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RECENT ADVANCE IN ANTI-CANCER ACTIVITY OF INDOLE DERIVATIVES

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ABSTRACT

Indole is a bicyclic aromatic heterocyclic organic compound comprising of a six membered benzene ring fusedto a five-membered nitrogen-containing pyrrole ring. It is an excellent scaffold in drug discovery which provides numerous opportunities in the discovery of novel drugs with different mechanism of action. It has a very unique property of mimicking different structures of proteins and binding to enzymes in a reversible manner. A vast research has occurred on indole and its derivatives which resulted in many approved indole containing drugs in the world market as well as many are in the pipeline stages. The recent identification of an indole analog as a potential new anticancer lead. Indole nucleus is continuously drawing interest for development of newer drug moiety due to its wide range of activities like anticancer, antibacterial, antifungal, anti-malarial, anticonvulsant and anti-inflammatory. The research is going on in nucleus. In recent years, a wide range of research has been done in the field of anti-cancer drug development. Since indole nucleus has shown quite good response as an anticancer agent, hence this nucleus has become an interest in the field of research. Indole is present in Vinca alkaloid which can be used as an anti-cancer agent. So keeping in mind this point indole has been used for better anti-cancer activity of target compound. This review was focused on the indole and its derivatives that are now in development.

KEYWORDS: Indole, Anticancer, Anti bacterial, Anti-inflammatory.

INTRODUCTION

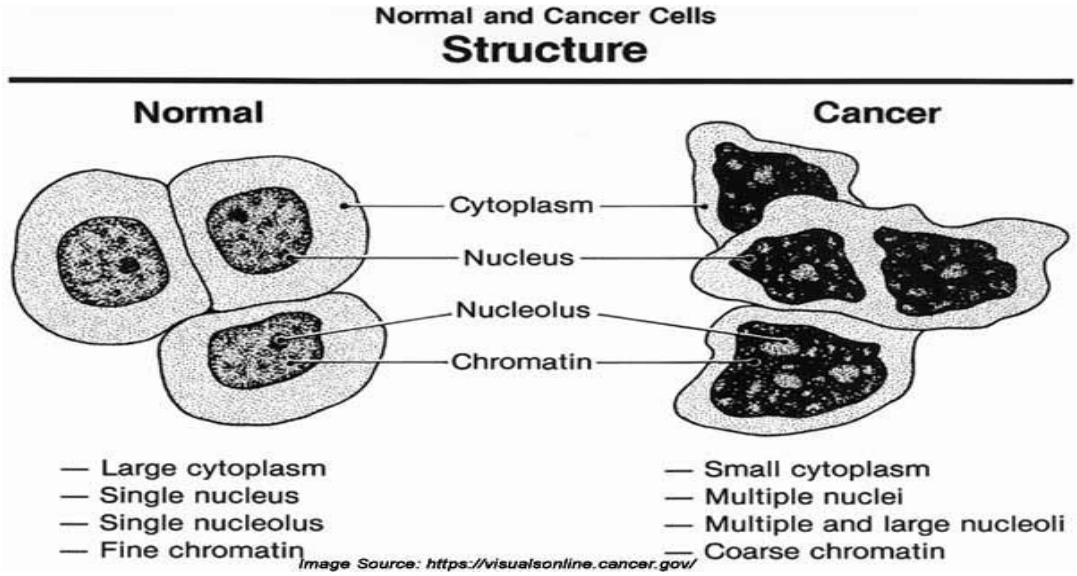
Cancer, known medically as a malignant neoplasm, is a broad group of various diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream.

Not all tumors are cancerous. Benign tumours do not grow uncontrollably, do not invade neighboring tissues, and do not spread throughout the body. There are over 200 different known cancers that afflict humans. Determining what causes cancer is complex.

Many things are known to increase the risk of cancer, including tobacco use, certain infections, radiation, lack of physical activity, obesity, and environmental pollutants. These can directly damage genes or combine with existing genetic faults within cells to cause the disease. Approximately five to ten percent of cancers are entirely hereditary.

Cancer can be detected in a number of ways, including the presence of certain signs and symptoms, screening tests, or medical imaging. Once a possible cancer is detected it is diagnosed by microscopic examination of a tissue sample.

Cancer is usually treated with chemotherapy, radiation therapy and surgery. The chances of surviving the disease vary greatly by the type and location of the cancer and the extent of disease at the start of treatment. While cancer can affect people of all ages, and a few types of cancer are more common in children, the risk of developing cancer generally increases with age.[1]



Types of cancer: Cancers are classified by the type of cells that constitutes the tumor and, therefore, the tissue presumed to be the origin of the tumor.

• Carcinoma: cancer that affects the epithelial tissues that lines internal organs. The most common cancers like **breast, prostate, lung and colon** cancer come under this category.

• Sarcoma: cancer that begins in connective or supportive tissue (e.g., bone, cartilage, fat, muscle, blood vessels).

• Leukemia: cancer related to blood-forming tissue.

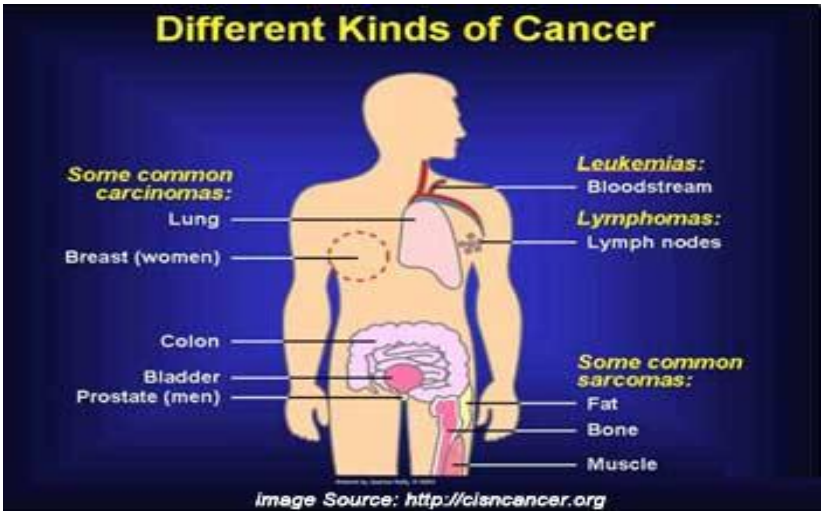
• Lymphoma: cancers that affects the lymphatic tissue.

• Myeloma: cancer that begins in bone marrow.

• Blastoma: cancer that begins in embryonic tissue.

• Central nervous system cancers: cancers that begin in the tissues of the brain and spinal cord.[2]

According to the National Cancer Institute, there are over 100 types of cancer. The most common types include lung, breast, and prostate cancer. These 3 alone account for an estimated 689,000 new cases every year.

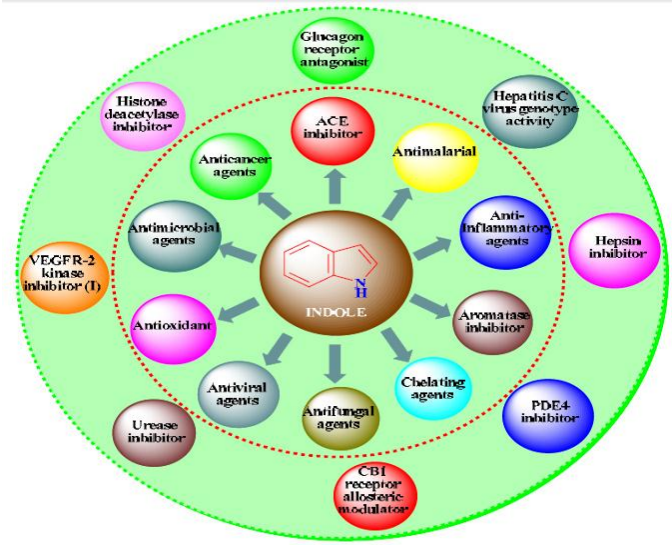


Indole

The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. A number of heterocyclic derivatives containing nitrogen atom serve as a unique and versatile scaffolds for experimental drug design. The name indole is deriving from the words indigo and oleum, since indole was first isolated by treatment of the indigo dye with oleum. Indole chemistry began to develop with the study of the dye indigo.

Indole is a benzopyrrole in which the benzene and pyrrole ring are fused through the 2- and 3- positions of the pyrrole nucleus. The indole ring is also found in many natural products such as the indole alkaloids, fungal metabolites and marine natural products.

Indole derivatives are found to contain several biological activities those antibiotic, anti-inflammatory, analgesic, anticonvulsant, antimalarial, anticancer, antiulcer.



Reactivity of Indole

Indole is aromatic heterocycle, but exhibit very distinctive reactivity. Here are some general rules.

❖ The nitrogen is not basic. (pKa -3.6)

❖ Indole can readily undergo aromatic electrophillic substitution. The C-3 position is the most nucleophillic, followed by the N and C-2 positions.

❖ The C-2 – C-3 bond can often react like alkenes.

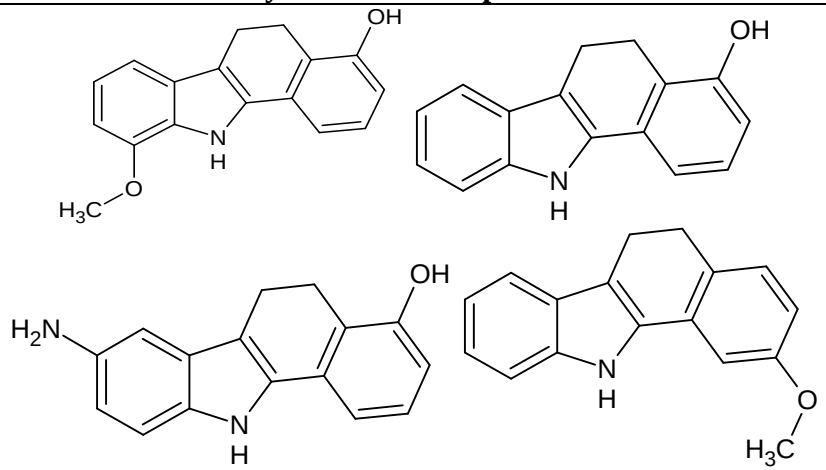
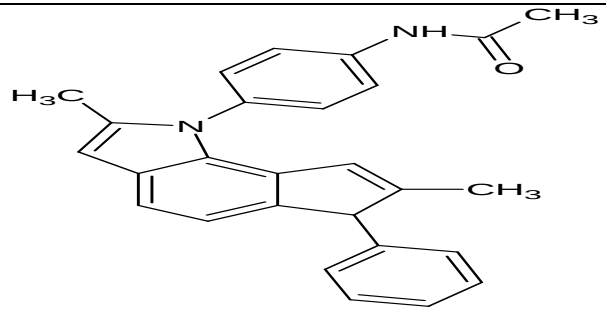
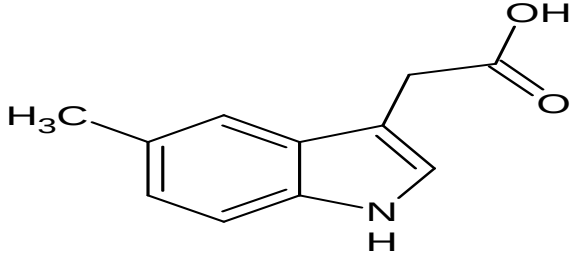
❖ Indole can be deprotonated at nitrogen. The resulting salts can be good nucleophiles.

❖ Highly ionic salts (e.g. Li+, K+) favours N substitution.

❖ Softer counter ions favours C-3 substitution When N is substituted, C-2 can be deprotonated.[3]

In The Recent Years A Number of Indole Derivatives Have Been Synthesized and Found to Display Anti-Cancer Activity.

Indole and their derivatives were evaluated for anticancer activity by various researchers. Here we are presenting a list of few anticancer activities reported by the researchers on indole and their derivatives.

Author	Synthesized Compounds	Therapeutic Indication	Cell lines
Hong et al[4]		Human nasopharyngeal carcinoma and Gastric adenocarcinoma.	HONE-1 & NUGC-3
Garcia et al[5]		(prostate) cancer	PC-3
Rossiteret al.[6]		Lung fibroflasts	V79

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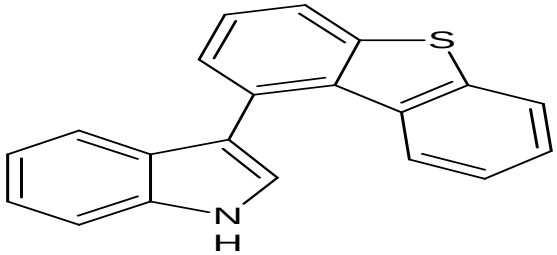
<td>Queirozet al.[7]</td>
<td>  </td>
<td>(Breast adenocarcinoma), (non-small cell lung cancer), and (CNS cancer).</td>
<td>MCF-7, CI-H460 & SF-268</td>
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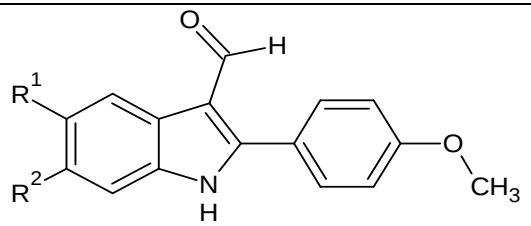
<td>Doris Kaufmann et al[8]</td>
<td> 
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<tr><th>COMP</th><th>R1</th><th>R2</th><th>COMP</th><th>R1</th><th>R2</th></tr>
<tr><td>a</td><td>OMe</td><td>H</td><td>H</td><td>Pr</td><td>H</td></tr>
<tr><td>b</td><td>H</td><td>OMe</td><td>I</td><td>i-Pr</td><td>H</td></tr>
<tr><td>c</td><td>H</td><td>F</td><td>J</td><td>n-Bu</td><td>H</td></tr>
<tr><td>d</td><td>F</td><td>H</td><td>K</td><td>Sec-Bu</td><td>H</td></tr>
<tr><td>e</td><td>H</td><td>Cl</td><td>L</td><td>Ter-Bu</td><td>H</td></tr>
<tr><td>f</td><td>Me</td><td>Cl</td><td>M</td><td>n-Pen</td><td>H</td></tr>
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<td>Human breast cancer cells.</td>
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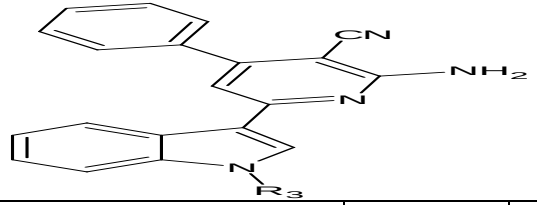
<td>Fan Zhang et al[9]</td>
<td> 
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<tr><th>COMP</th><th>R1</th><th>R2</th><th>R3</th></tr>
<tr><td>A</td><td>3,4,5 – trimethoxy</td><td>H</td><td>H</td></tr>
<tr><td>B</td><td>3- bromo-4,5- dimethoxy</td><td>H</td><td>H</td></tr>
<tr><td>C</td><td>2,3,4- trimethoxy</td><td>H</td><td>H</td></tr>
<tr><td>D</td><td>3,4,5- trimethoxy</td><td>5-Cl</td><td>H</td></tr>
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<td>Anti-tumor activity</td>
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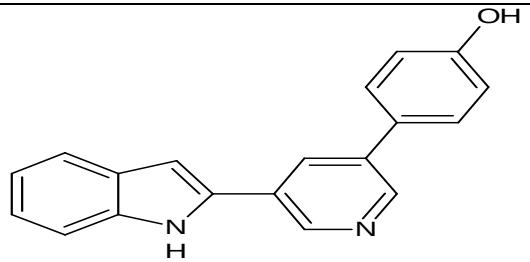
<td>UlrichJacquemard et. al[10]</td>
<td>  </td>
<td>CDK inhibitors</td>
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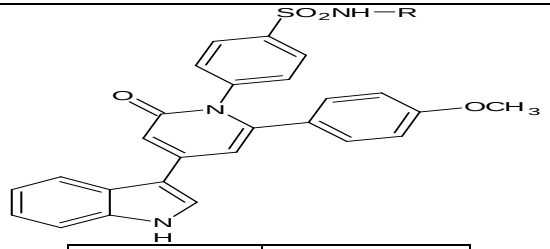
<td>EkhlassNassar et. al.[11]</td>
<td> 
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<tr><th>COMP</th><th>R</th></tr>
<tr><td>A</td><td>H</td></tr>
<tr><td>B</td><td>n-Propyl</td></tr>
<tr><td>C</td><td>C_6H_5</td></tr>
<tr><td>D</td><td>4-$MeOC_6H_4$</td></tr>
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<td>Antitumor and Antimicrobial Activity</td>
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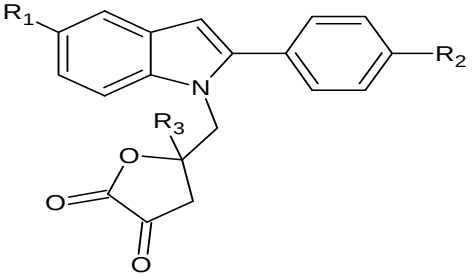
<td>Huasheng Ding et. al[12]</td>
<td> 
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<tr><td>A</td><td>H</td><td>H</td></tr>
<tr><td>B</td><td>OCH3</td><td>H</td></tr>
<tr><td>C</td><td>H</td><td>H</td></tr>
<tr><td>D</td><td>OCH3</td><td>H</td></tr>
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<td>Potent inhibitors for AKT-m TOR signaling pathway kinases</td>
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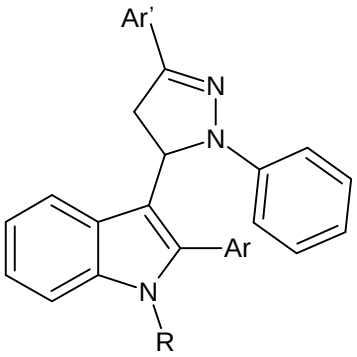
<td> 

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<tr><td>COMP</td><td>R</td><td>Ar</td><td>Ar’</td></tr>
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<tr><td>B</td><td>Allyl</td><td>4-MeC6H4</td><td>3NO2C6H5</td></tr>
<tr><td>C</td><td>Benzyl</td><td>C6H5</td><td>4PhC6H4</td></tr>
<tr><td>E</td><td>Benzyl</td><td>4-MeC6H4</td><td>C6H5</td></tr>
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<td>Antitumor activity</td>
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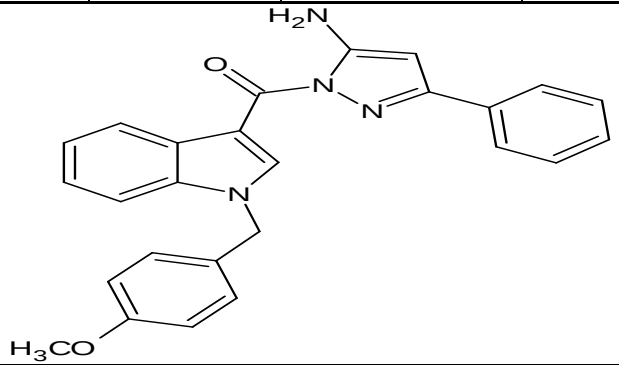
<td>Abdel-RahmanFarghaly et. al[14]</td>
<td> 
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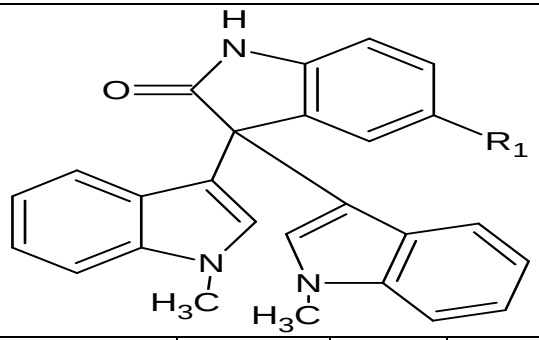
<td> 

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<tr><th>COMP</th><th>R1</th><th>R2</th><th>R3</th></tr>
<tr><td>A</td><td>H</td><td>H</td><td>H</td></tr>
<tr><td>B</td><td>4OCH3</td><td>H</td><td>H</td></tr>
<tr><td>C</td><td>5OCH3</td><td>H</td><td>H</td></tr>
<tr><td>D</td><td>6OCH3</td><td>H</td><td>H</td></tr>
<tr><td>E</td><td>5Cl</td><td>H</td><td>H</td></tr>
<tr><td>F</td><td>5Br</td><td>H</td><td>H</td></tr>
<tr><td>G</td><td>5NO2</td><td>H</td><td>H</td></tr>
<tr><td>H</td><td>H</td><td>H</td><td>CH3</td></tr>
<tr><td>I</td><td>H</td><td>F</td><td>H</td></tr>
<tr><td>J</td><td>4OCH3</td><td>F</td><td>H</td></tr>
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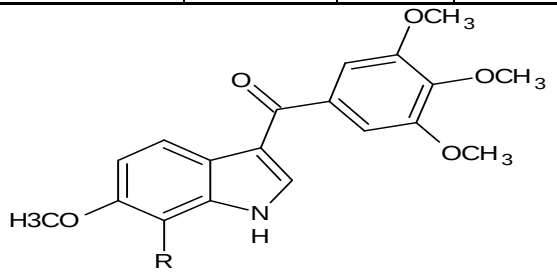
<td>Yu-Shan Wu et. al[16]</td>
<td> 

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<tr><th>COMP</th><th>R</th></tr>
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<tr><td>B</td><td>CH3</td></tr>
<tr><td>C</td><td>CH2CH3</td></tr>
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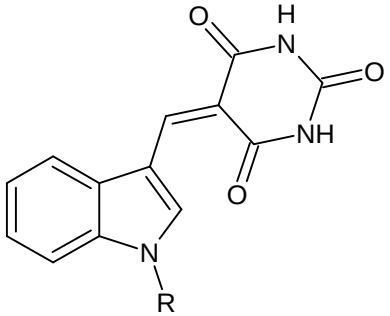
<td> 

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<tr><th>COMP</th><th>R</th><th>R1</th></tr>
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<tr><td>b</td><td>Butene</td><td>H</td></tr>
<tr><td>c</td><td>Butyne</td><td>H</td></tr>
<tr><td>d</td><td>C6H5ethane</td><td>H</td></tr>
<tr><td>e</td><td>C6H5COCH3</td><td>H</td></tr>
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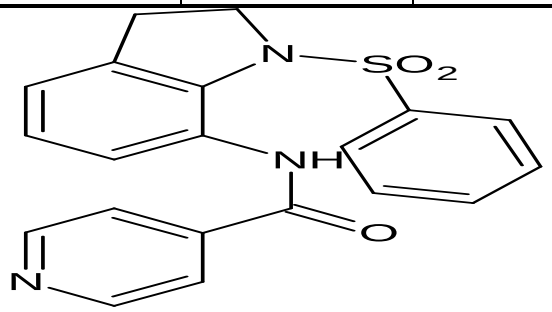
<td>Liou et al[18]</td>
<td> 
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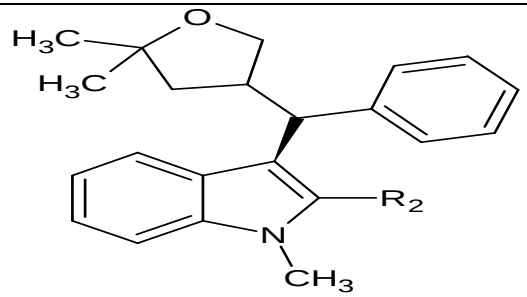
<td>Sigman et al[19]</td>
<td> 

R2= Ph, R1= H (G1 phase arrest), R2= H, R1= COOCH3(G2 phase arrest)</td>
<td>Anticancer activity</td>
<td>MCF-7 cells.</td>
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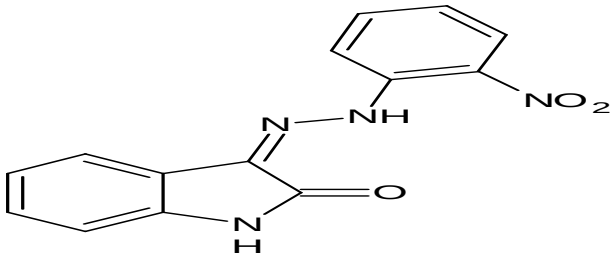
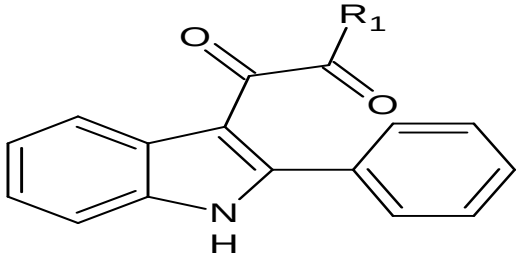
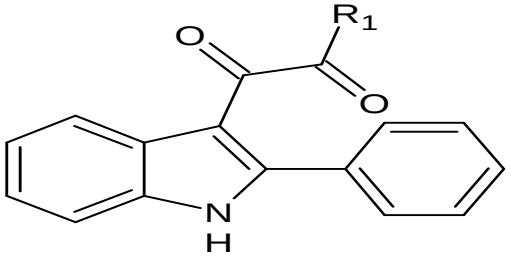
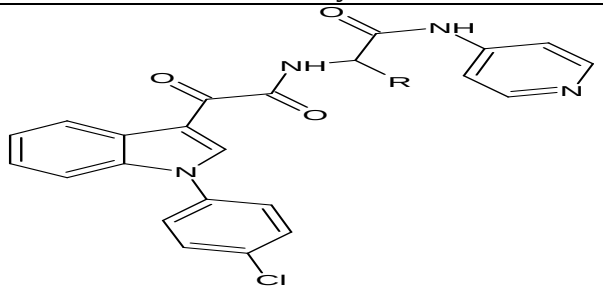
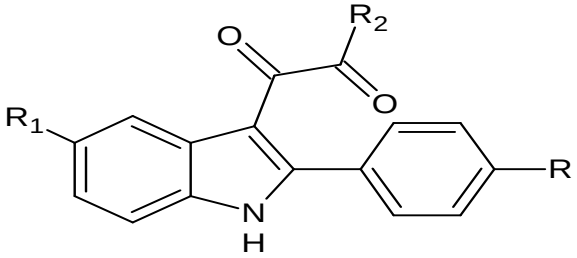
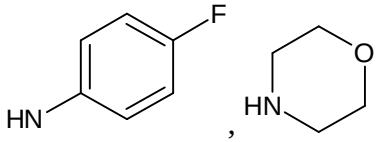
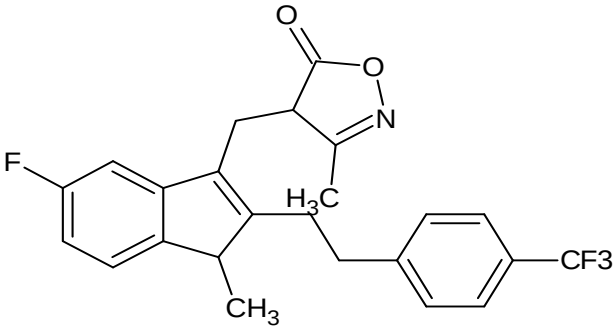
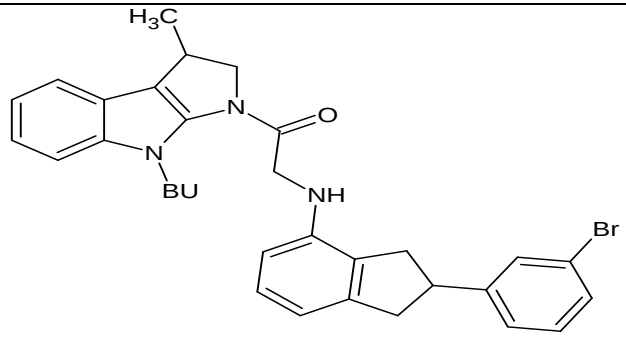
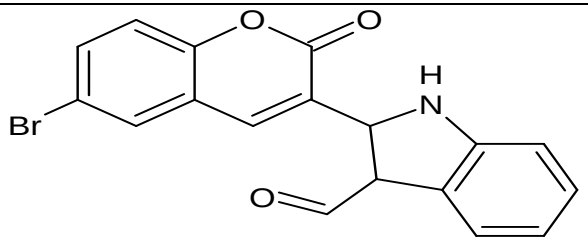
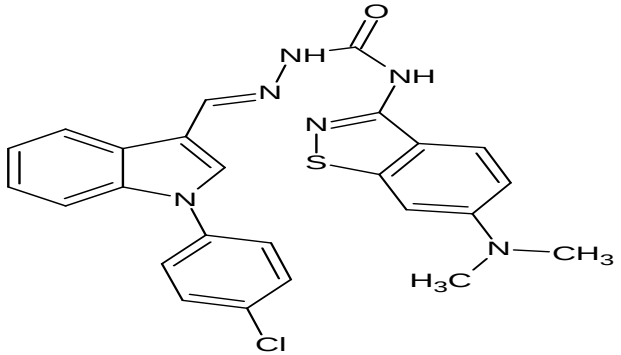
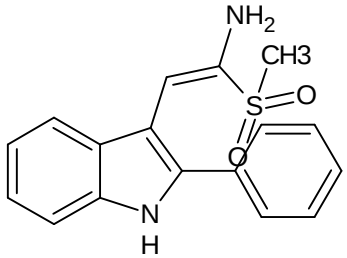
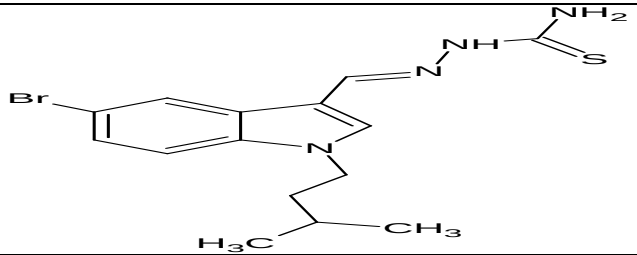
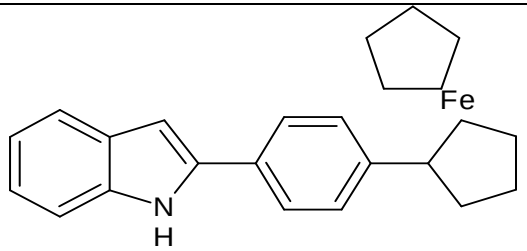
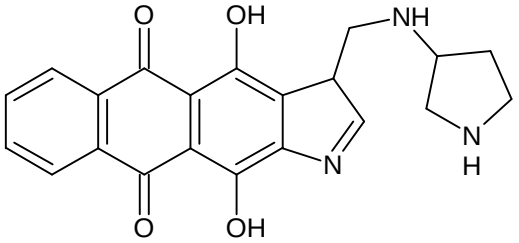
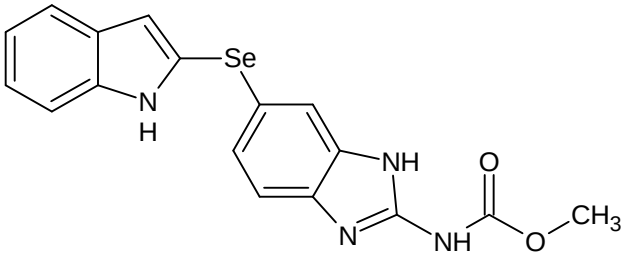
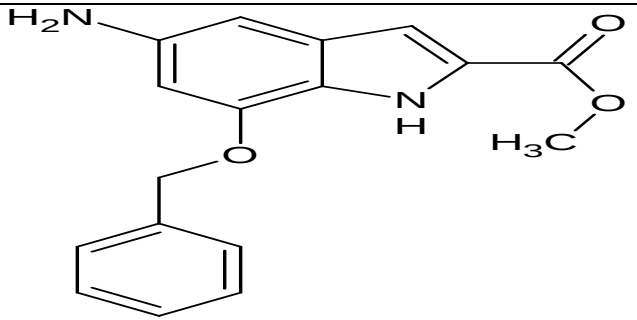
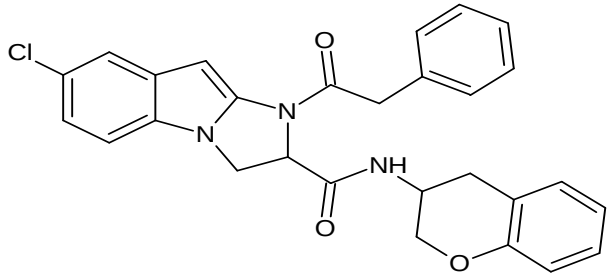
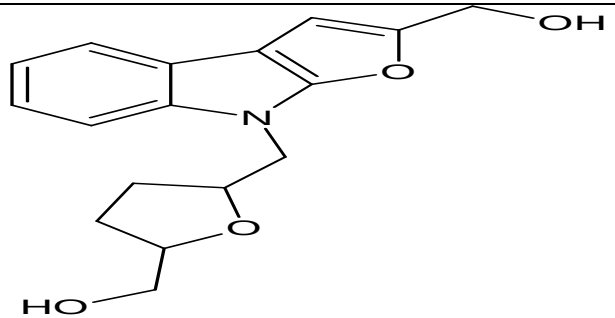
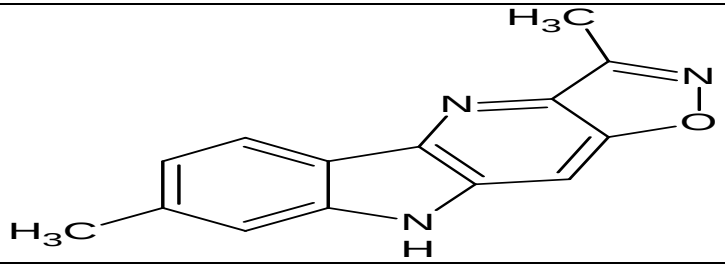
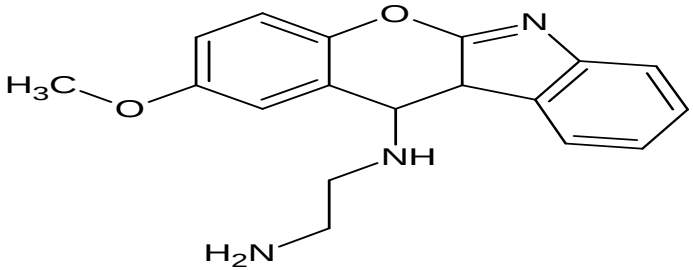
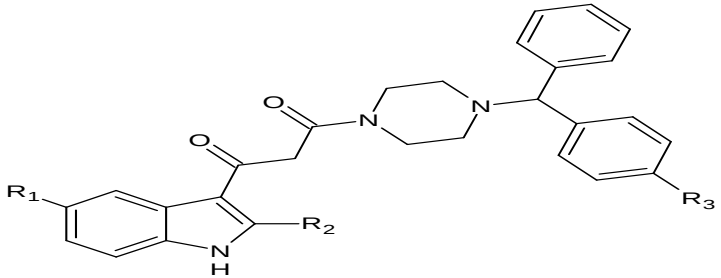
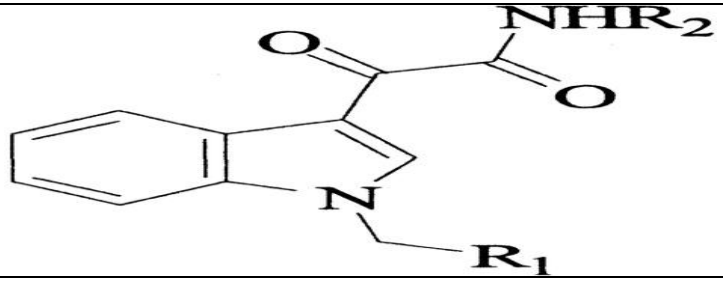
Popp and Pajouhesh *et al*[20]	 R= H, 1-CH3, 1-COCH3, 4-CF3, 5-Br, 5-Cl, 5- SO3H	Lymphoid leukaemia	--
I.Bennacefa et al.[21]		Anticancer activity	--
m.Takhi et al[22]	 R1= Secondary amines	Anticancer activity	--
Maud Antoine et.al[23]	 R= H,CH3, CH(CH3)CH2 CH3	Antitumor agents.	KB,SK-OV-3, NCI-H460 & SF-268

N.M Jagadeesh et al[24]	 R= H,Cl,Br, Me R1= H,Cl R2= ---NH2, 	Anticancer agents	MDM2-P53& PBR PROTEIN
Panathur*et al*[25]		Anticancer activity	SIRT1
Zhou *et al*[26]		Anticancer activity	SMMC-7721, A549 and SW480

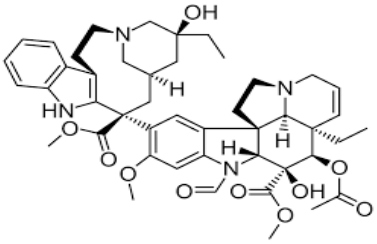
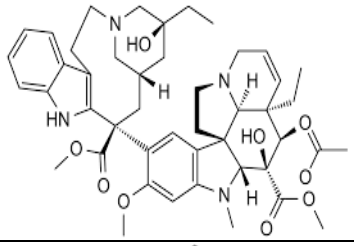
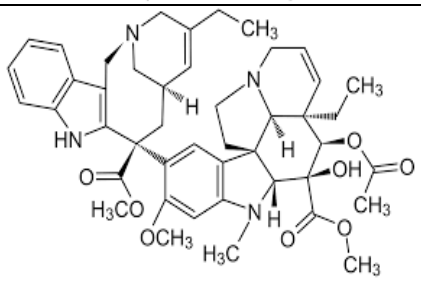
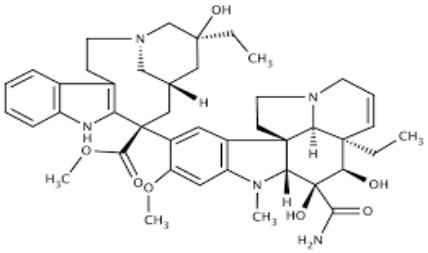
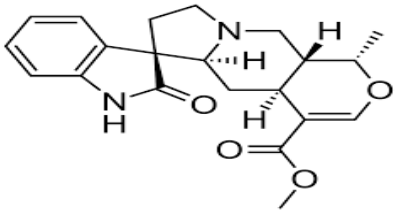
Kamath*et al*[27]		Antitumor activity	--
Ma *et al*[28]		Antitumor activity	HT29, H460, A549 and MDA-MB-231
Spallarossa*et al*[29]		Anticancer agents.	--
Chopparaetal[30]		BrineShrimp Lethality Bioassay	--

Radulovic*et al*[31]		Anticancer agents.	--
Shchekotikhin*et al*[32]		Anticancer agents.	
Guan *et al*[33]		Anticancer agents.	SGC-7901, A-549 and HT-1080
Ji*et al*[34]		Antitumor activity	--

Shiokawa*et al*[35]		Antitumor activity	MDA-MB-231
Zhuang*et al*[36]		Antitumor activity	--
Rajanarender*et al*[37]		Antitumor activity	--
Peng*et al*[38]		Antitumor activity	MV4-11 (human leukemia), A549 (lung cancer), HCT116 (colon cancer

Jun-Rong Jiang et al[39]		Anticancer activity	A-549, and ECA-109
Wen-Tai Li et al[40]		Orally Anticancer activity	P388

Indole ring containing few marketed drug shows anticancer activity

Compound Name	Chemical Structure	Use	References
Vincristine[41]		Anticancer drugs	Jake Hooker et al.
Vinblastine[42]		Anticancer drugs	Jordan MA et.al.
Vinorelbine[42]		Anticancer drugs	Jordan MA et.al.
Vindesine[43]		Anticancer drugs	Jordan MA et.al.
Mitraphylline[44]		Anticancer drugs	*GarcíaGiménez D* et.al.

CONCLUSION

From review of literature Compounds with bulky geometry and better topology increases biological activity. Most of the derivatives showed enhanced anti-cancer activity as compared to the standard drug. So, these type of derivatives of Indole can serve as future therapeutic leads for the discovery of anti-cancer drugs. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry.

The indole based pharmaceuticals will be produced on a large scale by modern drug discovery company by different research development processes and will become available commercially for therapeutic use. With the key benefits including favourable time to market and high rate of success in clinical trial compared with traditional pharmaceuticals due to diverse biological action with less toxicity, A further study to acquire more information concerning pharmacological activity is in progress. The biological profiles of these new generations of indole represent much progress with regard to the older compounds.

REFERENCES

1. UK cancer incidence statistics by age, Cancer Research UK. 2007.
2. www.unb.br/iq/labpseq/qo/olv/olv/about.htm-23k.
3. http://www.ch.ic.ac.uk/mimi/group%20meeting/Indole020307.pdf.
4. Hong, B. C.; Jiang, Y.; Chang, Y.; Lee, S. J Chin ChemSoc, 2006; 53: 647.
5. Garcia, L. C.; Martinez, R. Eur J Med Chem, 2002; 37: 261.
6. Rossiter, S.; Folkes, L. K.; Wardman, P. Bioorg Med ChemLett, 2002; 12: 2523.
7. Queiroz, M. R. P.; Abreu, A. S.; Carvalho, M. S. D.; Ferreira,P. M. T.; Nazareth, N.; Nascimento, M. S: Bioorg Med Chem, 2008; 16: 5584.
8. Doris, Kaufmann et. al., "Antimitotic activities of 2-phenyl indole-3-carbaldehyde in human breast cancer cell", Bioorganic and Medicinal chemistry, 2007; 15: 5122-5136.
9. Fan, Zhang : synthesized in vitro anti-tumor activity of 2- amino-3- cyano-6-(1H-indol-3-yl)-4-phenylpyridine derivatives. European Journal of Medicinal Chemistry, 2011; 46: 3149-3157.
10. Ulrich, Jacquemarde:t. Synthesized 3,5-bis(2-indolyl)pyridine and 3-[(2-indolyl)-5-phenyl]-pyridine derivatives as CDK inhibitors and cytotoxic agents. Bioorganic and Medicinal chemistry, 2008; 16: 4932-4953.
11. Ekhlass, Nassaret: ynthesis (in vitro) Antitumor and Antimicrobial Activity of some Pyrazoline, Pyridine, and Pyrimidine Derivatives Linked to Indole Moiety. Journal of American Science, 2010; 6(8): 463-471.
12. Huasheng, Ding: Novel indole α-methylene-γ-lactones as potent inhibitors for AKT – mTORsignaling pathway kinase. Bioorganic and Medicinal chemistry Letters, 2011; 15: 4799-4802.
13. Magdy, AH Zahran: Synthesized antitumor activity of indolylchalcones and their pyrazolineanalogs. Journal Of Chemistry science, 2005; 122: 587-595.

14. Abdel-Rahman, Farghaly: Synthesized indole derivatives containing pyrazoles with potential antitumor activity. ARKIVO, 2010; 11: 177-187.
15. Ahmed Kamal:ynthesis of 3,3-diindolyl oxyindoles efficiently catalysed by FeCl3 and their in vitro evaluation for anticancer activity. Bioorganic and Medicinal chemistry Letters, 2010; 20: 5229-5231.
16. Yu-Shan, Wu Synthesis and Evaluation of 3-Aroylindoles as Anticancer Agents. Journal of Medicinal Chemistry, 2009; 52: 4941-4945.
17. Palwinder, Singh: Design, synthesis and anticancer activities of hybrids of indoleandbarbituric acids. Bioorganic and Medicinal chemistry Letters, 2009; 19: 3054-3058.
18. Jing-Ping Liou, Kuo-Shun Hsu, Ching-ChuanKuo, Chi-Yen Chang, Jang-Yang Chang: A novel oral indoline-sulfonamide agent, J30, exhibits potent activity against human cancer cells in vitro and in vivo through the disruption of microtubule‖. JPET, 2007; 107.116.
19. 14. Matthew S. Sigman, Tejas P. Pathak, Keith M. Gligorich, Bryan E. Welm: ynthesis and Preliminary Biological Studies of 3-Substituted Indoles Accessed by a Palladium-Catalyzed Enantioselective Alkene Difunctionalization Reaction‖. J. Am. Chem. Soc., 2010; 132(23): 7870–7871.
20. 15. F.D. Popp and H. Pajouhesh: Potential anticonvulsants VI: Condensation of isatins with cyclohexanone and other cyclic ketones‖, J. Pharm. Sci.,1983; 72: 318–321
21. I. Bennacef, C. N. Haile, A. Schmidt, A. O. Koren, J. P. Seibyl, J. K. Staley, F. Bois, R.M. Baldwin, G. Tamagnan, Bioorg. Med. Chem., 2006; 14(22): 7582-7591.
22. M. Takhi, G. Singh, C. Murugan, N. Thaplyyal, S. Maitra, K. M. Bhaskarreddy, P. V. S.Amarnath, A. Mallik, T. Harisudan, R. Trivedi, K. Sreenivas, N. Selvakumar, J. Iqbal, Bioorg. Med. Chem. Lett., 2008; 18: 5150-5155).
23. Maud antoine1, Pascal marchandSide chain modifications of (indol-3-yl)glyoxamides as antitumor agents, Journal of Enzyme Inhibition and Medicinal Chemistry, October 2008; 23(5): 686-695.
24. N. M. Jagadeesh Synthesis and molecular docking study of N-alkyl/aryl indol-3-yl glyoxylamides as novel anticancer agents, International Journal of Pharmacy and Pharmaceutical Sciences, 2014; (6): 485-490.
25. Panathur N.; Gokhale N.; Dalimba U.; Koushik P. V.; Yogeeswari P.; Sriram D: New indole–isoxazolonederivatives:Synthesis, characterisation and in vitro SIRT1 inhibition studies. Bioorg.Med. Chem. Letts, 2015; 25: 2768–2772.

26. Zhou Y.; Duan K.; Zhu L.; Liu Z.; Zhang C.; Yang L.; Li M.; Zhang H.; Yang X: Synthesis and cytotoxic activity of novelhexahydropyrrolo[2,3-b]indoleimidazolium salts, Bioorg. Med. Chem. Letts, 2015.
27. Kamath P. R.; Sunil D.; Ajees A. A.; Pai K. S. R.; Das S: Some new indole–coumarin hybrids; Synthesis, anticancer and Bcl-2docking studies.Bioorg. Chem, 2015; 63: 101–109.
28. Ma J.; Bao G.; Wang L.; Li W.; Xu B.; Du B.; Lv J.; Zhai X.; Gong P: Design, synthesis, biological evaluation and preliminarymechanism study of novel benzothiazole derivatives bearing indole-based moiety as potent antitumor agents. Eur. J. Med. Chem, 2015; 96: 173-186.
29. Spallarossa A.; Caneva C.; Caviglia M.; Alfei S.; Butini S.; Campiani G,; Gemma S.; Brindisi M,; Zisterer D. M.; Bright S. A.;Williams C. D.; Crespan E.; Maga G.; Sanna G.; Delogu I.; Collu G.; Loddo R: Unconventional Knoevenagel-type indoles:Synthesis and cell-based studies for the identification of pro-apoptotic agents. Eur. J. Med. Chem, 2015; 102: 648-660.
30. Choppara P.; Prasad Y. V.; Rao C. V.; Krishna K. H.; Trimoorthulu G.; Rao G. U. M.; Rao J. V.; Bethu M. S.; Murthy Y. L. N: Design, synthesis of novel N prenylated indole-3-carbazones and evaluation of in vitro cytotoxicity and 5-LOX inhibitionactivities. Arabian J. Chem 2015;
31. Radulovic N. S.; Zlatkovic D. B.; Mitic K. V.; Randjelovic P. J.; Stojanovic N : Synthesis, spectral characterization,cytotoxicity and enzyme-inhibiting activity of new ferrocene–indole hybrid. Polyhedron, 2014; 80: 134–141.
32. Shchekotikhin A. E.; Glazunova V. A.; Dezhenkova L. G.; Luzikov Y. N.; Buyanov V. N.; Treshalina H. M.; Lesnaya N. A.;Romanenko V. I.; Kaluzhny D. N.; Balzarini J.; Agama K.; Pommier Y.; Shtil A. A.; Preobrazhenskaya :. Synthesis andevaluation of new antitumor 3-aminomethyl-4, 11-dihydroxynaphtho[2,3-f]indole-5,10-diones. Eur. J. Med. Chem. 2014; 86: 797-805.
33. Guan Q.; Han C.; Zuo D.; Zhai M.; Li Z.; Zhang Q.; Zhai Y.; Jiang X.; Bao K.; Wu Y.; Zhang W: Synthesis and evaluation ofbenzimidazolecarbamates bearing indole moieties for anti-proliferative and anti-tubulin activities. Eur. J. Med. Chem, 2014; 87: 306-315.
34. Ji X.; Xue S.; Zhan Y.; Shen J.; Wu L.; Jin J.; Wang Z.; Li Z: Design, synthesis and anti-proliferative activity of a novel class ofindole-2-carboxylate derivatives. Eur. J. Med. Chem, 2014; 83: 409-418.

35. Shiokawa Z.; Hashimoto K.; Saito B.; Oguro Y.; Sumi H.; Yabuki M.; Yoshimatsu M.; Kosugi Y.; Debori Y.; Morishita N.; DouganD. R.; Snell G. P.; Yoshida S.; Ishikawa: Design, synthesis, and biological activities of novel hexahydropyrazino[1,2-a]indolederivatives as potent inhibitors of apoptosis (IAP) proteins antagonistswith improved membrane permeability across MDR1expressing cells. Bioorg. Med. Chem, 2013; 21: 7938–7954.
36. Zhuang S.; Lin Y.; Chou L.; Hsu M.; Lin H.; Huang C.; Lien J.; Kuo S.; Huang L: Synthesis and anticancer activity of 2,4-disubstituted furo[3,2-b]indole derivatives. Eur. J. Med. Chem, 2013; 66: 466-479.
37. Rajanarendar E.; Reddy K. G.; Ramakrishna S.; Reddy M. N.; Shireesha B.; Durgaiah G.; Reddy Y. N: Synthesis and in vitroand in vivo anticancer activity of novel 3-methyl-5H-isoxazolo[50,40:5,6]pyrido[2,3-b]indoles. Bioorg.Med. Chem. Letts, 2012; 22: 6677–6680.
38. Peng W.; Switalska M.; Wang L.; Mei Z.; Edazawa Y.; Pang C El-Sayed I. E.; Wietrzyk J.; Inokuchi T: Synthesis and in vitroantiproliferative activity of new 11-aminoalkylaminosubstituted chromeno[2,3-b]indoles. Eur. J. Med. Chem, 2012; 58: 441-451.
39. Jun-Rong Jiang, FengXu, and Han-Gui Wu: Synthesis and Anticancer Activity of 1-(1H-Indol-3-yl)-2-(4-diarylmethylpiperazine-1-yl)ethane-1,2-dioneDerivatives, Journal of Chemistry 2016; Article ID 4617454: 5.
40. Wen-Tai, Li. Der-Ren Hwang, Ching-Ping Chen, Chien-Wei Shen, Chen-Long Huang, Tung- Wei Chen, Chi-Hung Lin, Yee-Ling Chang, Ying-Ying Chang, Yue-Kan Lo, Huan-Yi Tseng, Chu-Chung Lin, Jeng-Shin Song, Hua-Chien Chen, Shu-Jen Chen, Se−Hui Wu, Chiung-Tong: Chem. J. Med. Chem, 2003; 46(9): 1706–1751.
41. Jake Hooker and Walt Bogdanich, Tainted Drugs Tied to Maker of Abortion Pill, New York Times, January 31, 2008.
42. Jordan MA, Leslie W, Microtubules as a target for anticancer drugs, Nat Rev Cancer, Apr 4, 2004; "[1]".
43. Jordan MA, Leslie W, Microtubules as a target for anticancer drugs, Nat Rev Cancer, Apr 4, 2004.
44. García Giménez D, García Prado E, Sáenz Rodríguez T, Fernández Arche A, De la Puerta R. “Cytotoxic effect of the pentacyclicoxindole alkaloid mitraphylline isolated from Uncariatomentosa bark on human Ewing's sarcoma and breast cancer cell lines”. Planta Med., 2010; 76(2): 133-136.