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Review article

MINI-REVIEW ON ANTI-BREAST CANCER SYNTHETIC COMPOUNDS

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Abstract

Carcinoma of the breast is the most common prognosis and the second cause of cancer-related death among women. There have been alarming rises in BrCa therapy requests. For the treatment and prevention of BrCa, Researchers are resorting to drugs with higher efficacies, such as synthetic compounds, A great deal of chemotherapeutic medications have been associated to treatment resistance, cancer recurrence and side consequences. Selected simple synthetic compounds inhibit metastasis and stimulate apoptosis, slowing the spread of cancer. Therefore, these compounds have the ability to inhibit BrCa advancement, consequently increasing the longevity of patients and decreasing the number of mortality caused on by BrCa. We list chemical compounds that have been demonstrated in multiple studies to have cytotoxic effects on breast cancer cells in this review. Organic derivatives stimulate cell death, limit BrCa formation, and slow the growth of cancerous cells. We draw the conclusion that, in addition to methods of therapy, *The* chemicals are effective, and promising agents in the development of anti-breast cancer drug.

Key words: Anti breast cancer drug, Functional group, cancer cell lines, Inhibitory concentration.

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Introduction

Cancer is the second worldwide major cause of death due to industrial and communal enlargement. In last year, in the United States one million new cases of cancer and more than six lake cases of cancer deaths are reported. Furthermore, there is a frighten ascend in the occurrence of novel categories of tumor, prominence the difficulty as a communal issue for health arrangement universal. Even though the numeral of novel anticancer treatment has reported in the earlier, but the system for lowering the rate of the majority cancers exist in doubtful. Latest innovative chemotherapeutic agent strategies use to cure anticancer. Consequently, there is a continuous necessity to enhance substitute anticancer medicines with negligible side effects [1-3]. An oxidized derivative of indole known as 1H-indole-2, 3-dione,was foremost exposed by Erdmann and Laurent in 1840 as a result comes up from the oxidation of indigo dye [4]. The chemical was thought to be man-made for around 140 years until it was discovered to be present in Isatin genus plants, cannonball tree fruits (Couroupita guianensis Aubl), and Buffo frog parotid gland secretions. It is believed that plants, fungi, symbiotic bacteria, and marine mollusks all contain different types of substituted isatin, which they use to fight off harmful species. numerous medications have been licensed by the FDA for the therapy of breast cancer (BC), including Everolimus, eribulin, fulvestrant, pertuzumab, and numerous more. The use of these drugs has been restricted due to the occurrence of the conflict they address, and there are still several possibilities for a total evidence treatment that is optional on BC. Although wide spread investigation and promptly improvement in the majority cancers cure, there is a requirement to enhance a novel cluster of anticancer retailers concentrate on BC cells [5,6].

In this assessment we wrap nine functional groups namely,

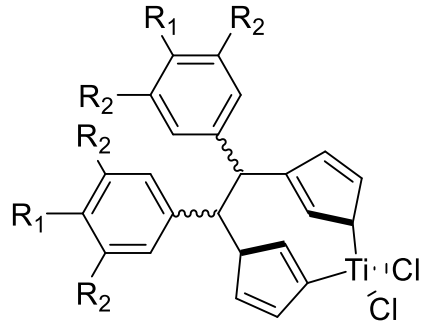
(1) Titanocene functional group,
(2) Oxadiazole functional group,
(3) Quinoline functional group,
(4) Indole or isatin functional groups,
(5) Imidazole functional group,

The cytotoxic effects of all these parent nucleus on breast cancer cell line are exemplify in this manuscript. By reviewing of this effect on diverse cell line we discovered several innovative thought concerns in novel anticancer drugs synthesis.

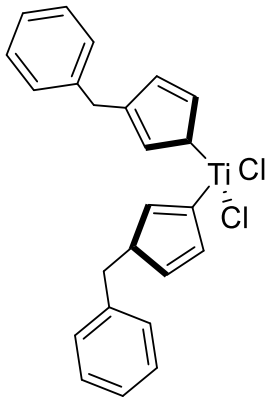
1) Titanocene Functional Group

A number of platinum agents, for instance cisplatin, which apply antiproliferative activity in Brest cancer focused on DNA [7]. Although cisplatin and its derivatives are increasingly used in healthcare settings, its main drawback is the risk of severe side effects and chemotherapy-induced nausea and vomiting [8]. As with other unexpected metal complexes, titanium complexes have garnered a lot of attention for their cytotoxicity against solid tumors that have become resistant to treatment. Their anticancer properties have been evaluated [9]. In recent years, numerous modified compounds based on titanium have been developed and are being evaluated as potential anticancer medicines. The new titanocene complexes **(1a-1c)** prepared by Sirignano *et al*. showed moderate to high anticancer activity against MCF-7 cells, as shown in Figure 1. Titanocene potentially binds to DNA and induces apoptosis, a cytotoxic mechanism that may be related to its structural similarity to cisplatin [10].

Figure 1: Titanocene and its ansa bridged intermediates



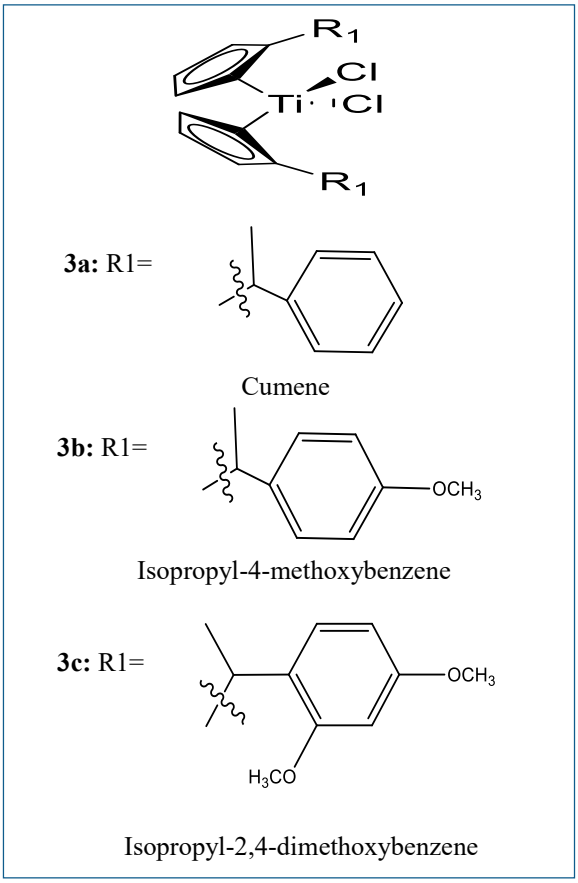
1a: Titanocene X, R_1=H, R_2 = OCH_3
1b: Titanocene Z, R1=N, N-$(CH_3)_2$, R_2 = H



1c: Titanocene Y

Novel synthesized compounds **3a-3c** (IC_{50} values of 86, 50 and 130 µM respectively) exhibited selectively inhibit MCF-7 cell proliferation by blocking topoisomerase I and II. These active compounds did not exhibit any anti-proliferation effects on non-tumor MCF-10A cell line, which demonstrate their selectivity towards MCF-7 breast cancer cell line [11].

Figure 2: Anti-proliferative and inhibitory effects of titanocene derivatives against topoisomerase I and II



2) Oxadiazole functional group

An important compounds having a different range of biological actions, including anticancer, antiviral, antibacterial, antineoplastic, fungicidal, and tyrosinase and cathepsin K inhibition, oxadiazoles were synthesized by Dawood and Gomha (2014). In organic synthesis, oxadiazole heterocycles serve as functional intermediates and are involved in electron transfer and hole-blocking processes extensively. Furthermore, oxadiazole heterocycles are highly effective amide and ester isosteres that can significantly increase activity through H-bond with the receptor. The pharmaceutical industry has seen a substantial expansion in the application of bio isosterism in the development of new, therapeutically active analogs. In comparison to cispatin's IC_{50} value of 0.42 µg/ml on HCT-116 colon cell lines, Intermediate **4a** and **4b** showed notable cytotoxicity at 0.73 µg/ml and compound 4b at 0.86 µg/ml, respectively.

Murthy *et al.* (2013) produced a range of chemicals and tested their cytotoxicity against five human most cancers cell lines, HepG2, A431 and A549 cell lines. Compounds **(5)** and **(6)** exhibit most activity in the direction of A431, followed by MCF7, A549 and HepG2 cell lines.

Figure 3: Thiadiazole derivatives

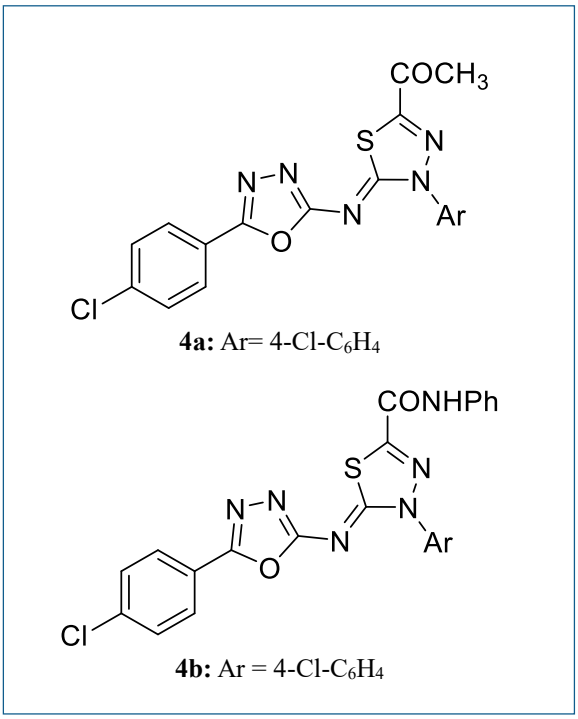
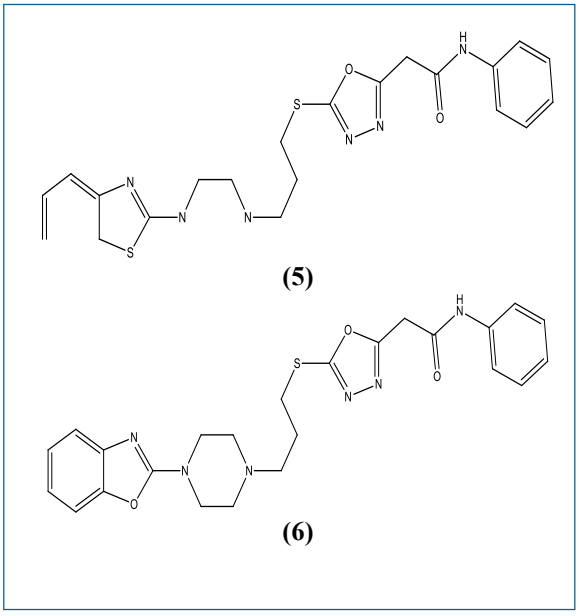
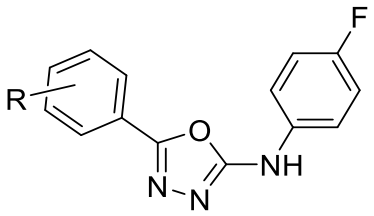


Figure 4: Oxadiazole derivatives.

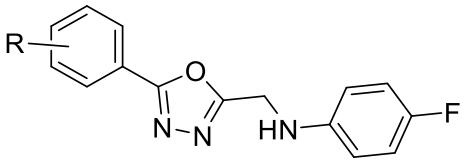


In 2016, Agarwal Mohit *et al*. synthesized two series of 1, 3, 4-oxadiazole analogues and assessed their anticancer efficacy using the NCI-60 different cancer cell lines. At a dose of 10 µM, different strains of breast cancer cell lines were significantly killed by intermediates (**7b**, **7e**, **7i**, **7j**, and **7n**). While **7i** and **7j** showed %GI of 41.88 and 46.11 against MDA-MB-235, respectively, **7b**, **7e**, and **7n** exhibited %GI of 37.80, 44.77, and 44.43 against T-47D [12, 13].

Figure 5:.Oxadiazole derivative with cytotoxicity



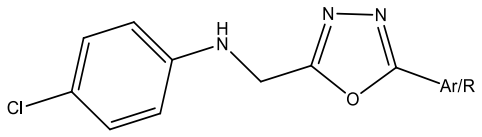
7b: R= 4-Cl **7i**: R= 4-F
7e: R= 4-OCH_3 **7j**: R= 2-Cl



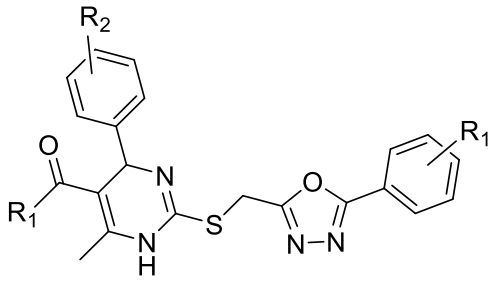
7n: R=3,4-$(OCH_3)_2$

Ragab, F., Abou-S, S. M. *et al.* 2017 synthesized compound **9a** and **9b** demonstrated higher activity against melanoma (SK-MEL-5), leukemia cell lines, colon (HCT-116), In contrast, they demonstrated moderate effectiveness versus breast cancer cell lines, with GI% ranging from 40.23 to 69.24 [14].

Figure 6: Pyrimidine derivatives



8a: Ar = 2-OH-C_6H_4, **8b**:Ar= 3,4-$(Cl_2)_2$-C_6H_3



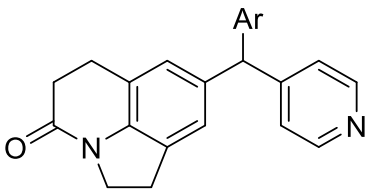
9a: R= 4-Cl, R_1= OC_2H_5, R_2= 4-Br
9b: R=4-Cl, R_1= OC_2H_5, R_2= 3-Cl

3) Quinoline derivatives

Quinoline derivatives complexes with diverse heterocycles haves present predominant anticancer activity intention in diverse spots like topo isomerase I, farmasyl transferase, Src tyrosine kinase, telomerase, protein kinase CK-II etc.

Yin, L., Hu, Q., Hartmann, R. W. *et al*. 2013 synthesized a sequence of pyridinylmethyl substituted pyrroloquinoline were considered and synthesized as a new approach for cancer with enhanced CVS condition. The cooperation of this conflict led to intermediates **10a-10d** as effective and discriminatory combo aromatase inhibitors, exclusively intermediate **10d** which demonstrated IC_{50} of 31.98 and 42 nM, correspondingly, and an preference towards, and hydroxylase, hydroxylase-, lyase.

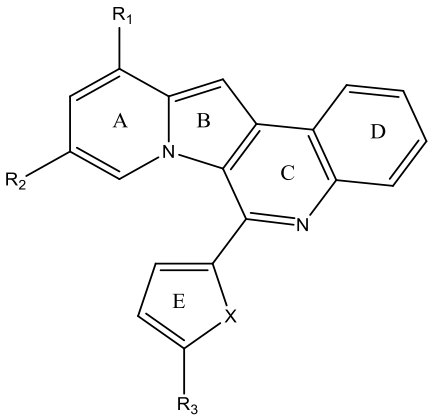
Figure 7: Pyridone derivatives



Ar,
10a; 4-OCH_3-C_6H_4
10b: 3-OCH_3-C_6H_4
10c: 3-Cl-C_6H_4
10d: 3-CH_3-C_6H_4

Kwon, S., Lee, Y., *et al.* 2018 synthesized Compound 11a to 11f are active against A549, MCF7 and HeLa cells. IC_{50} range of this compounds is 0.41- 4.2 µM in light irradiation. For A549 and MCF7 cells, 11a and 11f with –Cl at E ring were extra potent than IQs devoid of the Cl group , Compound 11c which contains –Br at A ring explained considerable dark cytotoxicities against A549 and MCF7 cells [15].

Figure 8: Indolidine derivatives

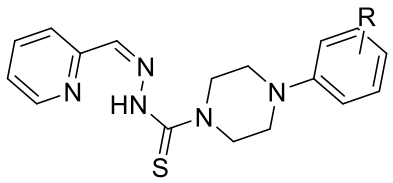


11a: R_1= H, R_2= H, R_3= Cl, X=S
11b: R_1=CH_3, R_2= H, R_3= H, X=O
11c: R_1=H, R_2= Br, R_3= H, X=O
11d: R_1=H, R_2= H, R_3= H, X=S
11e: R_1=CH_3, R_2= H, R_3= H, X=S
11f: R_1=CH_3, R_2= H, R_3= Cl, X=O

Mrozek-Wilczkiewicz, A., Malarz, K. *et al*. 2019 synthesized Compound **12a**, **12b** and **12c** are efficient against MCF7 cell lines in breast cancer. Compound **12c** principal lyres trained the

proliferation of the and U-251 cytotoxicities of (0.039 µM) and MCF-7 (0.022 µM) whereas the Hs-683 cells were somewhat sensitive to (IC_{50} = 4.68 µM) [16].

Figure 9: Pyridine-urea derivatives

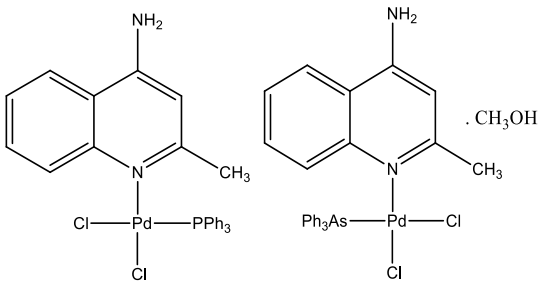


12a: R= 4-OCH_3, **12b**: R= 4-F, **12c**: R= 4- NO_2

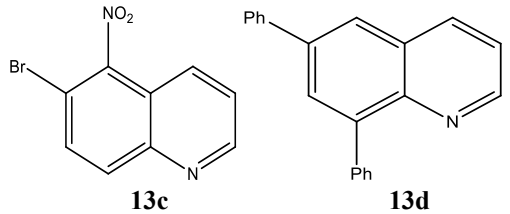
Thirunavukkarasu, T., Sparkes, H. A., Natarajan, K., 2018. Synthesized Compound 13a and 13b are valuable against Breast cancer MCF7 cell lines, IC_{50} value of this compound is 26 ± 1.4 µM and 29 ± 0.7 µM in that order [17] K, T. K., Ökten, S., T, Ş., Çakmak, O., 2018. Synthesized Compound 13c and 13d had comparable or superior antiproliferative effects on C6, HeLa and HT29 cell lines [18].

Alkahtani, H. M., Abdalla, A. N. *et al.* 2019 said in the MCF-7, intermediates 14a to 14l demonstrated cytotoxicity against MCF-7 cell line with (IC_{50}= 0.17-1.82 µM), that more cytotoxic than sorafenib as standard (IC_{50} = 2.49 µM) [19].

Figure 10: Quinoline derivatives

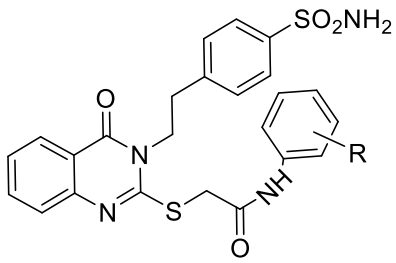


13a **13b**

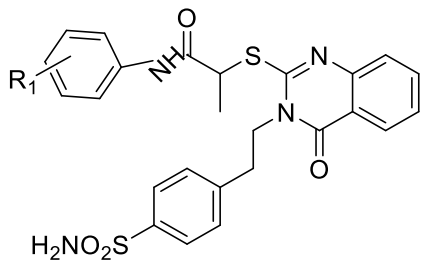


13c **13d**

Figure 11: Benzopyrimidone derivatives

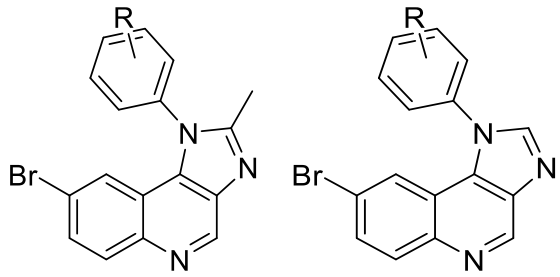


14a: R= -H, **14b**: R= 4-F, **14c**: R = 4-Cl, **14d:** R = 4-Br, **14e**: R = 4-CH_3, **14f**: R = 4-OCH_2CH_3, **14g**: R = 4-$COCH_3$, **14h**: R = 4-F, **14i**: R = OCH_3



14j: R= 3,4-$(OCH_3)_2$, **14k**: R= H, **14l**: R= 4-Cl

Lei, F, Xiao, Z., , *et al*. 2018 said *in vitro* cytotoxicity of Compound **15a** and **15b** explained superior activity against cell lines A549 than cell line MCF-7, PC-3 and HepG2, this explained the excellent prevention of cancer cell proliferation. **15a** and **15b** he enhanced activity consequence regarding the development of HepG2, and was highly active against the proliferation of PC-3 and A549 cell lines, but was insensitive to breast cancer. Compound **16a** characterized the finest activity on HepG2, and A549, PC-3 cell lines, with IC_{50} value of, 2.5-6.29 µM correspondingly [20].

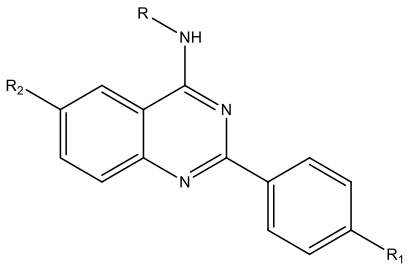


15a: R= Isobutyronitrile **16a**: R= Isobutyronitrile
15b: R = -OCH_3 **16b**: R= -OCH_3

(4) Indole or isatin functional groups

Researchers Mohamed, F., Wagdy, M. E., *et al*. 2015. It was found that the synthetic compound **17a** (2-phenyl-4-anilinoquinazoline) inhibits the breast cancer confrontation protein (BCRP) with high efficacy and selectivity. Intermediate **17b** exhibited broad anti-proliferative action [21].

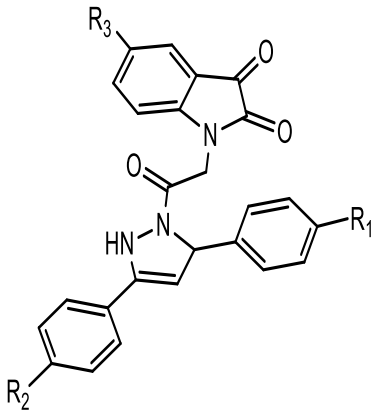
Figure 12: Substituted quinazoline derivatives



17a: R=3-$NO_2C_6H_4$, R_1&R2=H
17b: R=NH_2, R_1=Me,R_2=Cl

Havrylyuk, D., Kovach, N., *et al*. 2011 synthesized Compound **18a** and **18b** consequences on the SR cell line and CCRF-CEM cell line in blodd cancer. Compound **18d** is the mainly active compound, to be efficient against 26 cell lines. Compound 18d acquired cytotoxicity on different types of around sixty carcinoma cell lines at tenfold dilution of five doses (100 mM, 10mM, 0.1 mM, 0.01mM). Compound **18c** is efficient on HL-60 K-562, SR, NCI-H522, MOLT-4, RPMI-8226, CCRF-CEM, HCT-116, KM 12, SW-620, OVCAR-3 PC-3 and MCF-7 [22].

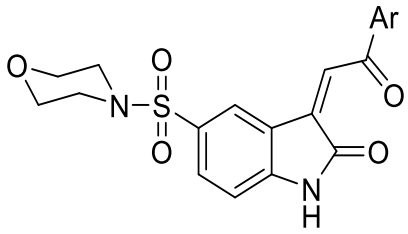
Figure 13: Pyrazole derivatives



18a: R_1=OCH_3, R_2=R_3= H, **18b**: R_1=Cl, R_2=R_3= H
18c: R_1= Cl, R_2= OCH_3, R3= H
18d: R_1= Cl, R_2= OCH_3, R_3= Br

El-Sharief, A. M. S., Ammar, Y. A. *et al*. 2019. Explain Compound 19(a-d) have exposed important selectivity towards HepG2 and HCT-116 extra than MCF-7 cell lines. Cytotoxic activity beside MCF7 cell lines IC_{50} values of the compound 19a-19d is 11.36 ± 0.44 µM , 9.56 ± 0.47 µM, 6.67 ± 0.36 µM and 14.46 ± 0.68 µM respectively [23].

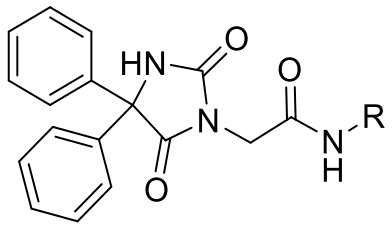
Figure 14: 3-Phenacylidene-2-indolinone derivatives



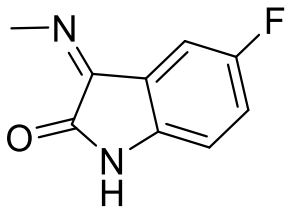
Ar,
19a: C_6H_5
19b: $C_6H_4NHCOCH_3$-3
19c: $C_6H_4OCOCH_3$-4
19d: $C_6H_4NHCOCH_3$-4

Alkahtani, H. M., Alanazi, M. M. *et al*. 2019. Synthesized Compound 20a and 20b illustrated further powerful cytotoxicity on MDA-MB-231 than standard with cytotoxicity of 63, 81 and 99.8 µM correspondingly. Generally, the consequences showed that compound 20a are the important strong compound with standard activity against the experimented value of 59 µM but the mean cytotoxicity of standard is 83 µM [24].

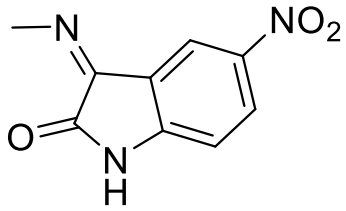
Figure 15: Isatin derivatives



20a: R =

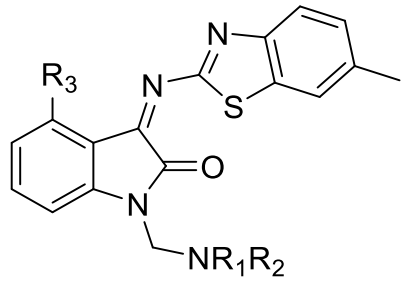


20b: R =



Hou, Y., Shang, C. *et al*. 2019. Compound **21a** (IC_{50} value 14.5 –19.76 µM) and **21b** (IC_{50} value 10.92–29 µM) exhibited the maximum activity against MCF7, MDA-MB231, and MDA-MB468. Compound **21b** (IC_{50} value 5.97 and 7.22 µM) was extra toxic than **21a** (IC_{50} value 31 and 39 µM) against non-cancer cells 184B5 and MCF-7 [25-28].

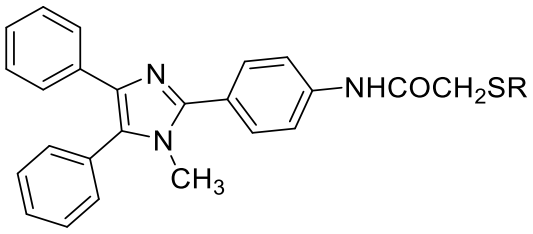
Figure 16: Schiff base of isatin derivatives



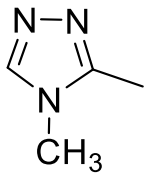
21a:R_1, R_2 = Morpholinyl, R_3 = H
21b: R_1, R_2 = Me, R_3 = Cl

5) Imidazole functional group

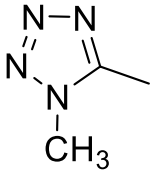
Özkay, Y., Işıkdağ, İ., *et al.* 2010 synthesized Compound **22a**, **22b** and **22c** have cytotoxic activity against MCF-7 and HT-29 lines. cytotoxicities of the **22a**, **22b** and **22c** against HT-29 cells and the **22b** and **22c** against MCF-7 cells are especially near to the cisplatin [29].



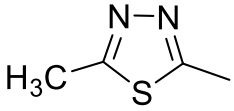
22a: R =



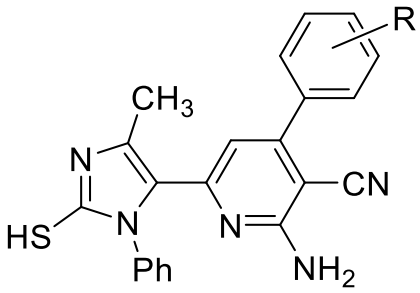
22b: R =



22c: R =



Abbas, I., Gomha, S., *et al*. 2015. The cytotoxicities of synthesized compound **23a**, **23b**, **23c** was evaluated against (MCF-7) and (HEPG-2) using the MTT assay with vinblastine and doxorubicin as standard [30,31].



23a: R = 4-Cl
23b: R = 4-OCH3
23c: R = 4-OH

Conclusion

This review summarizes various important anti-breast cancer intermediates are categorized by pharmacophores. Based on this sign, we can see that a set of group finished numerous efforts to try to find anti-breast cancer compounds with additional efficient, extra discriminatory results and slighter less important exploits. It cover the efficient cell line and IC_{50} value for diverse cell line, therefore it is supportive to synthesis of novel drugs. I expect that developers can have an activist considerate and thought to modification of anti-breast cancer intermediates *via* in this evaluation.

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