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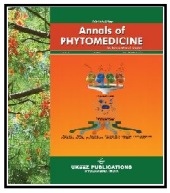

Review Article : Open Access

Recent advances in isatin-thiazole hybrids as potential anticancer agents

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Abstract

Cancer has become a rapidly expanding global threat. In current review, we examine the finding of derivatives based on isatin, thiazole and isatin-thiazole hybrids that have already been identified as anticancer agents. Isatin and thiazole derivatives can be found from natural resources, whereas isatin is found in human fluids for the metabolism of amino acid. Various isatin derivatives such as thiosemicarbazones, hydrazones, imines, among other heterocyclic moieties were screened for different anticancer effects. Few isatin derivatives have trail in pre-clinical and clinical screening as angiogenic inhibitors. Isatin hybrids and thiazole derivatives presented promising antineoplastic properties against different cancer cells by acting on various macromolecules. They also disclose several methods of action such as producing reactive molecules, for oxidative damage, target DNA and restrict few properties. The review emphasizes advances in the development of isatin, thiazole and isatin-thiazole hybrids as anticancer agents.

1. Introduction

Cancer has become a rapidly expanding global threat. According to the global health observatory report of WHO 2020 states that, over 10 million people lost their life due cancer worldwide. It is expected that till 2030, 26 million fresh cancer cases diagnoses and 17 million people loss their life due to cancer worldwide, with an estimated 2.3 million fresh cases of cancer. Female breast cancer the most commonly diagnosed cancer as it surpassed lung cancer (Ferlay *et al.*, 2020). Although, cancer chemotherapy has made significant advances in current years, but there is still a significant unmet demand of novel anticancer drugs having high potential effect, target selectivity, and low toxicity (Stewart and Wild, 2015). Therefore, there is required to explore new anticancer agents. Cancer can begin nearly anywhere in the human body, the cancer results from the DNA mutation, the instructive cells grow out of control (Taha *et al.*, 2019). It is a hereditary disorder caused by changes in genes, specifically tumour suppressor genes, DNA repair genes, and protooncogenes, which affect how cells behave, primarily how they grow and divide (Uddin and Veeresh,2020). Genetic changes can be happened because of error during cell division, detrimental substances in environment such as UV rays, chemicals in tobacco or they may be inherited from our parents (Shegokar and Sawant, 2014).

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Isatin (1H-indole-2,3-dione) has been recognized for around 150 years. It is an important nitrogen-containing aromatic heterocyclic chemical found in numerous plants as well as an endogenous polyfunctional heterocyclic compound with biological action in mammals (Medvedev *et al.*, 2019; Gezici, 2018). Over the last decade, isatin has gained attention as a helpful nucleus in medicinal chemistry and drug development. Previous research indicates that indole-2,3 dione andindole-2,3 dione containing derivatives show a broad range of pharmacological actions, *viz.*, antineoplastic (Wang *et al.*, 2017), antidiabetic (Xie *et al.*, 2017), antimicrobial (Srivastava *et al.*, 2020), anticonvulsant (Nikalje *et al.*, 2015), antibacterial (Chemchem*et al.*, 2020), anti-inflammatory (Lahari *et al.*, 2020), antiviral (Kumar *et al.*, 2021). However, only a few isatin derivatives have received clinical approval, including semaxanib, nintedanib, sunitinib, orantinib and toceranib (El-Naggar *et al.*, 2018).

Thiazole and its derivatives, on the other hand, are regarded as a key sulphur and nitrogen heterocyclic chemical with a broad range of pharmacological actions such as anticancer (Bera *et al.*, 2022; Sekar *et al.*, 2010), antimicrobial (Althagafi *et al.*, 2019), antiviral (Abdel-Latif*et al.*, 2021) and anti-epileptic (Mishchenko *et al.*, 2020)tiazofurin (Franchetti*et al.*, 1995), dasatinib (Li *et al.*, 2009), dabrafenib and ixabepilone (Yao *et al.*, 2014) are also thiazole-containing medicines that have been identified to be involved in the treatment of cancer, many of the derivatives are commercially available as anticancer therapies.

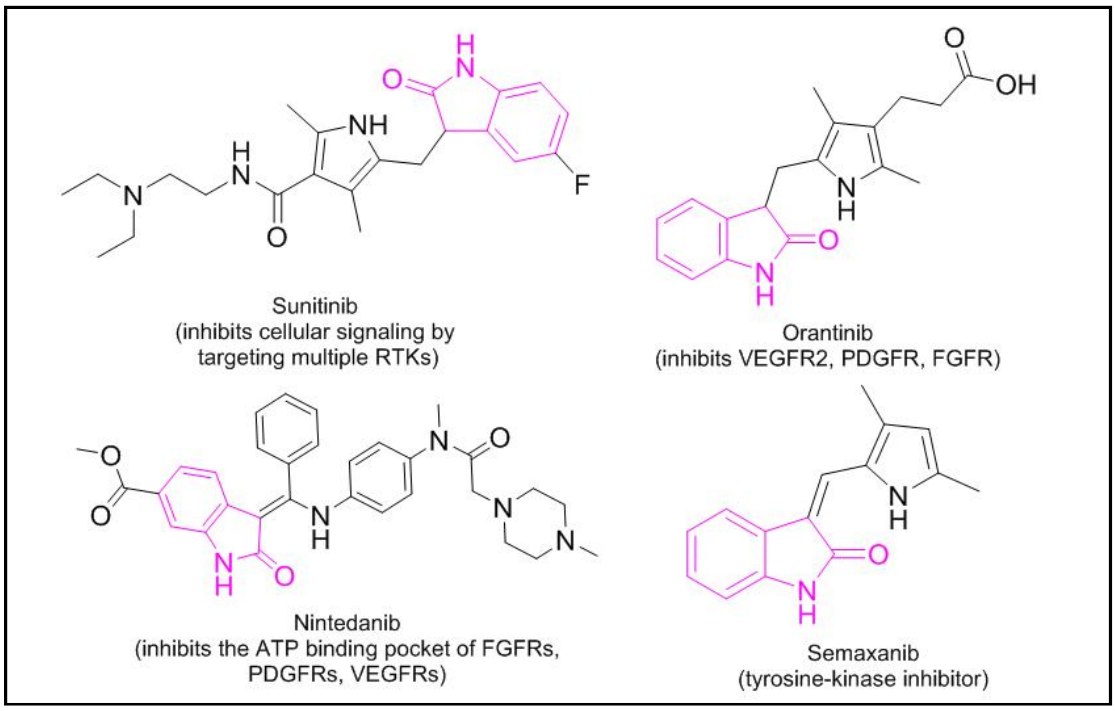


Figure 1: Clinically approved isatin-bearing anticancer drugs.

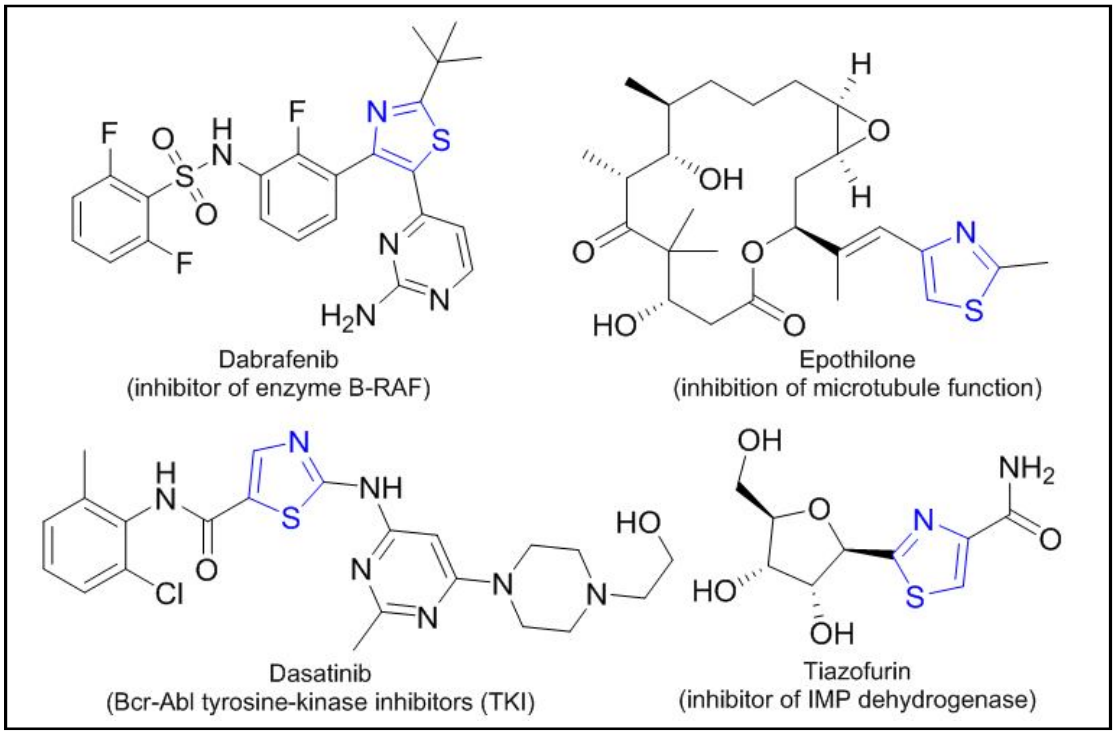


Figure 2: Clinically approved thiazole-bearing anticancer drugs.

Researchers have discovered some promising chemical architectures containing two or more biologically active pharmacophores using molecular hybrid-based approaches over the years (Viegas *et al.*, 2007; Mishra *et al.*, 2016). Furthermore, these hybrid molecules typically have more than one mechanism of action which may cause decreased adverse effect, enhance pharmacodynamic with pharmacokinetic features, improve efficacy, overcome drug resistance. *etc.* So, the review emphasizes advances in the development of isatin-thiazole hybrids as anticancer agents.

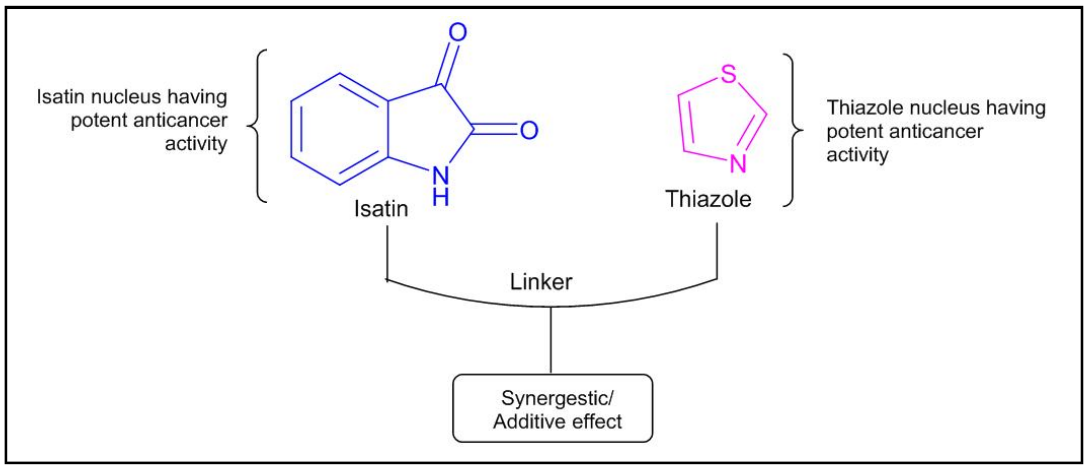


Figure 3: Isatin-thiazole containing hybrids.

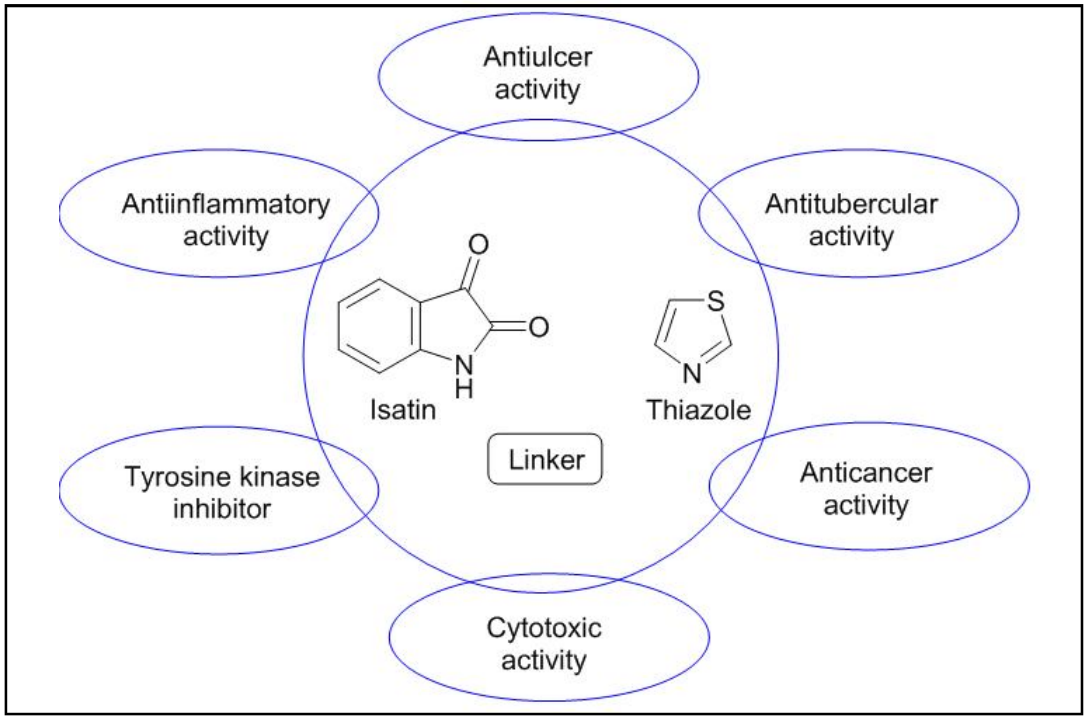
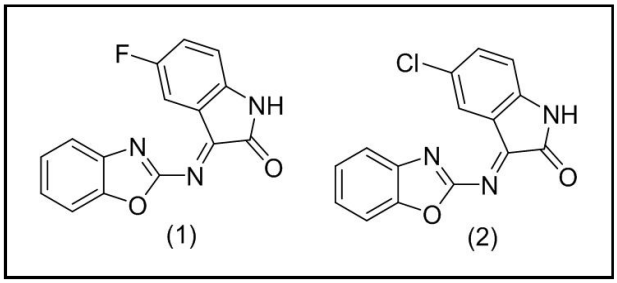


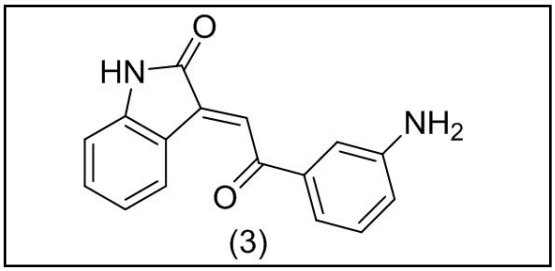
Figure 4: Biological characterization of isatin-thiazole hybrids.

2. Isatin as anticancer agent

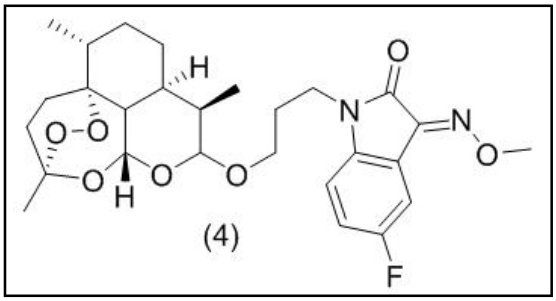
A series of benzoxazole-isatin derivativeswas synthesizedand evaluated by Susithra *et al. (*2022) using the MTT method on HeLa, IMR-32 and MCF-7 cancer cell lines using cisplatin as standard and also docked with Telomerase (5CQG) and GlcN-6-P synthase (2VF5). The result shows that compounds1 and 2 substituted with chlorine and fluorine group at 5thcarbonshows ahigh potential with a dock score value of -7.56 and -7.97.



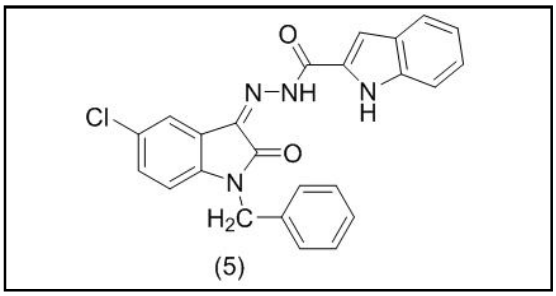
A set of isatin hybrid with a, b-unsaturated ketone was designed and developed using the association principle by Wang *et al.* (2017). These isatin hybrids were tested for their cytotoxic action on diverse cell lines, *viz.*, SGC-7901, BGC-823 and NCI-H460 by MTT assay. Compound **3** inhibited proliferation in all of the cancer cells examined and was found to be highly effective on the NCI-H460 cell lines, with an IC_{50} of 3.2 μM.



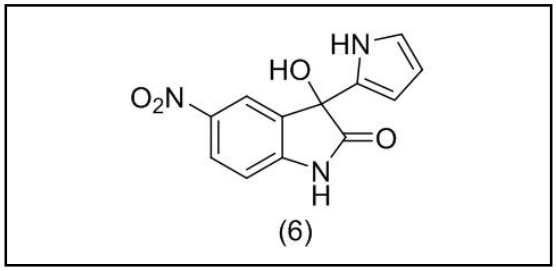
In another report nineteen propylene-tethered dihydro artemisinin-1*H*-indolin-2,3-dione, hybrids of 1*H*-indolin-2,3-dione was synthesized, by Zhang *et al.* (2022). Allsynthesized derivatives were tested *in vitro* antiproliferative screening against three different lung tumor cell lines. Among them, hybrid compound**4** expressed an excellent effect on resistant lung adenocarcinoma cell line, lung carcinoma epithelial cells line and lung adenocarcinoma cell line having an IC_{50} of 21.7-28.9 lμM.



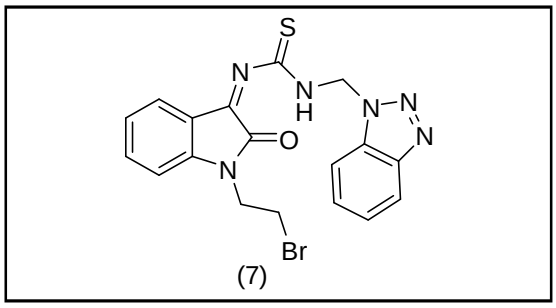
A series of different substituted isatin-indole conjugates was developed and tested for their *in vitro* anticancer activityon three cancer cell lines by (Al-Wabli*et al.*,2021). Esterification of indole-2-carboxylic and subsequently hydrazinolysis using hydrazine hydrate gives the intermediated which was treatedwith various substituted isatin derivatives to give novel isatin-indole derivatives. The antiproliferative activity of these derivatives was evaluated with A-549, ZR-75 and HT-29 tumor cells lines, in which compound **5** showed potent *in vitro* antineoplastic effects against all three cancer cell lines having an IC_{50} of 1.17.



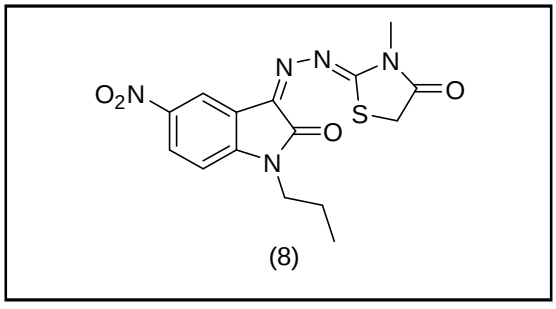
Santoso *et al.* (2021) evaluated *in vitro* cytotoxicity against HepG2 cell lineof a series of isatin-pyrrole scaffolds. The MTT method was used to perform cytotoxicity activity with HepG2 cells, the study reveals that isatins conjugated with pyrrole may give some potent anticancer drugs as the compound **6** of the synthesized series bearing nitro group showed the maximum cytotoxicity activity with an IC_{50} of 0.47 mM.



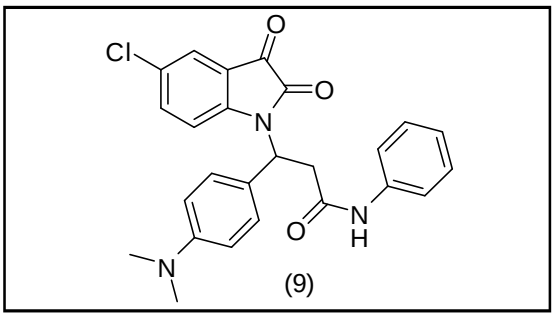
In another report (Kumar*et al.*, 2020) synthesized imidazole-linked isatins *via* condensing imidazole with various substituted isatins. The MTT assay on breast tumor cell line (MCF-7) and MCF-10A as a control, of synthesized scaffolds **7** showed a relatively potent activity caused by about 40% cell antiproliferation at 0.75 ¼M in MCF-7 cells,with 70% cell survival reported at 8.0¼ M in MCF 10 A cells, also the docking result of **7** shows the highest binding affinity towards phosphoinositide 3-kinases.



Yousef *et al.* (2020) synthesized thiazolidinenes and thiazolidinone-linked isatins and evaluated cytotoxicity against various cells, *viz.*, HepG2, MCF-7, HT-29. The MTT assay shows that the E-conformer of derivative **8** bearing nitro group was found to be more potent than doxorubicin against HepG2. Although, authors revel that thiazolidinenes-isatin scaffolds were found to be more potent than thiazolidinone. Also, the docking result shows that nitro-substituted isatin derivatives have a high binding affinity towards cyclin-dependent kinase 1.

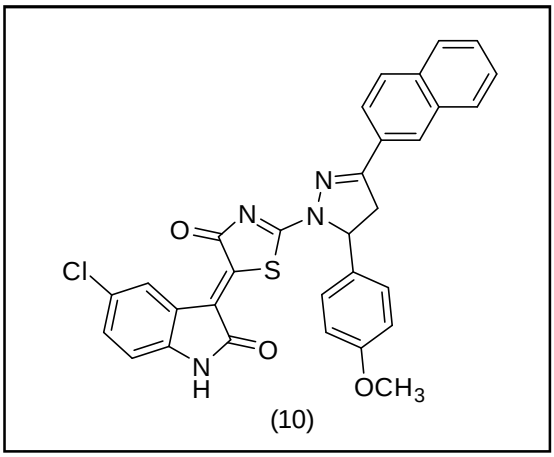


Deepthi *et al.* (2022) synthesized and tested a novel set of mannich bases of isatin derivatives as potent antiproliferative agents using MCF7 cell lines. The MTT assay shows that derivative **9** has more activity against MCF-7 cells incomparison with doxorubicin as a standard drug with an IC_{50} value of 41.65 ¼ M.



(9)

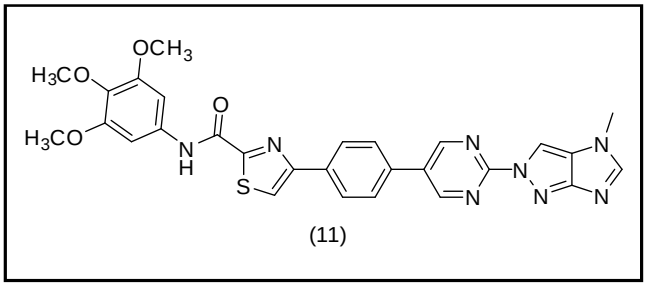
In another report (Meleddu *et al.*,2019) reported their investigation onisatin-dihydropyrazole hybridsfor their anticancer activity against different cell lines (IGR39, A549, MDA-MB-231, U87, BT474, MCF-7, SKOV-3, BxPC-3 and H1299). The study shows that derivative **10** containing methyl group in the 5thposition of the is atin nucleus is the most promising among all synthesized derivatives against IGR39, U87 and IGR39 compared to standard drug sunitinibhaving EC_{50} values range of 0.01 to 0.38 mM.



(10)

3. Thiazole as anticancer agent

Bandaru *et al.* (2021) developed and synthesized a series of new amine-based thiazole-pyrimidine derivatives *via* linking with fused imidazole-pyrazole derivatives and screened them against different human cancer cells lines, A2780 (ovarian), Colo-205 (colon), A549 (lung), MCF-7 *via* technique. Compounds with di/tri-substituted were found to be more potent as compared to mono-substituted compounds. Two derivatives **11** and **12** were dispatched with maximum anticancer effect compared to standard drug etoposide tested on all the cancer cell lines, also possible protein binding was identified. The comparative studies of violine plot and binding energies suggested that analogues were having potent binding sites at ATR kinase.



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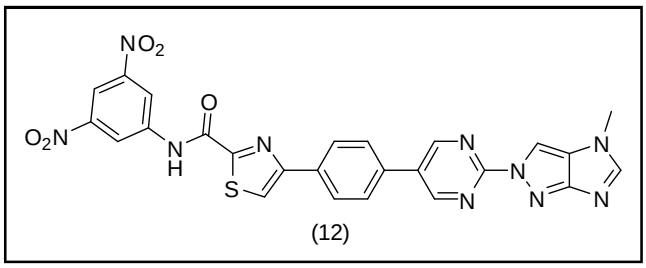
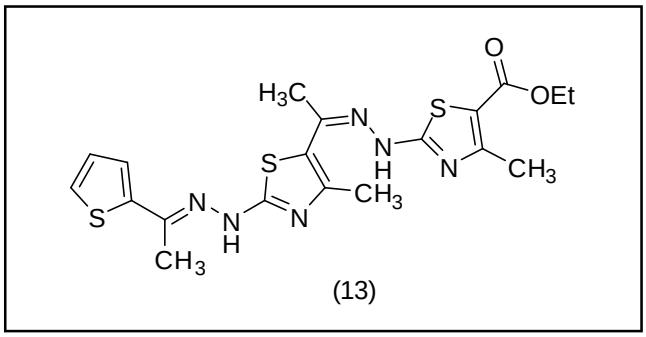


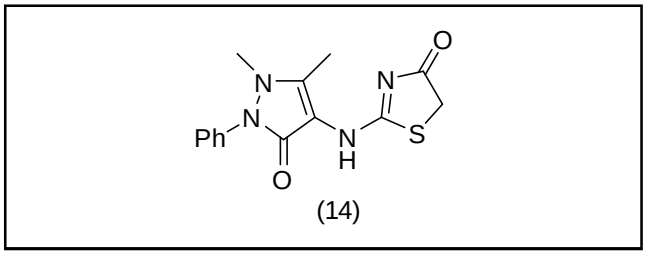
(12)

Gomha *et al.* (2021) developed a fresh series of 5-(1-(2-(thiazole-2-yl) hydrazone) ethyl) thiazole analogs. All derivatives were evaluated for anti-neoplastic activity using an MCF-7 cell line *via* MTT assay. It was found that analog **13** produces maximum activity having IC_{50}value of 14.6 mM as compared to cisplatin. Molecular docking studies were performed on the Rab7b target protein site and withthe help of the admet SAR tool *in silico* studies like toxicity and ADME were carried out.



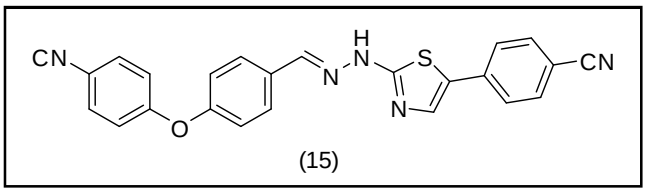
(13)

Othman *et al.* (2022) synthesized two series of pyrazoline-3-one linked with thienol (3,2-d) thiazoleordihydrothiazolo (4,5-d) thiazole scaffold *via* an N-H linker by using pyrazolinone-thiazolinone analogues as important antecedent. All the synthesize danalogues were screened for anti-proliferative effects on two different cancer cell lines, *viz.*, HepG-2 and MCF-7, analog**14** expressed the most anticancer effect on both the cell lines, further these compounds were also tested as multi-targeting kinase inhibitors on normal human cell line WI-38.



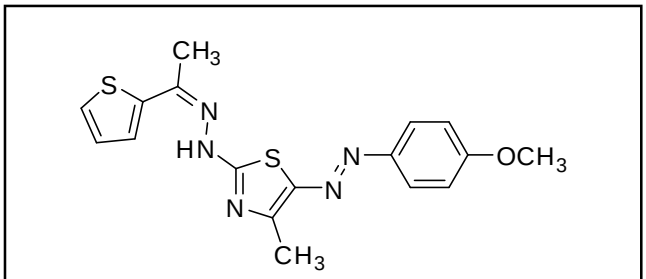
(14)

In another study (Altýntop *et al.*, 2018) reported a series of new thiazole derivatives and all the synthesizedan alogues were evaluated for anticancer effect at C6 rat glioma, A549 and NIH/3T3 (healthy) mouse embryonic. Among all the compounds, derivative **15** shows 45 and 71% inhibition on A549 and C6 cell line, respectively. In addition, the molecular docking study on serine/threonine kinase 1 (AKT1) enzyme shows satisfactory binding.



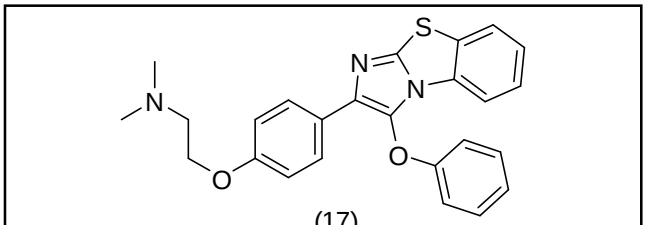
(15)

El-Naggar *et al.* (2022) synthesized various derivatives of hydrazinyl thiazole derivatives. All freshly synthesized derivatives were screened for *in vitro* antineo plasticaction against colorectal cancer HCT-116, HePG-2 and MCF-7 cell lines using the MTT technique. The synthesized scaffold **16** showed maximum activity with IC_{50} values of 3.81, 7.19, 8.22 ㎜ for HePG2, MCF-7 and HCT-116 respectively compared to roscovitine as standard drug although, chloro and methoxy substituted compounds also showed selective against HCT-116 and HePG-2 cell line.



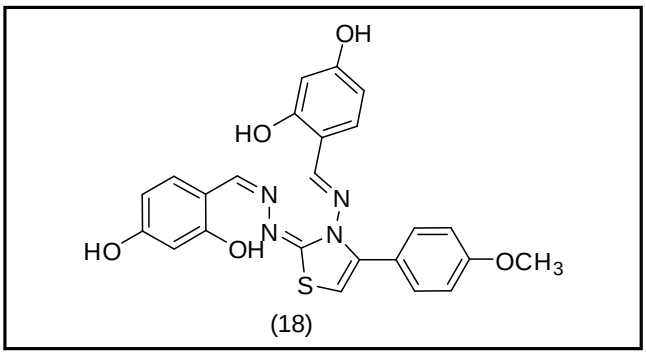
(16)

In another report (Ahmadi *et al.,* 2022) designed and synthesized novel derivatives of diaryl benzo [d] imidazo [2,1-b] thiazole analogues having aminoethoxy as a side chain and evaluated them on MCF-7 for cytotoxicity *via in vitro* by using the MTT assay thecytotoxic effects of the synthesized analogues were also assessed at the MCF-7 cell line. All the synthesized analogues expressed satisfactory inhibitory action on the tested cell line, using tamoxifen as the standard drug, among which compound **17** was found to be more potent and showed maximum cytotoxicity with an inhibitory effect of 81%.



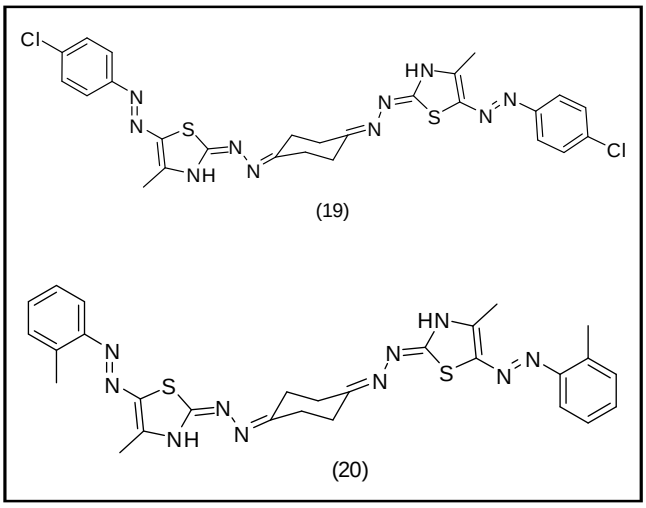
(17)

Mamidala *et al.* (2020) developeda series of novel thiazole compounds by using microwave-assisted multi-component reaction of thiocarbohydrazide, aldehydes with substituted phenacyl bromides. All the targeted thiazole compounds were tested for anticancer action *in vitro* method on various cancer cell lines BT-549, MDA-MB-231/ATCC,MCF-7HS 578T, T-47D and MDA-MB-468 cell lines. Among all the compounds **18** showed themost potent compound. Its cytotoxic effects against metastatic breast 231 cancer cell lines showed 49.4% cells passed away at 50 µg/ml. The docking analysis displayed a good binding affinity with a 6.195 kcal/moldock score.



(18)

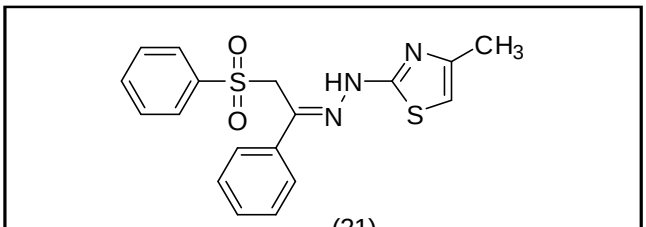
Dawood *et al.* (2021) designed and synthesized different series of bisthiazoles analogues, all the analogues were screened for anticancer activities *in vitro* panel of cancer cell lines. Analogue **19** has shown potentanticancer activities, onthe cervical tumor, Hela cell lines and derivative **20** against the KF-28 cell line. The molecular docking studies were also performed for all the analogues although, both the derivatives have shown higher binding effects and it suggests the inhibition of phosphorylated C-myc.



(19)

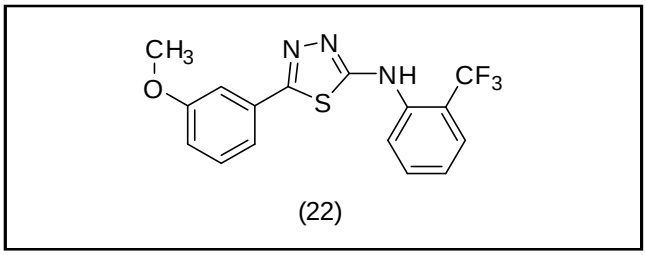
(20)

Farghaly *et al.* (2022) developed and synthesized a series of 1,3-thiazole analogues and also synthesized acetophenone derivatives using substituted phenacyl bromides as a starting product. All the synthesized analogues were tested againstthe multiplication on breast cancer cell lines, *viz.*, HepG2 and MCF-7. The *in vitro* cytotoxic effect, using MTT assay reveals that the 4-methyl thiazole analogue **21**, among all the synthesized derivatives exhibited nine folds more cytotoxicity activity than dasatinibin for MCF-7 cell linewith an IC_{50} of 1.24 ㎜. The docking result also showed that derivative **21** perfectly settle inside the EGFR binding site with a binding score of -7.99.



(21)

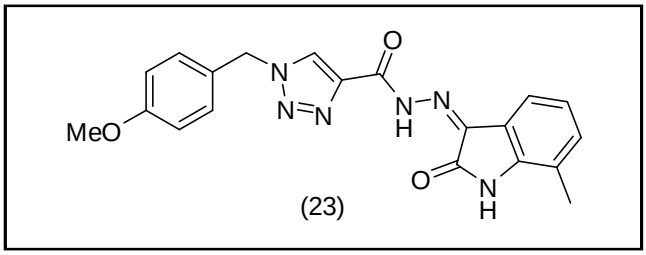
Janowska *et al.* (2022) designed and developed the 1,3,4-thiadiazole analogues and evaluate these analogues for cytotoxic activity using different breast cancer cell lines. The authors report that analogue **22** shows the maximum anticancer activity against MCF-7 having IC_{50} of 49.6 ㎜, etoposide was used as a reference drug. The same was found to be active against MDA-MB-231 cell line, it inhibited the 50% viability of the cells at a concentration of 53.4 ㎜. It also shows the binding affinity of 7.43 kcal/mol for Bax-protein and 7.34 kcal/mol for Caspase 8.



(22)

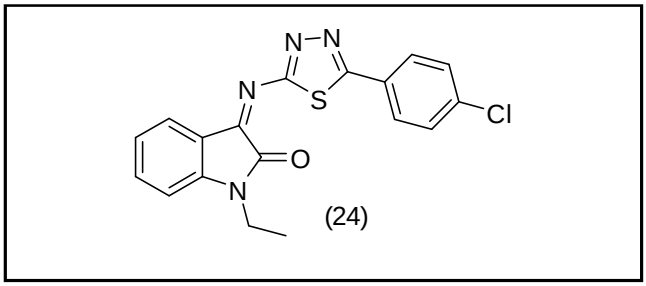
4. Isatin-thiazole hybrid as anticancer agent

Furthermore, some researchers have shown their interest in designing and evaluating the anticancer activity of isatin-thiazole hybrid moieties Aneja *et al.* (2019) designed a set of isatin-triazole hydrazones and tested them for anticancer action on MDA-MB-435s, MCF-7 and HepG2 cells. Authors found that electron donating groups containing isatin-triazole hydrazones derivatives **23** have better binding affinity for microtubule affinity-regulating kinase 4 and enzyme inhibition, as well as inhibition of cell migration with cell proliferation. The MTT assay shows that **23** effectively inhibits the proliferation of three cancer cell lines, *viz.*, MCF-7, MDA-MB-435s and HepG2 with an IC_{50} 6.22, 9.94 and 8.14 ㎜, respectively.



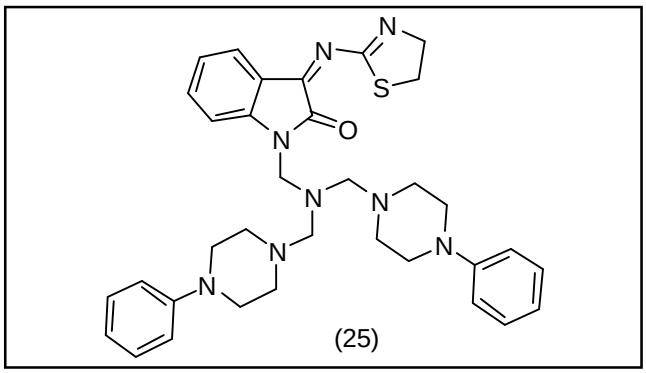
(23)

In another report (Kumar *et al.*, 2017) developed, synthesized and screened the *in vitro* anticancer action against MCF-7 cell lines of novel set of isatin attached hybrid with thiadiazoles. The MTT and SRB assay of synthesized analogues against MCF-7cell lines reveals that chlorobenzene derivative **24** among the entire synthesized derivative shows the most potent cytotoxic activity with IC_{50} 10.46 and 13.04 ㎎/ml for SRB and MTT assay.



(24)

Taher *et al.* (2011) synthesize two novel sets of isatin-thiazoline and isatin-benzimidazole hybrids by reacting isatin mannich base analogues by various aminothiazoline and benzimidazoline further the synthesized series was evaluated for cytotoxicity activity against human breast adenocarcinoma cell line (MCF-7) using sulforhodamine B (SRB) assay taking doxorubicin as standard drug. The study reveals that isatin-linked thiazoline schiff base **25** displayed the highest antibreast cancer activity with IC_{50} of 38.22 ㎜, although, isatin-benzimidazole series also exhibit satisfactory cytotoxicity activity.



(25)

5. Conclusion

Isatin serves as the main nucleus for a variety of cytotoxic and anti-cancer molecules. However, thiazole is a heterocyclic compound found in many anticancer agents due to its versatile nature.This article discusses the anticancer properties of isatin and thiazole molecules. In general, isatin and thiazole moieties are reported to trigger cancer cell death. The rational design of thiazole, isatin, and isatin-containing thiazole hybrids that target a specific receptor/enzyme/protein has led to significant progress in this field. Regarding this, thiazole and isatin analogues are confirmed as agents that inhibit metastasis, inhibitors of microtubule polymerization, inhibitor for protein kinases, apoptotic inducers and tumor suppressors. Lots of these drugs with particular receptors demonstrated strong anticancer effectiveness and selectivity with few toxicity and side effects. Several isatin and thiazole drug candidates with strong effectiveness and a favorable pharmacological profile are in clinical trials. Furthermore, data from preclinical and clinical trials are critically needed to identify the benefits of these novel molecules during the therapeutic development process.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Abdel-Latif, E.; Khatab, T.K.; Fekri, A. and Khalifa, M.E. (2021). Synthesis of new binary thiazole-based heterocycles and their molecular docking study as COVID-19 main protease (M pro) inhibitors. Russian Journal of General Chemistry, **91**(9):1767-1773.

Ahmad, N.; Shahhosseini, S.; Shirazi, F.H. and Zarghi, A. (2022). Synthesis, structural characterization, and cytotoxic activity of new benzo[d] imidazo [2, 1-b] thiazole derivatives against MCF-7 breast cancer cells. Iranian Journal of Pharmaceutical Research In Press, **21**(1):127-39.

Althagafi, I.; El-Metwaly, N. and Farghaly, T.A. (2019). New series of thiazole derivatives: Synthesis, structural elucidation, antimicrobial activity, molecular modeling and MOE docking. Molecules, **24**:174-81.

Altýntop, M.D.; Belgin, S.; Çiftçi, G.A. and Özdemir, A. (2018). Design, synthesis, and evaluation of a new series of thiazole-based anticancer agents as potent Akt inhibitors. Molecules, **23**(6):13-18.

Aneja, B.; Khan, N.S.; Khan, P.; Queen, A.; Hussain, A.; Rehman, T. and Alajmi, M.F. (2019). Design and development of Isatin-triazolehydrazones as potential inhibitors of microtubule affinity-regulating kinase 4 for the therapeutic management of cell proliferation and metastasis. European Journal of Medicinal Chemistry, **163**:840-852.

Al-Wabli, R.I.; Almomen, A.A.; Almutairi, M.S.; Keeton, A.B.; Piazza, G.A. and Attia, M.I. (2021). New isatin-indole conjugates: Synthesis, characterization, and a plausible mechanism of their *in vitro* antiproliferative activity. Drug Design, Development and Therapy, **14**:483-495.

Bandaru, C.M.; Nuthalapati, P.; Jadav, S.S.; Mandava.; Basaveswara, M.V.; Babu. K.S.; Sreenivasulu, R. and Alluri, R. (2021). Design, synthesis, anticancer evaluation, and molecular docking studies of thiazole-pyrimidine linked amide derivatives. Polycyclic Aromatic Compounds, **21**:1-17.

Bera, P.; Aher, A.; Brandao, P. and Debnath, U. (2022). Instigating the *in vitro* anticancer activity of new pyridine-thiazole-based Co(III), Mn(II), and Ni(II) complexes: Synthesis, structure, DFT, docking, and MD simulation studies. Journal of Chemical Information and Modeling, **62**:1437-1457.

Chemchem, M.; Menacer, R.; Merabet, N.; Bouridane, H.; Yahiaoui, S.; Moussaoui, S. and Belkhiri, L. (2020). Green synthesis, antibacterial evaluation and QSAR analysis of some isatin Schiff bases. Journal of Molecular Structure, **12**:178-93.

Dawood, K.M.; Raslan, M.A.; Abbas, A.A.; Mohamed, B.E.; Abdellattif, M.H.; Nafie, M.S. and Hassan, M.K. (2021). Novel Bis-thiazole derivatives: Synthesis and potential cytotoxic activity through Apoptosis with Molecular Docking approaches. Frontiers in Chemistry, **9**:48-67.

Deepthi, K.L.; Subhashini, N.J.P. and Maneshwar, T. (2022). Synthesis, molecular docking studies, antimicrobial, anticancer and antioxidant activity of some novel mannich bases of isatin scaffold. Asian Journal of Chemistry,**34**(5):1097-1104.

El-Naggar, A.M.; Zidan, A.; Elkaeed, E.B.; Taghour, M.S. and Badawi, W.A. (2022). Design, synthesis and docking studies of new hydrazinyl-thiazole derivatives as anticancer and antimicrobial agents. Journal of Saudi Chemical Society, **26**(4):1014-28.

El-Naggar, M.; Wagdy. M, Eldehna. and Hadia, Almahli. (2018). Novel thiazolidinone/thiazolo[3,2-a] benzimidazolone-isatin conjugates as apoptotic anti-proliferative agents towards breast cancer: One-Pot synthesis and *in vitro* biological evaluation. Molecules, **23**:14-20.

Farghaly, T.A.; Abbas, E.M.H.; Al-Soliemy, A.M.; Sabour, R. and Shaaban, M.R. (2022). Novel sulfonyl thiazolyl-hydrazone derivatives as EGFR inhibitors: Design, synthesis, biological evaluation and molecular docking studies. Bioorganic Chemistry, **212**:105684.

Ferlay, J.; Ervik, M.; Lam, F.; Colombet, M.; Mery, L. and Piñeros, M. (2020). Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer.

Franchetti, P.; Cappellacci, L.; Grifantini, M. and Barzi, A. (1995). Furanfurin and thiophenfurin: Two novel tiazofurin analogues. Synthesis, structure, antitumour activity, and interactions with inosine monophosphate dehydrogenase. Journal of Medicinal Chemistry, **19(**38**)**:23-37.

Gezici, S. (2018). Promising anticancer activity of lavender (*Lavandula angustifolia* Mill.) essential oil through induction of both apoptosis and necrosis. Ann. Phytomed., **7**(2):38-45.

Gomha, S.M.; Abdelhady, H.A.; Hassain, D.Z.H.; Abdelmonsef, A.H.; El-Naggar, M.; Elaasser, M.M.; Mahmoud, H.K. (2021). Thiazole-based thiosemicarbazones: Synthesis, cytotoxicity evaluation and molecular docking study. Drug Design, Development and Therapy, **15**:659-661.

Janowska, S.; Khylyuk, D.; Bielawska, A.; Szymanowska, A.; Gornowicz, A.; Bielawski, K.; Noworól, J.; Mandziuk, S. and Wujec, M. (2022). New 1,3,4-thiadiazole derivatives with anticancer activity. Molecules, **27**(6):181-190.

Kumar, N.; Sharma. C.S.; Singh, H.P. and Chauhan, L.S. (2017). Synthesis and *in vitro* evaluation of novel isatinincorporated thiadiazole hybrids as potential anti-breast cancer agents. Tropical Journal of Pharmaceutical Research, **16**(8):1957-1963.

Kumar, R.; Dhayabaran, V.V.; Sudhapriya, N.; Manikandan, A.; Gideon, D.A. and Annapoorani, S. (2020). p-TSA. H2O mediated one-pot, multi-component synthesis of isatin derived imidazoles as dual-purpose drugs against inflammation and cancer. Bioorganic Chemistry, **102**(4):104-116.

Kumar, R.; M, Gideon, D.A.; and Mariadasse, R. (2021). *In silico* evaluation of isatin-based derivatives withRNA-dependent RNA polymerase of the novel corona virus SARS-CoV-2. Journal of Biomolecular Structure and Dynamics, **22**:1-16.

Lahari, K. and Sundararajan, R. (2020). Design and synthesis of novel isatin derivatives as potent analgesic,anti-inflammatory and antimicrobial agents. Journal of Chemical Sciences, **132:**94-109.

Li, X.; He, Y.; Ruiz, CH.; Koenig, M. and Cameron, MD. (2009). Characterization of dasatinib and its structural analogs as CYP3A4 mechanism-based inactivators and the proposed bioactivation pathways. Drug Metabolism and Disposition, **37**:1242-1250.

Mamidala, S.; Mudigunda, V.S.; Peddi, S.R.; Bokara, K.K.; Manga, V. and Vedula, R.R. (2020). Design and synthesis of new thiazoles by microwave-assisted method: Evaluation as an anti-breast cancer agents and molecular docking studies. Synthetic Communications,**16:**2488-2497.

Medvedev, A.; Buneeva, O.; Gnedenko, O.; Ershov, P. and Ivanov, A. (2018). Isatin, an endogenous non peptide biofactor: A review of its molecular targets, mechanisms of actions, and their biomedical implications. Bio Factors, **44**(12):95-108.

Meleddu, R.; Petrikaite, V.; Distinto, S. and Arridu, A. (2019). Investigating the anticancer activity of isatin/dihydropyrazole hybrids. ACS Medicinal Chemistry Letters**, 10**(4):571-576.

Mishchenko, M.; Shtrygol, S.; Kaminsky, D. and Lesyk, R. (2020). Thiazole-bearing 4-thiazolidinones as new anticonvulsant agents. Scientia Pharmaceutica, **88**(1):1-16.

Mishra, S. and Singh, P. (2016). Hybrid molecules: The privileged scaffolds for various pharmaceuticals. European Journal of Medicinal Chemistry, **124**:500-536.

Nikalje, A.P.; Ansari, A.; Bari, S. and Ugale, V. (2015). Synthesis, biological activity, and docking study of novel isatin coupled thiazolidin-4-one derivatives as anticonvulsants. Archiv. der Pharmazie - Chemistry in Life Sciences, **20**:1-13.

Othman, I.M.M.; Alamshany, Z.M.; Tashkandi, N.Y.; Gad-Elkareem, A.M.; Abd El-Karim, S.S. and Nossier, E.S. (2022). Synthesis and biological evaluation of new derivatives of thieno-thiazole and dihydro-thiazolo-thiazole scaffolds integrated with a pyrazoline nucleus as anticancer and multi-targeting kinase inhibitors. RSC advances, **12**:561-577.

Santoso, M.; Fadlan, A.; Riza, M.; Fahmi, G. and Rahmayanti, A. (2019). Synthesis and *in vitro* cytotoxicity evaluation of isatin-pyrrole derivatives against HepG2 cell line. Open Chemistry, **19**(1):199-204.

Sekar, V.; Perumal, P.; Gandhimathi, S.; Jayaseelan, S. and Rajesh, V. (2010). Synthesis and anticancer evaluation of novel benzothiazole derivatives. Asian Journal of Chemistry, **22**(7):5487-5492.

Shegokar, R. and Sawant, S.(2014). Cancer research and therapy: Where are we today? International Journal of Cancer Therapy and Oncology, **2**(4):02048.

Srivastava, K.; Lakhmani, D.; Srivasatava, J. and Singh, R.B.; (2020). Synthesis and characterization of new thiazole involving isatin for studying theirantimicrobial activity.Indian Journal of Chemistry, **59**:485-487.

Stewart, B.W. and Wild, C.P. (2015). World Cancer Report 2014, World Health Organization, International Agency for Research on Cancer.

Susithra, E.; Rajkumar, S.; Komal, S.; Pansare, W.; Praveena, S.; Arun, P.S.; Chekkara, R. and Kiran, G. (2022). Design, synthesis, antimicrobial and anticancer activity of some novel benzoxazole-isatin conjugates. Biointerface Research in Applied Chemistry, **12**(2):2392-2403.

Taha, M.; Parveen, B.;, Osman, B.; Abdoon, I.H.; Mohamed, M.S.; Osman, W.J.A.; and Ahmad, S. (2019). *In vitro* profiling of plants used in sudanese traditional medicine for antioxidant and anti-breast cancer activities. Ann. Phytomed., **8**(1):119-126.

Taher, A.T.; Khalil, N.A. and Ahmed, E.M. (2011). Synthesis of novel isatin-thiazoline and isatin-benzimidazole conjugates as anti-breast cancer agents. Archives of Pharmacal Research, **34**:1615-1621.

Uddin, M.; and Veeresh B. (2020). Systematic review on screening the role of chemosensitizer or synergistic drug and doxorubicin as dual drug loaded nanoparticle in overcoming multidrug resistant breast cancer. Ann. Phytomed., **9**(2):113-124.

Viegas, C.; Danuello, A.; Bolzani, V.S.; Barreir, E.J. and Fraga C.A.F. (2007). Molecular hybridization: A useful tool in the design of new drug prototypes. Current Medicinal Chemistry, **14**(17):1829-1852.

Wang, J.; Yun, D.; Yao, J.; Fu, W. and Huang, F. (2017). Design, synthesis and QSAR study of novel isatin analogues inspired Michael acceptor as potential anticancer compounds. European Journal of Medicinal Chemistry, **144**:493-503.

Xie, Z.; Wang, G.; Wang, J.; Chen, M.; Peng. Y.; Li, L.; Deng. B.; Chen. S and Wenbiao, Li. (2017). Synthesis, biological evaluation, and molecular docking studies of novel isatin-thiazole derivatives as a-Glucosidase inhibitors. Molecules, **22**(4):659-668.

Yao, Y.; Chen, S.; Zhou, X.; Xie, L. and Chen, A. (2014). 5-FU and ixabepilone modify the micro RNA expression profiles in MDA-MB-453triple-negative breast cancer cells. Oncology Letters. **7**(2):541-547.

Yousef, M.A.; Ali, A.M.; El-Sayed, W.M.; Qayed, W.S.; Farag, H.H.A. and Aboul-Fadl, T. (2020). Design and synthesis of novel isatin-based derivatives targeting cell cycle checkpoint pathways as potential anticancer agents. Bioorganic Chemistry, **105**:1043-66.

Zhang, Z.; Zhang, D. and Zhou, Y. (2022). The anti-lung cancer activity of propylene tethered dihydroartemisinin-isatin hybrids. Arabian Journal of Chemistry, **15**(4):1-8.

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