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RECENT ADVANCES IN ANTICANCER PROFILE OF ISATIN AND DERIVATIVES

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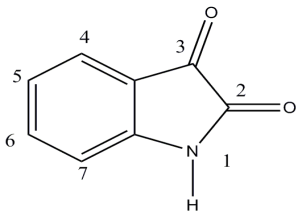
ABSTRACT
Isatin (1*H*-indole-2, 3-dione) and its analogues are important class of heterocyclic compounds that can be used as precursors for drug synthesis. Isatin is an indole nucleus substituted with carbonyl groups at 2nd and 3rd position. Chemically it can be modified in to different compounds such as Schiff bases, mannich bases, thiosemicarbazones, *spiro* compounds. Besides, in numerous analogues it is clubbed with another heterocyclic moiety to give the active agents. It is nucleus possessing versatile activity such as antimicrobial, anticancer, antifungal, anti-malarial, antiviral and anti-tubercular. Today cancer is the second most dreadful disease after cardiovascular disease. Many pharmacophore have the potential as anticancer agent Therefore, keeping in mind the anticancer potential of isatin and derivatives, important anticancer research has been gathered in this review.

KEYWORDS: Isatin, 1*H*-indole-2, 3-dione, anticancer.

INTRODUCTION

Cancer is generic term which includes a range of malignant disease. It is characterized by abnormal cell growth leading to malignant tumors or neoplasm. Cancer can occur in any part of body and can affect people of any age group, different socio-economic strata and race. Normal cells multiply and die (apoptosis) in an orderly manner but cancerous cell fails to undergo apoptosis. Cancer is the second most dreadful disease after cardiovascular disease. Many pharmacophore have the potential as anticancer agent. Isatin is one such nucleus which is reported to possess versatile activity such as antimicrobial[1,2], anticancer[3], antifungal[4], anti-malarial[5], antiviral[6] and anti-tubercular.[7,8] Therefore, keeping in mind the anticancer potential of isatin and derivatives, important anticancer research has been gathered in this review.

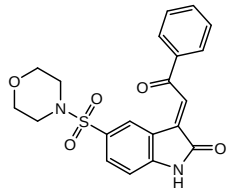
ISATIN



Isatin; *1H*-Indole-2, 3-dione

ANTICANCER ACTIVITY OF ISATIN AND ANALOGUES

El-Sharifa *et al*. synthesized "2-oxoindoles derivatives, fused pyrrole [2, 3–*b*] indoles and *spiro* indole derivatives". Among the synthesized derivatives, four compounds 1, 2, 3 and 4 come out most potent on *in vitro* cancer cell lines study.[9]



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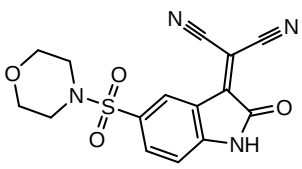

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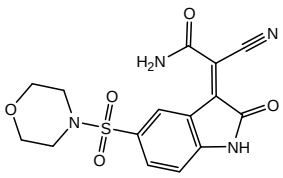

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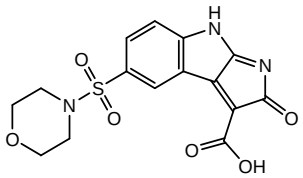

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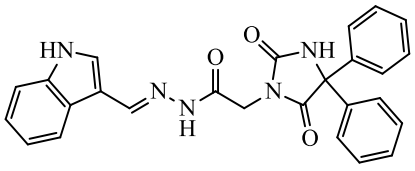
Alkahtani *et al*. synthesised a new class of "5, 5-diphenylhydantoin derivatives containing benzylidene or isatin". The anticancer activity was assessed against "cervical cancer cell line- HeLa, lung cancer cell line-A549" and "breast cancer cell line MDA-MB-231" in which compounds 5, 6, 7 and 8 come out active with IC_{50} values of 109 µM, 59 µM, 81 µM, and 113 µM, respectively.[10]



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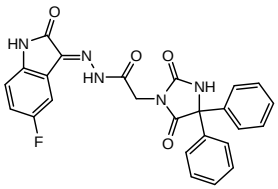

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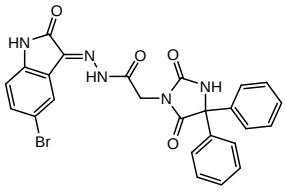

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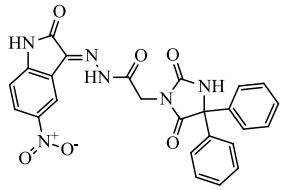

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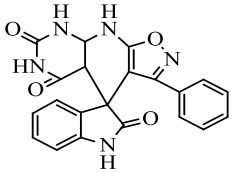

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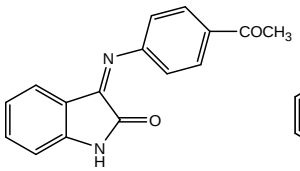

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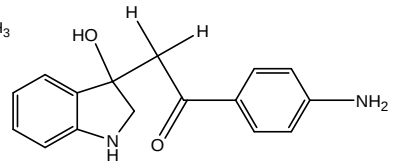

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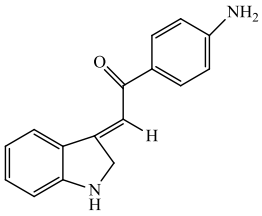
Kausar and coworker prepared isooxazole fused spirooxindole compounds. The anticancer activity of compound 9 was evaluated on "breast cancer cell line MDA-MB468" and result revealed that cell life decrease with increase in concentration of compound 9.[11] Ammar *et al*. carried out the cytotoxicity study of the prepared compounds against "three human carcinoma cell lines, MCF-7, HepG-2, and HCT-116, and MCF-12A normal breast cell line" Four compounds i.e. compound 10, 11, 12 and 13 comes out most potent when compared to standard drug Imatinib.[12]



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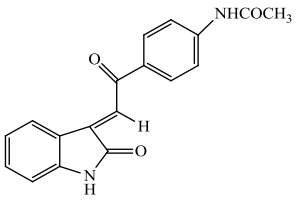

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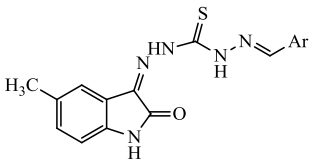

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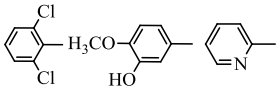

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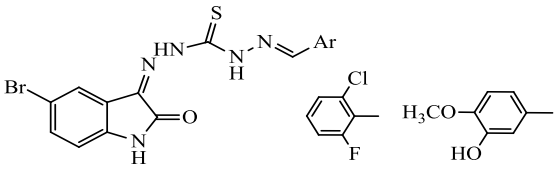
Gabr *et al.*, prepared a new series of "isatin-β-thiocarbohydrazones". Among the synthesized compounds 14, 15, 16, and 17exhibited remarkable activity against cervical cancer (Hela) cell line and compounds 14, 15, 16, 17, 18 and 19 showed activity against "kidney fibroblast cancer (COS-7) cell lines".[13] Incorporating thiosemicarbazone, pyrazoles and azomethine moiety at C2 position a new class of "3-(3-Trifluoromethylphenyl)-6-iodo-4(3H)-quinazolinone analogues" were prepared by Abbas et al. The "*in-vitro"* anticancer activity was assessed on "human cancer cell line (HepG2), breast cancer cell line MCF7 and human lungs adenocarcinoma epithelial cell line A549". Compound 20 showed good anticancer activity with IC50 value comparable with doxorubicin against HepG2 and "MCF7 cell lines".[14]



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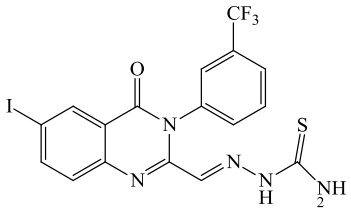

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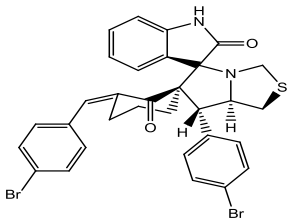
"Using 1, 3 cycloaddition reaction of azomethine ylide", which were generated from reaction of isatin and thiazolidine carboxylic acid, Lotfy et al, prepared new spirooxindole-pyrrolothiazole heterocycles containing pyrrolidine and oxindole. *In vitro* anticancer evaluation against "cancer cell line MCF7 and K562" showed that the compound 21 is most potent member of series against "MCF7 breast cancer cells (IC_{50} values 15.32±0.02) and K562 leukemia cells (IC_{50} values 14.74±0.7μM)".[15] Two new class of "novel 4/3-((4-oxo-5-(2-oxoindolin-3-ylidene)-thiazolidin-2-ylidene)-amino) benzenesulphonamides" were prepared and screened for *in vitro* antiproliferative activity (against breast cancer cell line MCF7 and colorectal cancer caco-2 cell line) and inhibition of metalloenzyme carbonic anhydrase. Investigation demonstrated that compound 22 is active against MCF7, while compound 23 showed activity against caco-2 cells. This study was reported by Eldehna and coworkers.[16]



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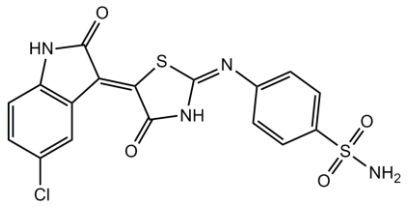

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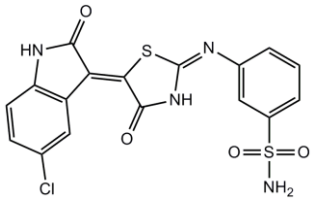

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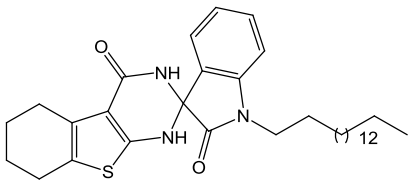
Ismail and coworker synthesized "novel spiro[pyrazolo-[4, 3-*d*]-pyrimidin]-7'(1'*H*)-one and spiro-[benzo-[4, 5]-thieno[2, 3-*d*]-pyrimidin-2, 3'-indoline]-2', 4(*3H*)-dione". Most of compound showed anticancer activity, but compound 24 comes out most active with IC_{50}~6-22µM.[17] A class of eighteen novel 8-substituted tryptanthrin analogues was synthesized by Guda *et al.* After structure confirmation analogues were evaluated for anticancer (MTT assay method) and antioxidant activity (DPPH radical scavenging assay. In particular compounds 25 and 26 were most potent cytotoxicity against "three tumor cell lines with IC_{50} values of 11.60 ± 1.821 mM, 9.42 ± 1.239 mM against MCF-7, 6.01 ± 1.116 mM, 7.19 ± 0.991 mM against A549 and 12.20 ± 0.239 mM, 9.42 ± 1.594 mM against HeLa", respectively.[18]



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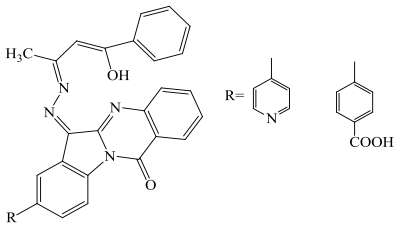

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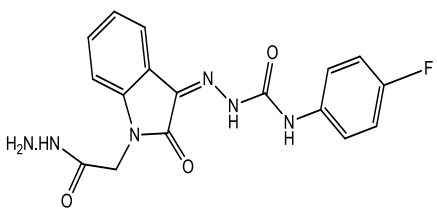
Sathianarayanan *et al*., synthesised isatin semicarbazones derivatives and assessed them for antioxidant, cytotoxic and apoptotic activity against mammary carcinoma. "*In vitro* cytotoxicity" assessment against "breast cancer cell line MCF-7 and BT-549", showed that compound 27 have anticytotoxicity activity and is also involved in apoptptic process.[19] El-Azab *et al.*, synthesised conjugate compounds of quinazolinone and isatin moieties. The antitumor activity was assessed on "breast cancer cell line MDA-MB-231 and colon cancer cell line LOVO". In comparison to standard drug 5FU and Erlotinib, many synthesized compounds showed antitumor activity. Among the synthesized compound 28 induced apoptosis in breast cancer cell line MDA-MB-231 cells and showed inhibitory effect against EGFR-TK (at a concentration of 10 µM).[20]



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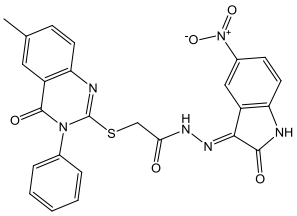

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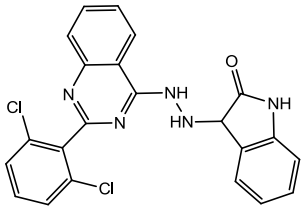

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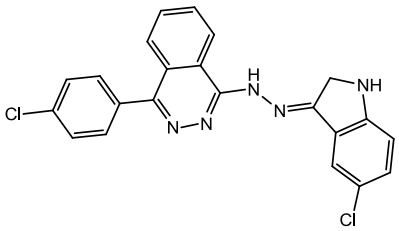
Isatin conjugates with quinazoline/phthalazine hydrazine were prepared and studied them for their "antiproliferative activity", toward triple negative "breast cancer TNBC MDA-MB-231 cell line" by Eldehna and coworkers. Study concluded that compound 29 and 30 were most active conjugate against the studied cell line and possess, respectively, 2.37 and 2.44 times activity than the standard 5-Fluorouracil.[21] Using "tetrabutylammonium fluoride (TBAF)" as catalyst and "THF" as a solvent alkynylation of Isatin was carried out by Parvathaneni and coworkers. The prepared "3-hydroxy-3-ethynylindolin-2-one derivatives" were evaluated for *in-vitro* cytotoxicity on cancer cell lines. Three synthesized analogue exhibited good inhibition of "Akt kinase activity" with IC $_{50}$ ranging from 7.7-9.8 µM.[22] Venkateshwarlu *et al*., synthesized "isatin-3-[*N*-2-(2-benzalaminothiazol-4-yl)]-hydrazone derivatives" and assessed them for antioxidant, antimicrobial and cytotoxic potential. Two compound 31 and compound 32 showed cytotoxicity activity against "HBL—100 cell lines and HeLa cell lines", having nearly equal cytotoxicy with "IC_{50} values of 246.53 µM and 247.29 µM", respectively. Compound 32 (R=5-Cl, R1=OH&R2=OCH3) also showed good antioxidant activity.[23]



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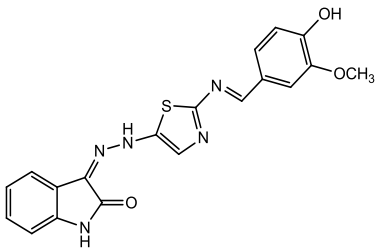

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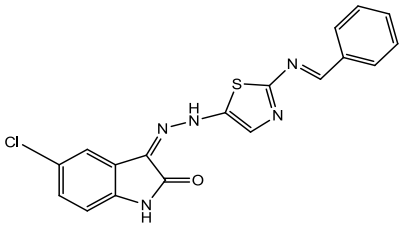

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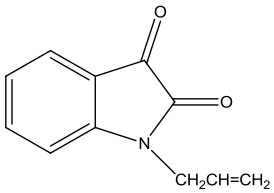
Bian *et al*., evaluated the effect of synthesized N-Allylisatin (allyl 1) on cell cycle, apoptosis rate and mitochondrial memberane potential of heptocellular carcinoma HepG2 cells. Investigation indicated that compound 33, Allyl 1 inhibit "HepG2 cell viability" in a time and dose dependent manner and induce cell cycle arrest at the G2/M phase.[24] Bikshapathi *et al*. synthesised a series of "oxindole derivatives (1-alkyl-3-hydroxy-3-(trifluoromethyl) indolin-2-one, n = 16)" and investigated them for their "cytotoxic activities against SKOV3, B16F10, PC3, and THP1 cancer cell lines. Although five derivatives were found to be active on all the cancer cell lines but significant cytotoxicity was shown by compound 34 on THP-1 cell line" with IC50 value of 18 µM.[25] Taking dibromo isatin as starting material, N-alkyl analogues were prepared by Vine et al. Examination of the compound against MDR cell lines U937 VbR and MES-SA/Dx5 showed that synthesized compound are capable to combat MDR by circumventing P-glycoprotein mediated drug efflux. In particular, compound 35 and 36 (*N*-benzylation derivative of 5, 7-dibromoisatin) showed significant "cytotoxicity *in vitro* against a range of human cancer cell lines".[26]



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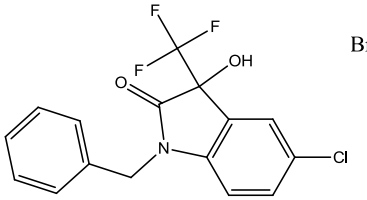

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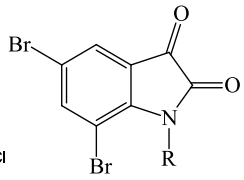

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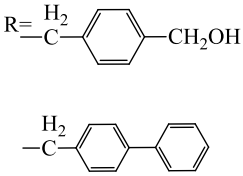

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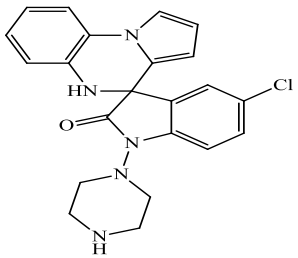

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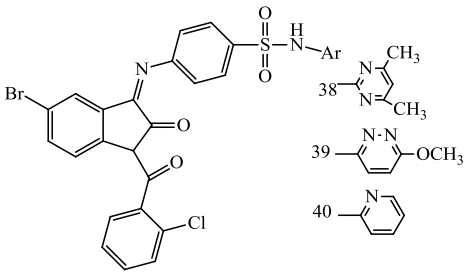

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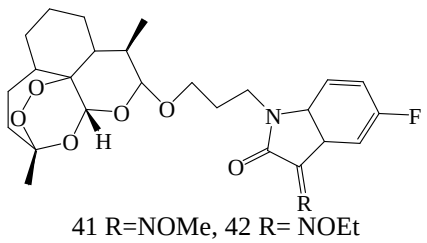
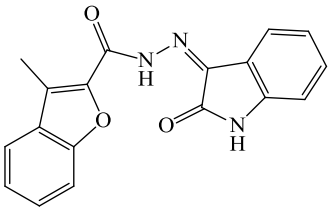
Using green chemistry technique Kamal *et al*. synthesised "5-*H*-spiro-[indoline-3, 4-pyrrolo-[1, 2-a]-quinoxalin]-2-one derivative". Antiproliferative evaluation on five different human cancer cell line showed that compound 37 have anticytotoxic effect on "human prostate cancer cell (DU-145)". The result of "Flow cytometric study" reveals that compound 37 induce "cell cycle arrest in the G0/G1 phase while Western blot analysis" shows that reduction in "Cdk4 level" is responsible for "apoptotic cell death".[27] In continuous to their earlier study Kumar *et al*., synthesised new class of "4-(1-Aryl-5-halo-2-oxo-1, 2-dihydro-indol-3-ylideneamino)-*N*-substituted benzenesulfonamide derivatives". Anticancer activity study indicated that compound 38 was active against "HCT116" while compounds 39 and 40 were effective agents against RAW264.7 cancer cell lines.[28] Novel Spiro Pyrazole-Oxindole newly synthesized compounds screened for their antiproliferative activity against human breast cancer (MCF-7), human colon cancer (HCT-116) and human liver cancer (HepG2), as well as the normal skin fibroblast cell (BJ-1) through *in vitro* MTT assay. The obtained results indicated that all congeners under investigation exhibited selective cytotoxicity against HCT-116 and MCF-7 cell lines as compared to the reference doxorubicin, with antiproliferative activity ranging from 84.6% to 97.9%.[29] A series of N-(4) thiomorpholinyl isatin/5-haloisatin thiosemicarbazones and their copper (II) complexes were prepared. The *in vitro* antiproliferative study of the compounds against cancer cells; MCF-7 (breast cancer), A431 (skin cancer), and PNT2 (human normal prostate epithelium) showed significant antiproliferative activity for both ligands and complexes.[30] Three series of artemisinin-isatin hybrids were designed, synthesized and evaluated for their antiproliferative activity against breast cancer cells (MCF-7, MDA-MB-231 and doxorubicin-resistant MCF-7 (MCF-7/DOX)), as well as the cytotoxicity towards

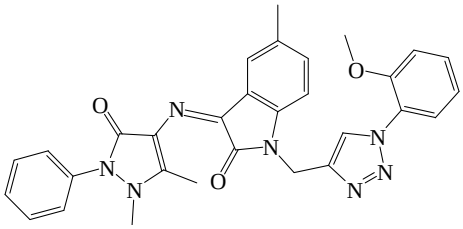
normal MCF-10A breast cells. In particular, hybrids 41, 42 were found to be most active against all tested breast cancer cell lines, and their activity was not inferior to that of doxorubicin.[31] Novel benzofuran-isatin conjugate (3-methyl-N'-(2-oxoindolin-3-ylidene) benzofuran-2-carbohydrazide) with promising potential anticancer activities in colorectal adenocarcinoma HT29 and metastatic colorectal cancer (CRC) SW620 cell lines were prepared. Compound 43 treatment exhibited anticancer effects through inhibition of HT29 and SW620 cell viability, migration, and invasion, in a dose-dependent manner.[32] Isatin-based Schiff bases were synthesized which showed significant to moderate antiproliferative properties against MCF7 (breast), HCT116 (colon), and PaCa2 (pancreatic) cancer cell lines with potency compared to reference drugs 5-fluorouracil (5-FU) and Sunitinib. Among all, compound 44 (3-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)imino)-1-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-5-methylindolin-2-one) exhibits promising antiproliferative properties against the MCF7 cancer cell line with 2 fold more potency than Sunitinib.[33]



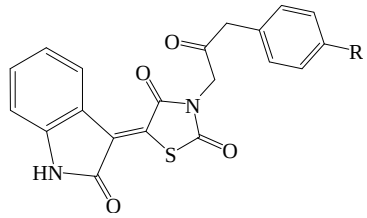
41 R=NOMe, 42 R= NOEt



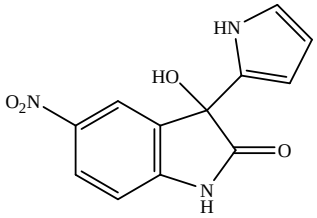
43



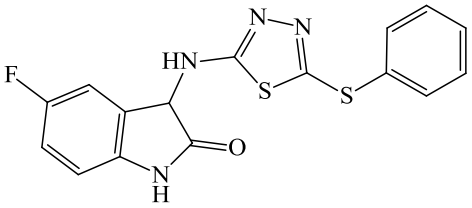
44



45 R=H, 46 R=-OCH_3



47



48

New quinoline and isatin derivatives having the main characteristics of VEGFR-2 inhibitors were synthesized. The antiproliferative effects of these compounds were estimated against A549, Caco-2, HepG2, and MDA-MB-231. Compounds 45 and 46 showed comparable activities with doxorubicin against the Caco-2 cells.[34] Another study reported the synthesis and *in vitro* cytotoxicity evaluation of isatin-pyrrole derivatives, obtained from the appropriate isatins with pyrrole, with good yields and purity. Furthermore, the MTT assay on the human liver cancer HepG2 cell lines revealed moderate activity in all compounds, which was highest in sample 47 (IC_{50} 0.47 µM).[35] A new series of new benzoxazole-isatin conjugates were designed, synthesized, and were biologically evaluated for their in vitro antimicrobial and cytotoxic activities. The data of the biological activity have shown that the compounds substituted with halogens, i.e., electron-withdrawing groups (-Cl, -Br, -NO2 group) substitution at R1 (5 th) position, are more active than the remaining.[36] Condensation of isatin and 5-chloroisatin with chitosan was carried out to get chitosan thiosemicarbazones (TSCs). The partial incorporation of thiosemicarbazone moiety in chitosan was shown by FT-IR and 13C NMR spectroscopic studies, powder X ray diffraction, and CHNS microanalysis. As revealed by colorimetric MTT assays, the *in vitro* anticancer activity of the 5-chloroisatin chitosan TSCs showed better activity than isatin chitosan TSCs against the cell lines.[37] Anticancer Activity of Novel 1, 3, 4-Thiadiazole- and Aziridine-Based Indolin-2-ones was carried out. Among all three series of indolin-2-ones, the majority of compounds demonstrated broad-spectrum activity toward various cancer cell lines. Compound 48 showed a potent activity of IC50 = 1.47 µM against a panel of breast cancer cell lines.[38]

CONCLUSION

Conclusion of the study shows that analogues of Isatin can be obtained in different ways. The most important position for alteration is 1, 3 and 5th position. The modification of isatin nucleus is not limited to compounds such as Schiff bases, mannich bases, thiosemicarbazones, *spiro* compounds besides, in numerous analogues it is clubbed with another heterocyclic moiety to give the active agents. Many of the synthesized analogues show potent anticancer activity. This review may be useful for further optimization of isatin to yield new chemical entity as potential anticancer agents.

CONFLICT OF INTEREST

None

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Declared none

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