clinical trials.

INDOLE-3-GLYOXYLAMIDE<sup>3</sup>

Indole-3-Glyoxylamide is a 2-(1H-indol-3-yl)-2-oxoacetamide in which the indole ring fused with glyoxylamide side chain at 3<sup>rd</sup> position.



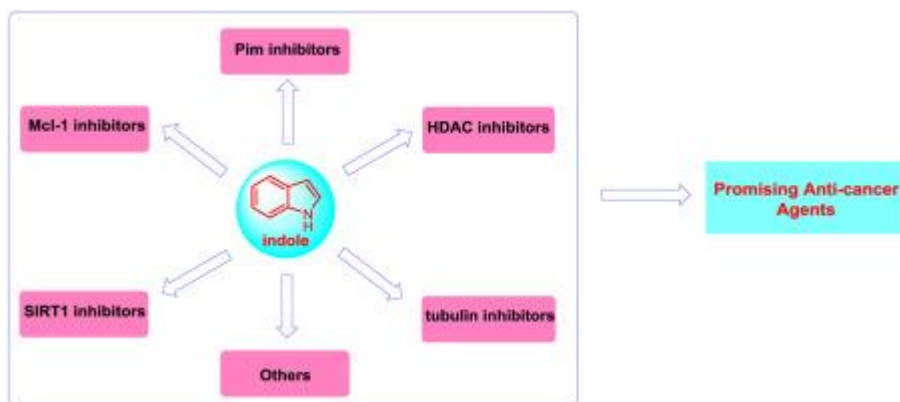
## 2-(1H-indol-3-yl)-2-oxoacetamide

### Chemical Properties of Indole-3-glyoxylamide

- a) **Chemical Name-** 2-(1H-indol-3-yl)-2-oxoacetamide  
 b) **Formula -** C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>

- c) **Molecular weight-** 188.18  
 d) **Appearance-** Yellow powder  
 e) **Solubility-** Soluble in Chloroform, Dichloromethane, Ethyl Acetate, DMSO, Acetone, etc.  
 f) **SMILES-**  
C1=CC=C2C(=C1)C(=CN2)C(=O)C(=O)N

Several small synthetic molecules that have an indole nucleus as a core structure have been identified as tubulin inhibitors. Among these, several aroylindoles, diarylindoles and indolylglyoxyamides have shown good inhibition towards the tubulin polymerization.

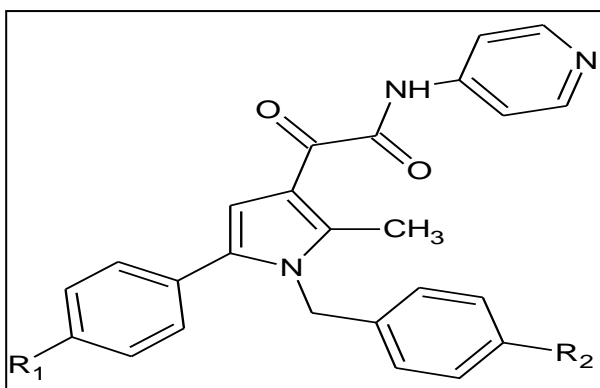


This article reviews the tubulin inhibition activities of several important new indole classes such as indolylglyoxyamide and its derivatives. Because the indole glyoxylamide nucleus present in Indibulin drug (Ongoing Phase-I clinical trials) The versatility of new generation indolylglyoxyamide would represent a fruitful pharmacophore for development of better anticancer agents. Researchers have been attracted toward designing more potent indolylglyoxyamide derivatives having inhibition of tubulin polymerization. This review article has also been made about the fused indole analogs as tubulin inhibitors.

### 1. Ebrahim Saeedian Moghadam, et al., 2018 Design, synthesis and cytotoxicity evaluation of indibulin analogs.<sup>(4)</sup>

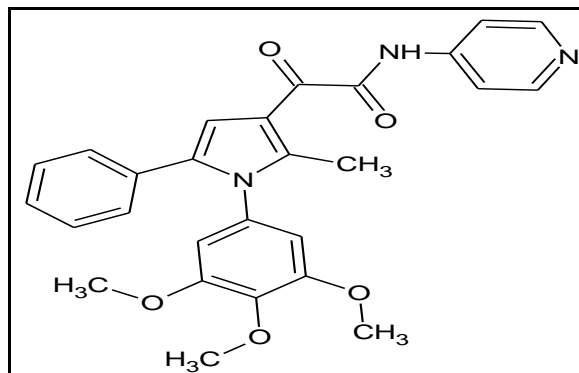
The design and synthesis of new indibulin analogs were carried out in order to investigate their anti-cancer activity. The target compounds 4a-i were synthesized in multi-step reactions starting with the related indole derivatives. Compound 4f shows the highest cytotoxic activity on HT-29 and Caco-2 cell lines with the respective half maximum inhibitory concentration

(IC<sub>50</sub>) values of 5.1 μm and 7.3 μm. In the case of the T47-D cell line, compound 4c exerts the best cytotoxic activity with an IC<sub>50</sub> value of 11.5 μm. In the cell cycle analysis on HT-29 cells, compound 4f at 5.1 μm showed an increase in the percentage of cells in the sub-G1 phase.



2. **Ebrahim saeedian moghadam.et.al.,2018** synthesized 2-[2-methyl-5-phenyl-1-(3,4,5- trimethoxyphenyl)-1h-pyrrol-3-yl]-2-oxo-n-(pyridin-4-yl) acetamide(5) as a novel compound derived from the indibulin and combretastatinscaffolds, which are known anti-mitotic agents, using a multistep reaction then tested its cytotoxic activity against three breast cancer cell lines,

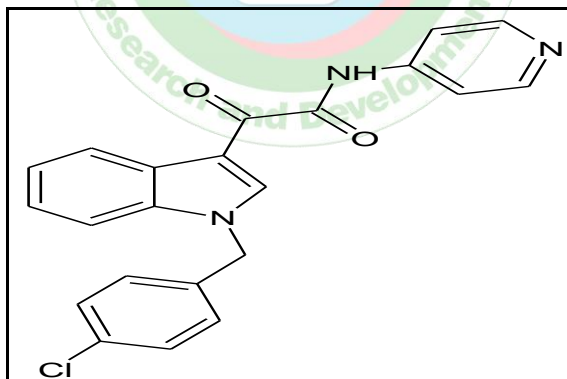
namely, mcf-7, t47-d, and mda-mb 231 as well as normal cell line nih-3t3, by 3-(4,5-dimethylthiazolyl2-yl)-2,5-diphenyl tetrazolium bromide (mtt) assay. The biological activity results showed good cytotoxicity on cancerous cell lines (ic50 value 27.7–39.2  $\mu$ m) and low toxicity on normal cell line (nih-3t3, ic50 value > 100  $\mu$ m).



3. **Sonia Gapoor, et al 2018 Indibulin dampens microtubule dynamics and produces synergistic antiproliferative effect with vinblastine in MCF-7 cells: Implications in cancer chemotherapy.**<sup>6</sup>

Indibulin, a synthetic inhibitor of tubulin assembly, has shown promising anticancer activity with a minimal neurotoxicity in preclinical animal studies and in Phase I clinical trials for cancer chemotherapy. Indibulin Further, the combination of indibulin with an anticancer drug vinblastine was found to exert synergistic cytotoxic effects on MCF-7 cells. Interestingly, indibulin displayed a stronger effect on

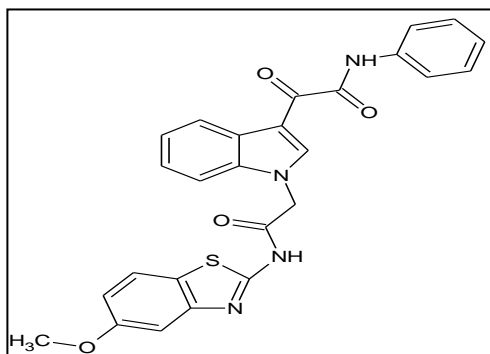
the undifferentiated neuroblastoma (SH-SY5Y) cells than the differentiated neuronal cells. Unlike indibulin, vinblastine and colchicine produced similar depolymerizing effects on microtubules in both differentiated and undifferentiated SH-SY5Y cells. The data indicated a possibility that indibulin may reduce chemotherapy-induced peripheral neuropathy in cancer patients.



4. **Sravanthi Devi Guggilapu.et.al., 2017 Synthesis of thiazole linked indolyl-3-glyoxylamide derivatives as tubulin polymerization INHIBITORS**<sup>7</sup>

synthesized a series of thiazole linked indolyl-3-glyoxylamide derivatives and evaluated their in vitro cytotoxic activity against DU145 (prostate), PC-3 (prostate), A549 (lung) and HCT-15 (colon) cancer cell lines by employing the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Among all the synthesized compounds, compound 13d

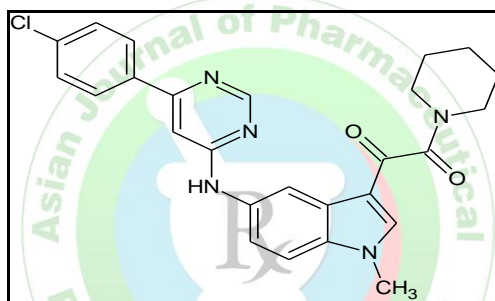
displayed cytotoxicity of IC<sub>50</sub> = 93 nM towards DU145 cancer cell line. The most active compound 13d was also tested on RWPE-1 cells and was found to be safe compared to the DU145 cells. The target compounds were also evaluated for their inhibition activity of tubulin polymerization.



**5. Sravanthi Devi Guggilapu.et.al.,2017 Synthesis of C5-tethered indolyl-3-glyoxylamide derivatives as tubulin polymerization inhibitors<sup>8</sup>**

synthesized a series of C5-tethered Indolyl-3-glyoxylamide derivatives and evaluated their *in vitro* cytotoxic activity against DU145 (prostate), PC-3 (prostate), A549 (lung) and HCT-15 (colon) cancer cell lines by employing the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Among

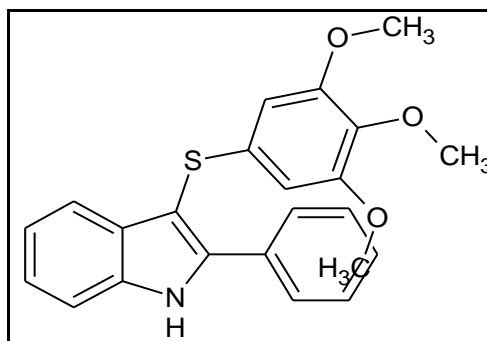
all the synthesized compounds, compound 7f displayed cytotoxicity of  $IC_{50} = 140$  nM towards DU145 cancer cell line. The treatment of DU145 cells with 7f led to inhibition of cell migration ability. Structure of representative bioactive compounds containing indole and pyrimidine moieties.



**6. Renukadevi Patil.et.al., 2016 Indole molecules as inhibitors of tubulin polymerization: potential new anticancer agents<sup>9</sup>**

synthesis, anticancer and tubulin inhibition activities of several important new indole classes such as 2-phenylindoles, oxindoles, indole-3-acrylamides,

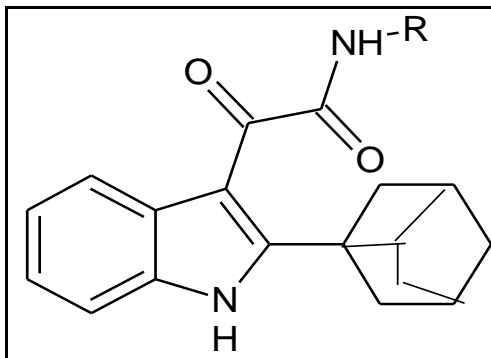
indolines, aroylindoles, carbozoles, azacarbolines, and annulated indoles.



**7. Hong-Yu Hu , et al., 2016 Novel N-Substituted 2-(2-(Adamantan-1-yl)-1H-Indol3-yl)-2-Oxoacetamide Derivatives: Synthesis and Biological Evaluation<sup>10</sup>**

In this study, a series of novel N-substituted 2-(2-(adamantan-1-yl)-1H-indol-3-yl)-2-oxoacetamide derivatives were synthesized, and evaluated for their cytotoxicity in human cell lines including Hela (cervical cancer), MCF7 (breast cancer ) and HepG2

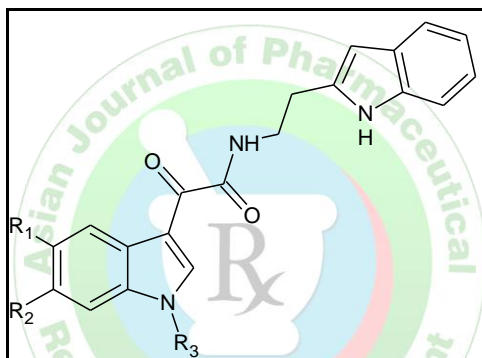
(liver cancer). Several compounds were found to have potent anti-proliferative activity against those human cancer cell lines and compound 5r showed the most potent biological activity against HepG2 cells with an  $IC_{50}$  value of  $10.56 \sim 1.14$   $\mu$ M.



**8. Mukund P. Tantak et.al., 2016 Sequential one-pot synthesis of bis(indolyl)glyoxylamides: Evaluation of antibacterial and anticancer activities<sup>11</sup>**

A series of bis(indolyl)glyoxylamides 10a–n has been designed and synthesized. In situ generated indole-3-glyoxal chloride from the reaction of readily available indole 9 with oxalyl chloride was treated with tryptamine to produce bis(indolyl)glyoxylamides 10a–n in 82–93% yields. All the synthesized bis(indolyl)glyoxylamides were well characterized and tested for

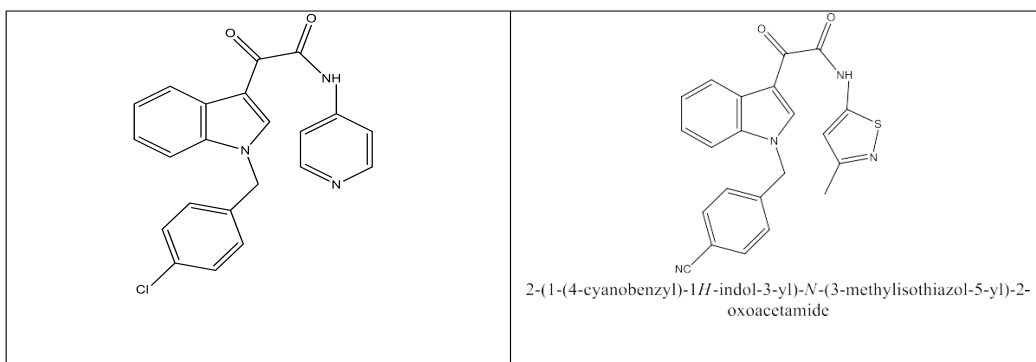
their antibacterial activity against Gram-positive and Gram-negative bacterial strains. Compounds 10d, 10g and 10i were found to display potent antibacterial activity against Gram-negative strain. Further, the cytotoxicity of bis(indolyl)glyoxylamides 10a–n were evaluated against a panel of human cancer cell lines.



**9. Helen.E.Colley.et.al.,2015 An orally bioavailable, indole-3-glyoxylamide based series of tubulin polymerization inhibitors showing tumor growth inhibition in a mouse xenograft model of head and neck cancer<sup>(12)</sup>**

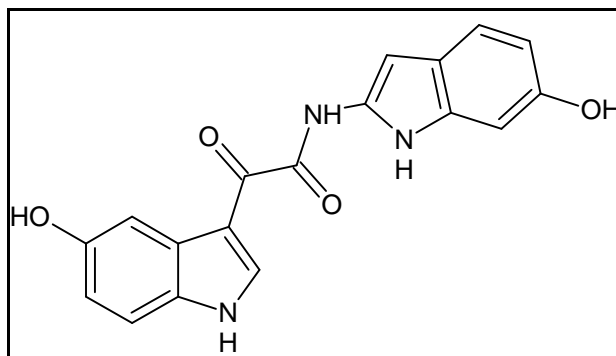
A new series of related compounds, modified according to a strategy of reducing aromatic ring count and introducing a greater degree of saturation, which retain potent tubulin polymerization activity but with a distinct SAR from previously documented libraries. A subset of active compounds from the reported series is shown to interact with tubulin at the colchicine binding

site, disrupt the cellular microtubule network, and exert a cytotoxic effect against multiple cancer cell lines. Two compounds demonstrated significant tumor growth inhibition in a mouse xenograft model of head and neck cancer, a type of the disease which often proves resistant to chemotherapy, supporting further development of the current series as potential new therapeutics.



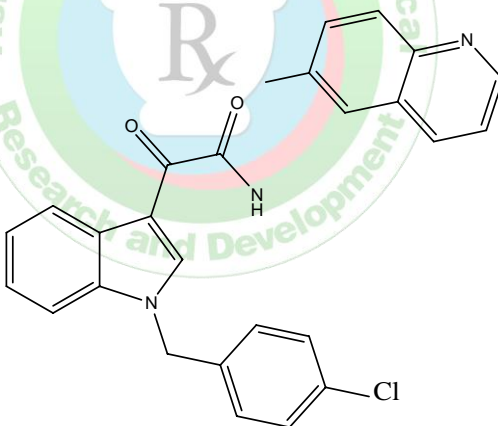
10. Mardia T. El Sayed.et.al., 2015 **Indoles as anti-cancer agents**<sup>13</sup> Indoles are natural products which are well known for its anti-cancer activity due to its ability to induce cell death for many cancer cell lines. This review addresses indoles as natural products,

mechanism of indoles, facilitated induction and recent studies with indoles and related compounds that were investigated via anti-cancer screening and that led to drug approval.



11. Yang Zheng.et.al.,2015 **Fe-catalyzed regioselective Friedel–Crafts hydroxyalkylation of 4 N-substituted glyoxylamide with indoles**<sup>(14)</sup>

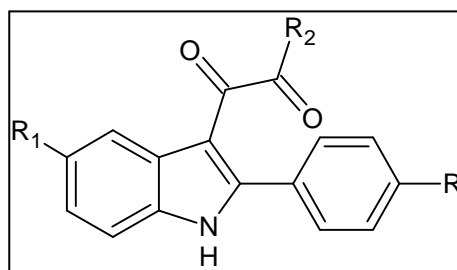
An efficient regioselective Friedel–Crafts hydroxyalkylation of N-substituted glyoxylamide with various indoles catalyzed by Lewis acids was developed. The reactions proceeded smoothly at room temperature and the 2-hydroxy-2-(1H-indol-3-yl)-N-substituted acetamide resulted from the reactions catalyzed by FeSO<sub>4</sub> were synthesized in excellent yields (up to 93%). While the bisindole compounds were obtained when FeCl<sub>3</sub> was used as a catalyst in excellent yields (up to 92%).



12. N.M.Jagadeesh.et.al.,2014 **Synthesis And Molecular Docking Study Of N-Alkyl/Aryl-2-Aryl Indol-3-Yl Glyoxylamides As Novel Anticancer Agents**.<sup>15</sup>

Synthesis of series of new appropriately N- alkyl/aryl-2-aryl indol-3-yl glyoxylamides by reaction of 2-arylindoles,oxalyl chloride and different amines in one pot reaction. Structure of all the new compounds were

elucidated by spectral analysis and evaluated *in silico* docking study with MDM2 receptor bind p53 and PBR protein.

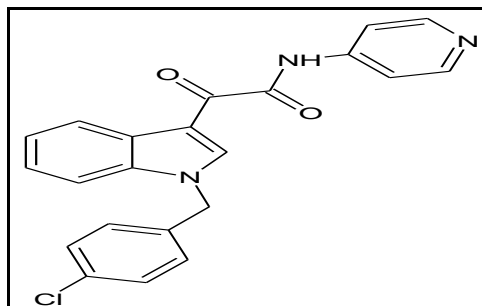




### 13. Nagendra Kumar Kaushik.et.al.,2013 Biomedical Importance of Indoles<sup>16</sup>

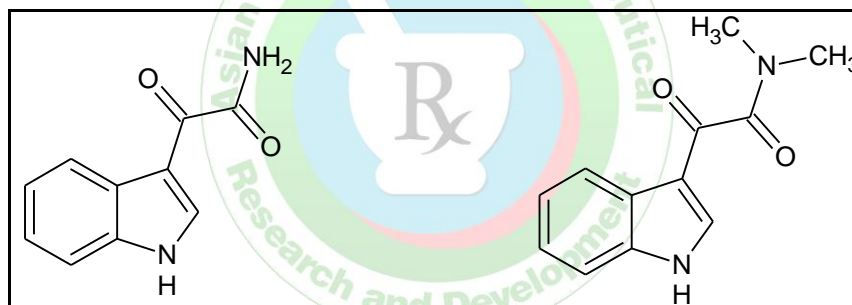
Indole nucleus is an important element of many natural and synthetic molecules with significant biological

activity. This review covers some of the relevant and recent achievements in the biological, chemical and pharmacological activity of important indole derivatives in the areas of drug discovery and analysis



14. Vijayakumar N. Sonar.et.al.,2012<sup>17</sup> reported that the title compounds, C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>, (I), and C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>, (II), the two carbonyl groups were oriented with torsion angles of 149.3 (3) and 88.55 (15)<sup>0</sup>, respectively. The single-bond distances linking the two carbonyl groups were 1.528 (4) and 1.5298 (17) Å, respectively. In (I), the molecules were linked by an elaborate system of N—H···O hydrogen bonds, which form adjacent R<sup>2</sup><sub>2</sub>(8) and R<sup>4</sup><sub>2</sub>(8) ring motifs to generate a ladder-like construct. Adjacent ladders are

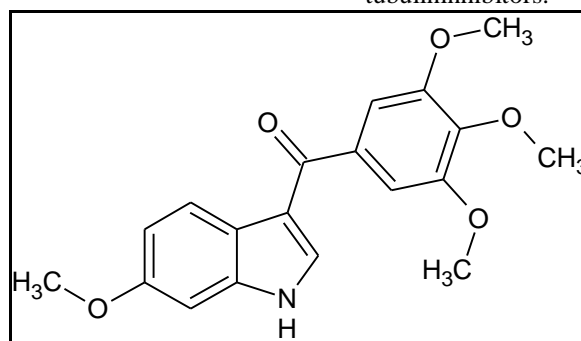
further linked by N—H···O hydrogen bonds to build a three-dimensional network. The hydrogen bonding in (II) was far simpler, consisting of helical chains of N—H···O-linked molecules that follow the 2<sub>1</sub> screw of the *b* axis. It said that it was the presence of an elaborate hydrogen-bonding system in the crystal structure of (I) that leads to the different torsion angle for the orientation of the two adjacent carbonyl groups from that in angle for the orientation of the two adjacent carbonyl groups from that in (II).



### 15. Shivaputra A Patil.et.al.,2012<sup>18</sup>

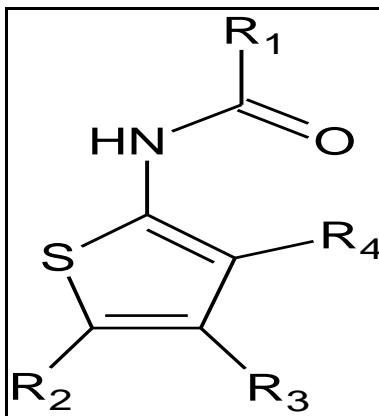
Indole molecules as inhibitors of tubulin polymerization: potential new anticancer agents reviews the synthesis, biological activities and SARs of

tubulin inhibitors such as several aroylindoles, arylthioindoles, diarylindoles and indolylglyoxyamides. Brief mention has also been made about the fused indole analogs as tubulin inhibitors.



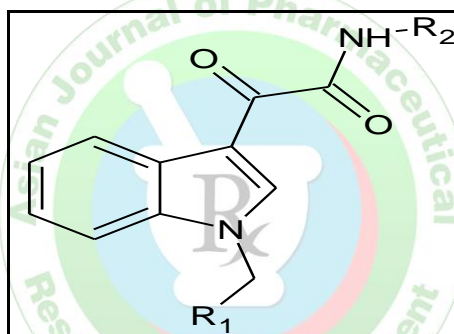
16. Ran Cao.et.al.,2012 Discovery of Novel Tubulin Inhibitors via Structure-Based Hierarchical Virtual Screening<sup>(19)</sup> To discover novel tubulin inhibitors, we performed structure-based virtual screening against the colchicine binding pocket. In combination with a hierarchical docking and scoring procedure, the

structural information of an additional subpocket in colchicine site was applied to filter out the undesired docking hits. This strategy automatically resulted in 63 candidates meeting the structural and energetic criteria from a screening library containing approximately 100 000 diverse druglike compounds.



17. **Tien-Heng Huang.et.al., 2011** Antiproliferative Effects of N-Heterocyclic Indolyl Glyoxylamide Derivatives on Human Lung Cancer Cells<sup>(20)</sup> N-Heterocyclic indolyl glyoxylamide compounds are derived from the antimicrotubule agent D24851, which exhibits anticancer activity after oral administration. The actions of these compounds on lung cancer cells are still unknown. Here, we investigated the effects of two N-heterocyclic indolyl glyoxylamides, BPR0C259

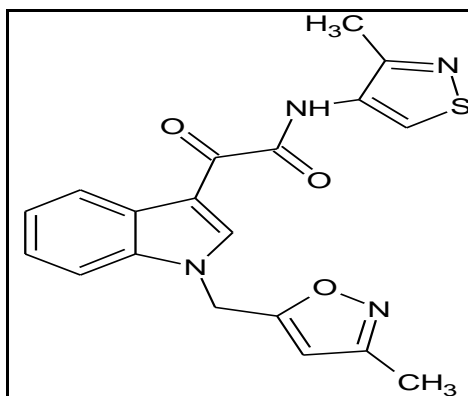
and BPR0C123, on non-small human lung cancer cells. Materials and Methods: 3-[4,5- dimethylthiazol-2-yl]2,5-diphenyltetrazolium bromide (MTT) assay was used to determine the half maximal inhibitory concentration (IC<sub>50</sub>), cell viability and radiation response of A549 cells and H1299 cells. Apoptosis was determined by sub-G1 ratio, colony formation assay and caspase-3 activation. Cell cycle distribution was detected using flow cytometry.



18. **Chih-Bo Hu.et.al.,2010** BPR0C261 is a novel orally active antitumor agent with antimitotic and anti-angiogenic activities.<sup>(21)</sup>

BPR0C261 is a synthetic small molecule compound cytotoxic against human cancer cells and active prolonging the lifespan of leukemia mice. In the present study, we further investigated the mechanisms of its anticancer action and found that BPR0C261 inhibited microtubule polymerization through

interacting with the colchicine binding sites on tubulins, disrupted microtubule arrangement and caused cell cycle arrest at G2/M phase in cancer cells. BPR0C261 also inhibited the clonogenic growths of cancer cells and showed cytotoxicity against human cervical cancer cells of multidrug-resistant phenotype

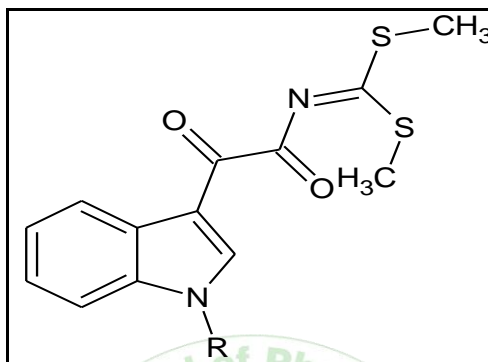




### 19. Peter Kutschya<sup>1</sup>, et.al., 2010 Glyoxyl Analogs of Indole Phytoalexins: Synthesis And Anticancer Activity<sup>(22)</sup>

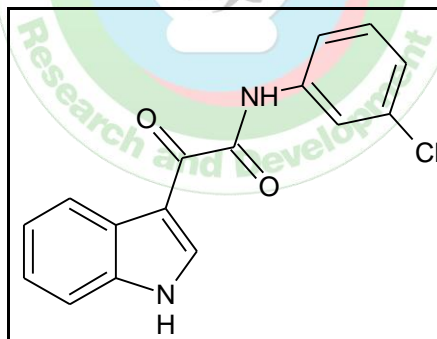
Glyoxyl analogs of indole phytoalexins brassinin, 1-methoxybrassinin, brassitin, 1-methoxybrassinin and 1-methoxybrassinin B were prepared, using (1H-indol-3-yl)-, (1-methoxyindol-3-yl)- and [1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)indol-3-yl]glyoxyl chlorides as starting compounds. Synthesized products were examined for their antiproliferative activity against human cancer cell lines Jurkat (T-cell acute lymphoblastic leukemia), MCF-7 (breast adenocarcinoma, estrogen receptor positive), MDA-

MB-231 (breast adenocarcinoma, estrogen receptor-negative), HeLa (cervical adenocarcinoma), CCRF-CEM cell line (T-cell acute lymphoblastic leukemia) and A-549 cell line (lung adenocarcinoma), and their activity compared with natural phytoalexins and corresponding (1H-indol-3-yl)acetic acid derivatives. The highest potency with IC<sub>50</sub> 3.3–66.1 μmol l<sup>-1</sup> was found for glyoxyl analogs of 1-methoxybrassinin B.



20. Beining Chen et.al., 2009 report here the synthesis of a library of indole-3-glyoxylamides and their evaluation as potential antiprion agents<sup>(23)</sup>. A number of compounds demonstrated submicromolar activity in a cell line model of prion disease together with a defined structure-activity relationship, permitting the design of

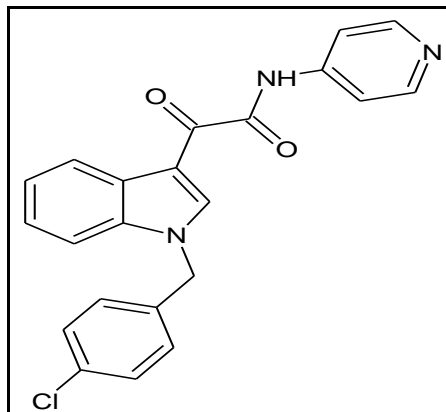
more potent compounds that effected clearance of scrapie in the low nanomolar range. Thus, the indole-3-glyoxylamides described herein constitute ideal candidates to progress to further development as potential therapeutics for the family of human prion disorders.



### 21. Anke Wienecke et.al., 2009 Indibulin, a Novel Microtubule Inhibitor, Discriminates between Mature Neuronal and Nonneuronal Tubulin<sup>(24)</sup>

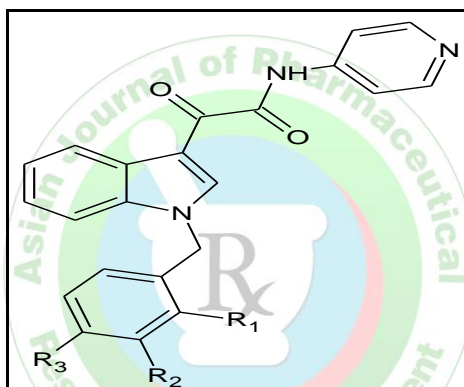
Microtubule inhibitors interfere with microtubule dynamics, causing cell cycle arrest and apoptosis. These effects are responsible for the chemotherapeutic activities of members of the taxane and Vinca alkaloid families in oncology. Unfortunately, a major side effect of the taxanes and Vinca alkaloids is the development of peripheral neuropathies. Indibulin (N-[pyridin-4-yl]-[1-(4-chlorobenzyl)-indol-3-yl]-glyoxyl-amid; D-24851; ZIO-301), a novel synthetic small molecule microtubule inhibitor, destabilizes microtubules and has antitumor activity but does not exhibit neurotoxicity in preclinical animal studies. In the

present study, it has been found that indibulin is able to discriminate between highly posttranslationally modified tubulin present in mature neuronal microtubules, and less-modified tubulin present in immature neuronal or nonneuronal microtubules. Vincristine and colchicine act on either tubulin equally well. The binding site of indibulin on mature neuronal microtubules seems to be inaccessible due to the posttranslational modifications, a theory that is supported by the observation that indibulin did not disrupt the integrity of highly modified microtubules present in neurites of pheochromocytoma (PC12) cells.



**22. Pascal Marchand et.al., 2009 Synthesis and structure–activity relationships of N-aryl(indol-3-yl)glyoxamides as antitumor agents<sup>(25)</sup>**

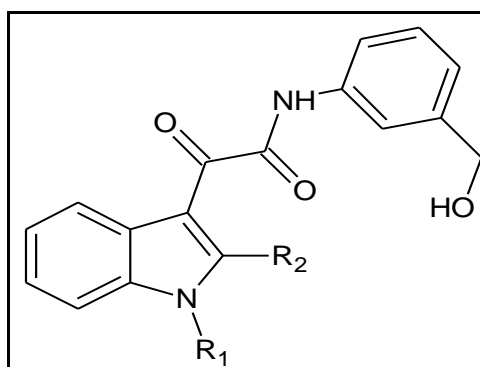
The synthesis and study of the structure–activity relationships of cytotoxic compounds based on N-pyridinyl or N-aryl-2-(1-benzylindol-3-yl)glyoxamide skeleton, represented by the lead structures D-24241 and D-24851, are described. The presence of N-(pyridin-4-yl) moiety was crucial for activity and 2-[1-(4-chloro-3-nitrobenzyl)-1H-indol-3-yl]-2-oxo-N-(pyridin-4-yl)acetamide (55), the most potent derivative, showed IC<sub>50</sub> = 39 nM, 51 nM and 11 nM against HeLa/KB (human cervix carcinoma), L1210 (murine leukemia) and SKOV3 (human ovarian carcinoma) cell lines proliferation assay, respectively, as active as the lead compounds.



**23. Mark J. Thompson et.al 2009 Design, Synthesis, and Structure-Activity Relationship of Indole-3-glyoxylamide Libraries Possessing Highly Potent Activity in a Cell Line Model of Prion Disease.(26)**

Transmissible spongiform encephalopathies (TSEs) are a family of invariably fatal neurodegenerative disorders for which no effective curative therapy currently exists. We report here the synthesis of a library of indole-3-glyoxylamides and their evaluation as potential antiprion agents. A number of compounds demonstrated submicromolar activity in a cell line model of prion disease together with a defined

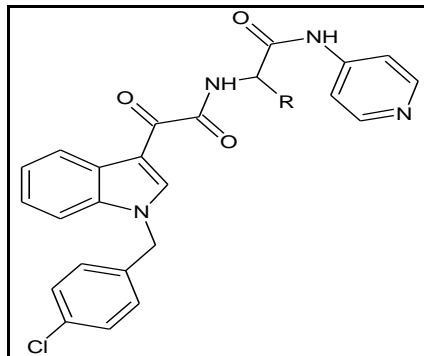
structure-activity relationship, permitting the design of more potent compounds that effected clearance of scrapie in the low nanomolar range. Thus, the indole-3-glyoxylamides described herein constitute ideal candidates to progress to further development as potential therapeutics for the family of human prion disorders.



#### 24. Maud Antoine.et.al.,2008 Side chain modifications of (indol-3-yl)glyoxamides as antitumor agents.(27)

New series of analogues of N-(pyridin-4-yl)-2-[1-(4-chlorobenzyl)-indol-3-yl]glyoxamide D-24851 were synthesized, characterized and tested for their in vitro anticancer properties. In the first series, an amino acid spacer was introduced in the glyoxamide chain of D-

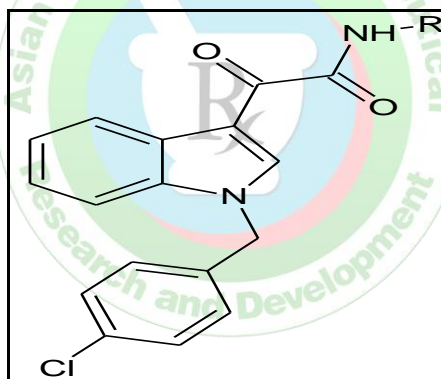
24851. In the second series, the glyoxamide chain was moved to positions 4 and 5 of indole skeleton. These new compounds were tested on four cancer cell lines (KB, SK-OV-3, NCI-H460 and SF-268), with promising activity for the glycine derivative.



#### 25. David A. James.et.al.,2008 Indole- and indolizine-glyoxylamides displaying cytotoxicity against multidrug resistant cancer cell lines.(28)

SAR studies of a series of indole- and indolizine-glyoxylamides that demonstrate substantial in vitro anti-proliferative activities against cancer cell lines, including multidrug resistance (MDR) phenotypes. The

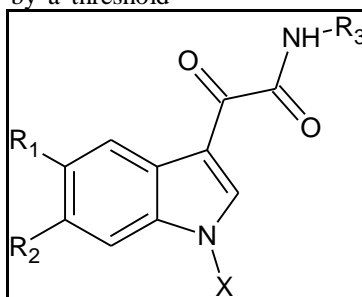
in vitro cytotoxic effects have been demonstrated across a wide array of tumor types of various origins (e.g., breast, colon, uterine).



#### 26. Marina N. Semenova.et.al.,2007 In vivo Evaluation of Indolyl Glyoxamides in the Phenotypic Sea Urchin Embryo Assay(29)

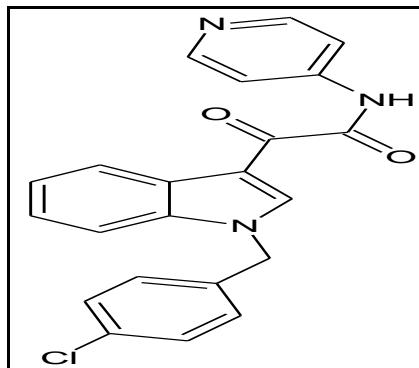
one-pot' phenotypic in vivo assay for the rapid evaluation of potential tubulin inhibitors using the sea urchin embryo model. An effect of a small molecule on two specific developmental stages of sea urchin embryo, namely:(i) fertilized egg test for antimitotic activity and(ii) behavioral monitoring of a free-swimming blastulae for changes in the embryo swimming pattern could be quantified by a threshold

concentration resulting in respective abnormalities. Derivatives of the clinical candidate D-24851 featured good correlation between activity in tubulin polymerization assay and our in vivo data. Importantly, we demonstrated that in these series, the N-substitution of indole is non-essential to attain profound in vitro and cellular effects.



**27. Andrea Brancale et al., 2006** Several tubulin polymerization inhibitors characterized by the presence of indole nucleus (30) that have been obtained from natural sources or have been prepared by semi-synthesis. An increasing number of synthetic indoles have been reported. Anti-tubulin agents obtained by synthesis having indole as a core nucleus had been

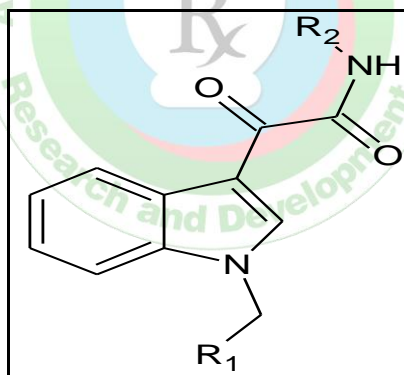
reviewed. The synthesis, the biological activity, and the structure-activity relationship aspects of 3-formyl-2-phenylindoles, heterocombretastatins, diarylindoles, 2-arylindoles, D-24851, 2-aryl-3-arylindoles, 3-aryl and 1-arylindoles, and arylthioindoles are also been discussed.



**28. Wen-Tai Li et al., 2003 Synthesis and Biological Evaluation of N-Heterocyclic Indolyl Glyoxylamides as Orally Active Anticancer Agents (31)**

A series of N-heterocyclic indolyl glyoxylamides were synthesized and evaluated for in vitro and in vivo anticancer activities. They exhibited a broad spectrum of anticancer activity not only in murine leukemic cancer cells but also in human gastric, breast, and uterus cancer cells as well as their multidrug resistant

sublines with a wide range of IC<sub>50</sub> values. They also induced apoptosis and caused DNA fragmentation in human gastric cancer cells. Among the compounds studied, 7 showed the most potent activity of growth inhibition (IC<sub>50</sub> 17-1711 nM) in several human cancer cells.



**Result and Discussion**

- The versatility of new generation indolylglyoxyamide would represent a fruitful pharmacophore for development of better anticancer agents.
- This review focused on overview of drug molecule of indole-3-glyoxyamide.
- It shows that various modification at 2<sup>nd</sup> position of indole nucleus and side chain of glyoxyamide and shows prominent tubulin inhibition.
- We hope that the review could give a guide to develop newer anti-cancer agents with greater potency against drug-sensitive and drug-resistant cancers in the future.

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