Send Orders for Reprints to reprints@benthamscience.net

Current Cancer Therapy Reviews, 2023, *19*, 237-259

REVIEW ARTICLE

Hetero Cyclic Compounds in the Treatment of Triple-Negative Breast Cancer

Sudip Kumar Mandal[1,#], Agnidipta Das[2], Anindya Bose[3], Vagish Dwibedi[4], Paramita Ganguly[5], Sipra Sarkar[6], Ranjana Prakash[7], Biplab Kumar Dey[8], Sanjeet Mandal[9], and Santosh Kumar Rath[10,*,#]

[1]Department of Pharmaceutical Chemistry, Dr. B. C. Roy College of Pharmacy and A.H.S., Durgapur, 713206, West Bengal, India; [2]Department of Pharmaceutical Science, Central University of Punjab, Bathinda, 151001, Punjab, India; [3]School of Pharmaceutical Sciences, Siksha O Anusandhan University, K8 Kalinga Nagar, Bhubaneswar, India; [4]University Institute of Biotechnology, Chandigarh University, Mohali, Punjab, 140413, India; [5]Pandaveswar School of Pharmacy, Pandaveswar, West Bengal, India; [6]Department of Pharmaceutical Technology, Brainware University, 398-Ramkrishnapur, Road, Barasat, Kolkata, 700125, West Bengal, India; [7]School of Chemistry & Biochemistry, Thapar Institute of Engineering & Technology, G-Block, Patiala, 147004, Punjab, India; [8]Dean, Faculty of Pharmaceutical Science, Assam Down Town University, Panikhaiti, Guwahati, Assam, India; [9]Global College of Pharmaceutical Technology, Krishnanagar, Nadia, WestBengal, India; [10]School of Pharmaceuticals and Population Health Informatics, Faculty of Pharmacy, DIT University, Dehradun, Uttarakhand, 248009, India

Abstract: Triple-negative breast cancer (TNBC) holds just about 15% of all breast tumours and subtypes of breast cancer with distinct characteristics of negative expressions for the progesterone receptor, estrogen receptor, and human epidermal growth factor receptor 2. Unfortunately, treatment options for TNBCs are minimal. Most currently available therapies proved inefficient in holding back this aggressive natural treatment of TNBC, in most cases calling for an immediate need for more effective and safer anti-TNBC agents. Based on research reported in recent years, this review presents the report's overview of anti-TNBC compounds and their efficacy, being classified according to the structures. Breast Cancer type 1 and type 2 genes (BRCA1/2) mutations are associated with TNBC. Poly (ADP-Ribose) Polymerases (PARPs) are a family of enzymes involved in numerous cellular processes, including DNA repair. PARP-1 inhibition is involved in the loss of DNA repair *via* BRCA-dependent mechanisms. PARP-1 inhibitors like Olaparib, Rucaparib, Niraparib, and Talazoparib have proved as promising therapeutic medications as monotherapy and in combination with cytotoxic therapy or radiotherapy in various types of cancers. This review is focused on presenting the status of therapeutics against TNBC. The critical spotlight of this review is to encapsulate the versatility and notable success of heterocyclic pharmacophores-based molecules in treating TNBC.

ARTICLE HISTORY

Received: March 04, 2022
Revised: October 17, 2022
Accepted: November 11, 2022

DOI:
10.2174/1573394719666221230111838

Keywords: Breast cancer, triple-negative breast cancers, heterocyclic compound, BRCA1 gene, FDA-approved drug, lump.

1. INTRODUCTION

Cancer, a life-threatening ailment, is affecting humankind severely [1]. Regardless of being the highest priority of researchers in developing therapeutic formulations for cancer treatment, breast cancer (BC) continues to be highly prevalent in women across the globe [2, 3]. The breast cells develop rapidly to form a tumour that further leads to malignancy, visible in X-Ray as a lump at the site of ducts or lobules or tissues associated with fatty or fibrous tissue of the breast [4, 5]. BC occurs almost entirely in women, but it is uncommon for men to get affected [6]. Though incidence is prevalent in women around the age of 45 to 55 years [7], the mortality rate has declined in the recent past due to advances in early diagnosis, proper management, and, most essentially, the introduction of adjunct drug therapy. Because of benign cancers, it is evident that most lumps in the breast do not lead to malignancies [8]. Some tumours are non-cancerous and therefore do not infect the breast or cause tissue damage, thus not life-threatening [9]. Women susceptible to serious BC have lumps that infect the breast, tissues, and lymph nodes [10]. The different types of breast cancer primarily include non-invasive, invasive, metastatic, and intrinsic or molecular sub-types of cancer. The noninvasive style does not spread out of the original tissue, while the invasive type of cancer spreads throughout the breast by the ducts and glands [11]. Triple-negative breast cancer, known as TNBC, is considered to be a subtype of BC with distinct characteris-

*Address correspondence to this author at the School of Pharmaceuticals and Population Health Informatics, Faculty of Pharmacy, DIT University, Dehradun, Uttarakhand-248009, India; E-mail: skrath1985@gmail.com
[#]*These authors contributed equally to this work.*

1573-3947/23 $65.00+.00

tics of negative expressions for progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2) [12].

Compared to other types of BCs, TNBC is featured with a highly aggressive nature but with short-lived adverse effects [13, 14]. A worldwide annual diagnosis of patients comprising 1 million cases showed TNBC (basal-like BC) in 170,000 individuals [15]. TNBC, an immune histochemically distinct subtype with great variety, holds just about 15-20% of all BC [16]. Younger women are considered more prone to TNBC, which is characterized by high relapse rates, visceral and CNS metastases, and premature death [17]. Most currently available therapies are proving ineffective in holding back this innate aggressive TNBC in most cases. The poor prognosis and targeted therapies lead to a high mortality rate [18].

The major highlights of this review are focused on discussing the present status of therapeutics against TNBC and examining some important candidates that can manage and treat TNBC. In this review, we endeavoured to encapsulate hetero-core-based 'pharmacophores' versatility in cancer therapy, especially for TNBC.

2. BREAST CANCER AND TRIPLE NEGATIVE BREAST CANCER

The recognition and characterization of carcinogenic stem cells and BC subtypes have led to a paradigm shift in modern breast cancer research. The molecular classification of BC is a much-needed and inevitable element for their proper diagnosis, prognosis, and treatment through new-targeted therapies. The molecular type was also found to play a crucial role in patient survival and stratifying the ER-positive population [19].

A thorough study of several intrinsic BC subtypes has led the way to classify them into basal-like subtypes, typical breast-like subtypes, $ErbB^{2+}$ subtypes, luminal A subtypes, and luminal B subtypes. Later, two more subtypes were introduced: the claudin-low type and Her2 enriched type (Fig. **1**). The molecular subtypes have gained greater importance in the TNBC basal-like subtype, comprising low survival time, got focused by various natural, synthetic and semi-synthetic approaches [19-25].

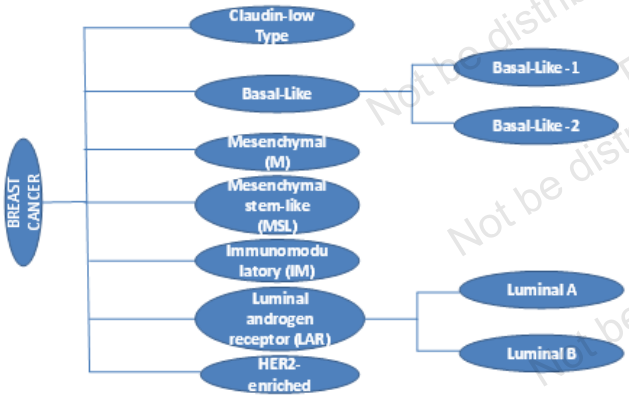


Fig. (1). Breast cancer classification.

Lehmann *et al.,* in 2011, provided a detailed classification of TNBC by profiling gene expression from tumour samples of TNBC patients. According to their study, TNBC can be of six types: Mesenchymal (M), Mesenchymal stem-like (MSL), Immunomodulatory (IM), Luminal androgen receptor (LAR), Basal-like 1 (BL1), and Basal-like 2 (BL2) [26]. Later, the authors revised the classification into four classes: M, LAR, BL1, and BL2 [27]. BL represents basal-like phenotypes of BC, where gene expression for BL1 occurs in DNA damage repair (DDR) and cell cycle. Gene expression for BL2 takes place in growth factor signalling pathways. M represents two mesenchymal-related subtypes associated with the transition of mesenchymal epithelium and its relation with chemoresistance. LAR subtype consists of high expression of the luminal androgen receptors associated with luminal-like gene expression, and this subtype consists of ER-positive, luminal-like subtype of BC. HER2-enriched subtype was coined by the PAM50 algorithm [28].

2.1. Triple-Negative Breast Cancer

The expressions of PR (-Ve), ER (-Ve), and HER2(-Ve) were found to cause poor prognosis and were liable for the aggressive character of TNBC [7]. TNBC comes under basal-like subtypes closely associated with the BRCA1 mutation. TNBC is an aggressive, risky cancer with a considerably higher growth rate than typical breast cancer [29].

2.2. Association with BRCA1 Mutation Status

The BRCA1 gene encodes a nuclear protein (190 kDa) containing a phosphate group to form a tumour suppressor protein and maintain the stability of the genome. The tumour suppressor protein can prevent uncontrolled cell growth, hence regulating the cell division that can prevent widespread BC. The mutations in BRCA genes (BRCA 1 and 2) are supposed to be accountable for the most common hereditary breast cancer. In most cases, the sporadic and genetic types of BCs associated with the BRCA1 gene are TNBC. TNBC, along with BRCA1, share some common characteristics such as the involvement of several integral proteins in DNA repair, low ER level, PR, HER2 expressions, and elevated level of expression for basal-like cytokeratins (CK5,14,17), p63, EGFR /HER1 and P-Cadherin [29].

Amongst all malignancies, breast, ovarian, prostate, and pancreatic cancers are mainly the consequences of germ-line BRCA gene mutations [29]. BRCA genes are crucial elements in DNA-repair mechanisms, thereby functional BRCA1 or BRCA2 deficiency causes reduced DNA double-strand breaks repair and predisposes to cancers. BRCA gene mutation carcinomas and basal-like breast cancer share some exciting and relevant similarities and drawbacks of BRCA or pertinent other pathways. TNBC has been reported in BRCA mutating patients, and 80-90% comes under the basal-like subtype. Sporadic BCs hardly contain BRCA gene mutations, but an expression or function alteration due to BRCA gene mutations can cause uneven breast cancer development [30].

Among the sporadic breast cancers, 11-14 percent were reported to contain a reduced BRCA1 expression due to

BRCA1 promoter methylation allied with the TNBC phenotype of high histological grade [30, 31].

While identifying the risk and management or prevention of the BC family, BRCA1 and BRCA2 mutations' molecular screening showed great importance. The more significant sign of phenotypes with triple negativity and early age of onset are the two critical components of hereditary breast cancer. An experiment conducted among fifty-four candidates on early-onset triple-negative types of women BC patients in search of BRCA genes resulted in the identification of five mutations of the BRCA1 gene (deleterious) and one mutation for BRCA2 (harmful) [32].

2.3. Comparison with Other Types of Breast Cancers

Among all BCs, 15-20 percent were found to be TNBC, especially TNBC associated with a basal-like subtype that consists of a higher histological grade, elevated Ki67 index, obvious cellular pleomorphism, unordinary mitotic figures, and raised mitotic activity. The characteristics of basal-like subtypes include instability of the genome, enhancing alteration of DNA copy number, and deletions and gains to be low at the genomic level. This subtype can deregulate vital elements from the cell cycle, including p53 abnormalities and the RB pathway. While accounting for the mutations, in 82% of patients, mutations were observed, with only 13% found in the luminal-A group [30].

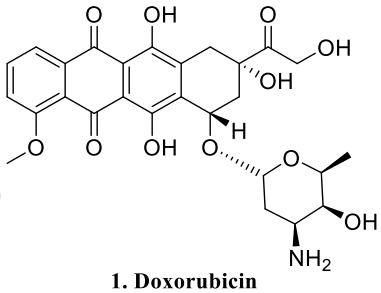
2.4. Clinical Characteristics

TNBC is perilous due to clinical characteristics like aggressive behaviour and metastases, onset at a younger age, high tumour grade and mean size, high node positivity rate, and occurrence of peak early within 1st and 3rd year from diagnosis. Because of histology, from the ductal origin, most TNBCs originate and mainly occur in viscera, specifically in the brain and lungs, while relatively less in bones. The basal-like tumours are associated with a marked increase in mitotic count, pushing invasion borders, geographic necrosis, stromal lymphocytic response, and ER/HER2 negativity [33].

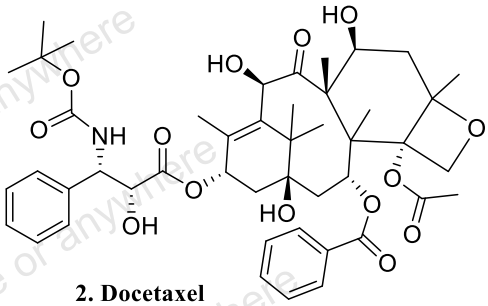
2.5. Prognosis for TNBC

According to the investigators, basal-like breast cancer faces a poorer prognosis than the luminal type. Therefore, a lesser survival rate occurs for TNBC than the luminal subtype. A significant difference was found in diagnosing TNBC and ER-positive breast cancer patients. TNBC always showed more aggressive visceral and soft tissue relapses than ER-positive breast cancer, whereas bone relapses are less common in TNBC. When the status of TNBC is compared with HER2-positive breast cancers, a more significant risk was found in developing cerebral metastasis in TNBC patients [33].

Several molecular markers proved productive in predicting and obtaining prognostic information for the BC patients of stage II and stage III while treated with chemotherapy by neo-adjuvant docetaxel/doxorubicin. The TNBC prognosis is associated with a higher Response Rate (RR), higher pathologic complete RR, and little overall survival in addition to relapse-free survival in contrast to the on-triple-negative type [34].



1. Doxorubicin



2. Docetaxel

2.6. Current Status of Therapy and Management for TNBC

TNBC is responsive against chemotherapy, but the number of accepted specific molecular targeted candidates to treat is deficient and needs attention. Various analytical studies on chemotherapeutic molecules have suggested that in an adjuvant setting, cytotoxic agents proved beneficial in TNBC treatment. TNBC and HER2 amplified patients exhibited higher RRs and complete pathological response (pCR) with about 45% more due to the administration of neoadjuvant chemotherapy than the use of Doxorubicin, 5-fluorouracil (5-FU) and cyclophosphamide [30]. Though there is much evidence for the chemo-sensitivity of TNBC, the optimal choice and schedule of cytotoxic remain unclear. Recently, researchers have focused on an intensive approach like anthracycline and taxane or DNA-damaging platinum-based therapies against TNBC [29].

3. HETEROCYCLIC ANTICANCER COMPOUNDS

Various natural and synthetic moieties or combinations prove efficacious in cancer therapy [35-38]. Due to their resourcefulness and exceptional physicochemical properties, most heterocyclic compounds and fragments are frequently marketed pharmaceutical products. They, thus, hold an essential role in medicinal chemistry research. The promising performance of the hetero-moieties has encouraged investigators in search of hopeful potency and efficacy to treat various carcinomas. Particularly, scaffolds with dynamic cores and the intrinsic versatility of the compounds proved beneficial for anticancer research [39].

Heterocyclic compounds exist in a wide variety of structures. They have been efficiently proven effective against a bunch of diseases and, therefore, approved by FDA ("Most Frequent Rings in FDA Approved Drugs," 2015) [40]. Descriptions of overall heterocyclic compounds investigated is

not a feasible task; thereby, important scaffold present in drugs have been depicted according to major classes.

The heterocyclic compounds acting on cancer can be classified into three categories

- Nitrogen-Based Heterocyclic compounds
- Oxygen-Based Heterocyclic compounds
- Sulphur-Based Heterocyclic compounds

3.1. Nitrogen-based Heterocyclic Compounds in Cancer

Regarding nitrogen-containing hetero-molecules, indole and its derivatives have established themselves as one of the essential common elements of most nitrogen-containing heterocyclic FDA-approved drugs. The compounds with a basic indole structure in the core, with their potency as tubulin polymerization inhibitors, have attracted considerable attention in oncology Tables **1** and **2** [41-71].

Table 1. Nitrogen containing FDA approved drugs for cancer.

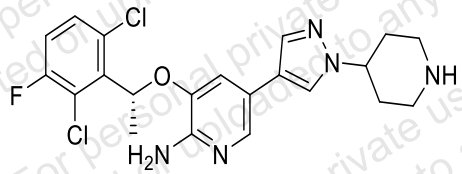
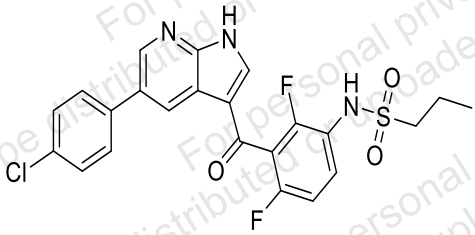
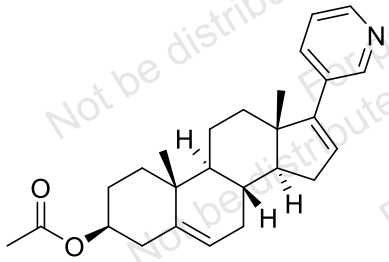
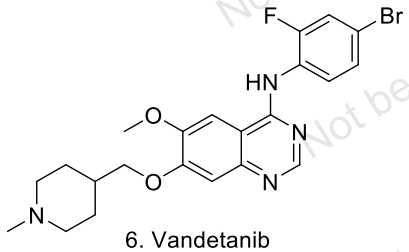
FDA Approved Drugs	Approved For	References
 3.Crizotinib (Xalkori®)	Non-small-cell lung carcinoma (NSCLC) - Late-stage	[42, 43]
 4.Vemurafenib (Zelboraf®)	Metastatic or unresectable melanoma	[44]
 5. Abiraterone Acetate (Zytiga®)	Metastatic prostate cancer (castration-resistant)	[45]
 6. Vandetanib (Caprelsa®)	Metastatic medullary thyroid cancer	[46, 43]

Table 1. Contd…

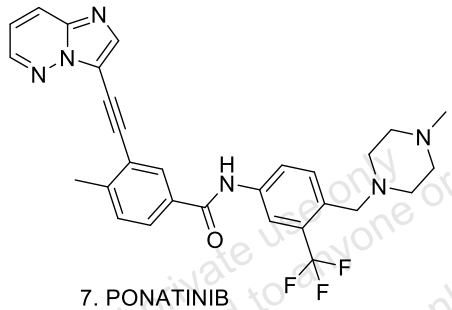
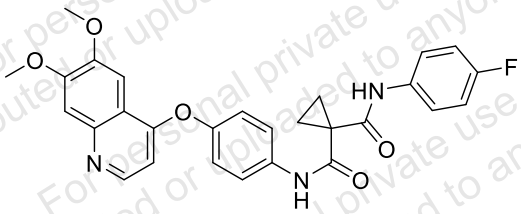
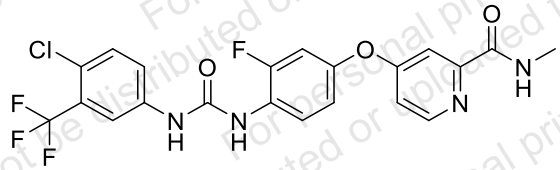
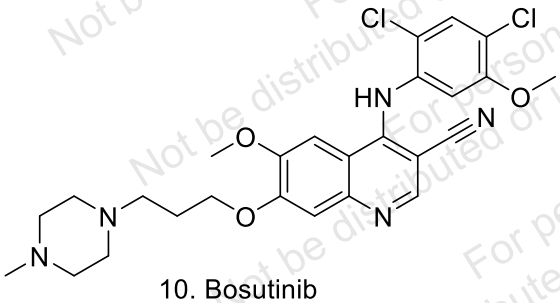
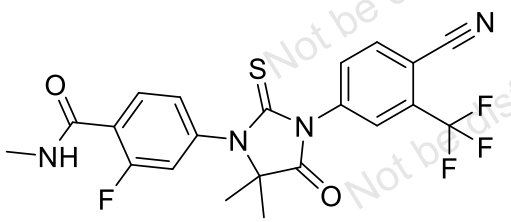
FDA Approved Drugs	Approved For	References
 7. PONATINIB (Iclusig®)	Chronic myeloid leukaemia/ lymphoblastic leukaemia	[47, 43]
 8. Cabozantinib (Cometriq®)	Metastasized medullary thyroid cancer	[48]
 9. Regorafenib (Stivarga®)	Metastatic colorectal cancer	[49]
 10. Bosutinib (Bosulif®)	Chronic myelogenous leukaemia	[50]
 11. Enzalutamide (Xtandi®)	Metastatic prostate cancer (castration-resistant)	[51, 52]

Table 1. Contd…

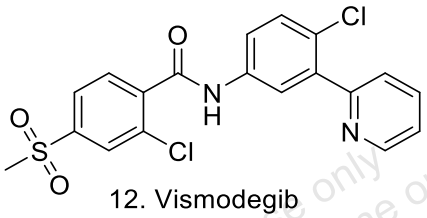
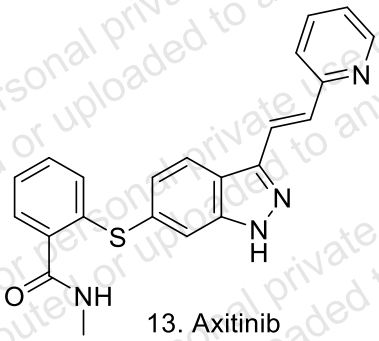
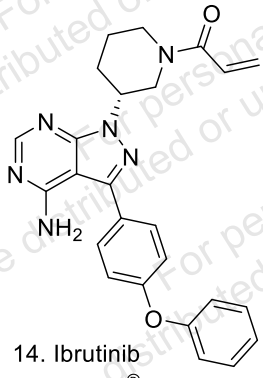
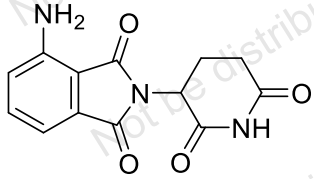
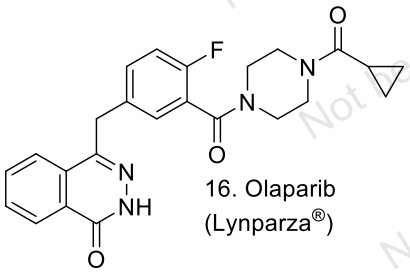
FDA Approved Drugs	Approved For	References
 12. Vismodegib (Erivedge®)	Basal cell type of carcinoma	[53]
 13. Axitinib (Inlyta®)	Renal cell cancer	[54]
 14. Ibrutinib (Imbruvica®)	Mantle cell lymphoma	[55]
 15. Pomalidomide (Pomalyst®)	Multiple myeloma	[56]
 16. Olaparib (Lynparza®)	Advanced ovarian cancer	[57]

Table 1. Contd…

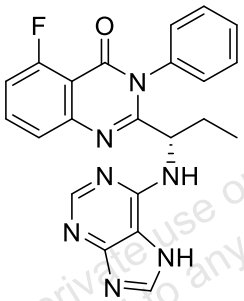
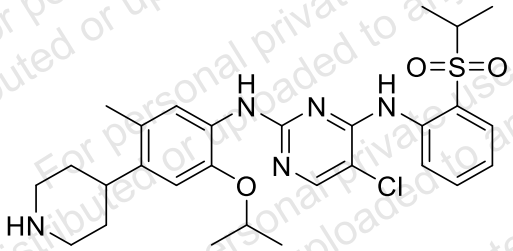
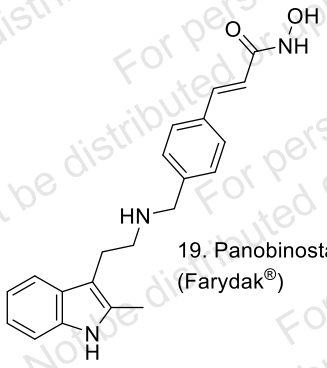
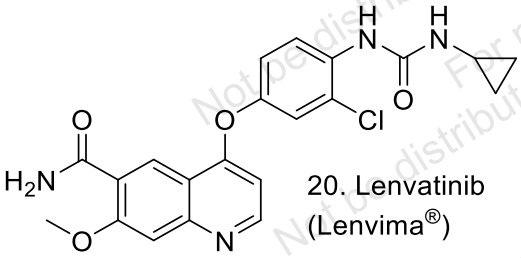
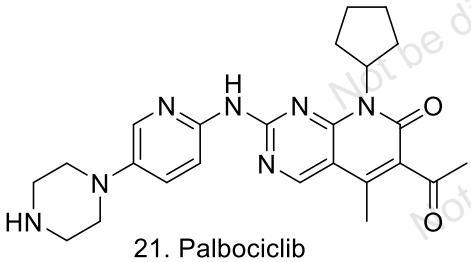
FDA Approved Drugs	Approved For	References
 17. Idelalisib (Zydelig®)	Chronic lymphocytic leukaemia	[58]
 18. Ceritinib (Zycadia®)	Non-Small Cell Lung Cancer (NSCLC) of metastatic type	[59]
 19. Panobinostat (Farydak®)	Multiple myeloma	[60]
 20. Lenvatinib (Lenvima®)	Differentiated and progressive thyroid cancer	[61]
 21. Palbociclib (Ibrance®)	Metastatic BC	[62]

Table 2. Nitrogen-containing drugs under research.

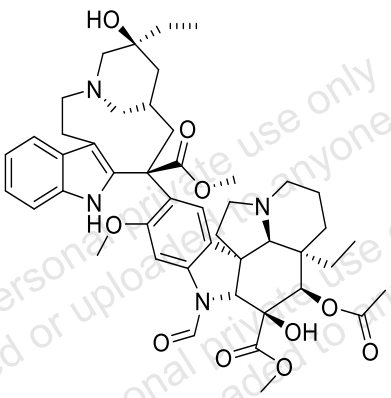
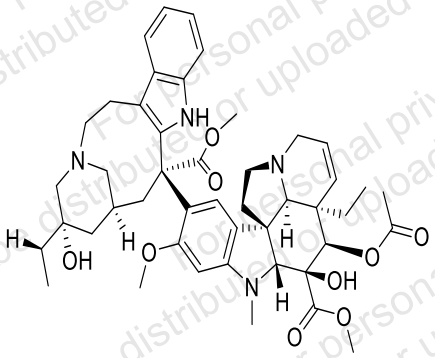
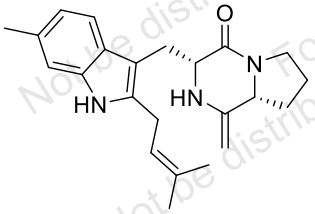
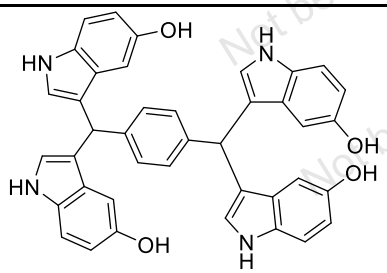
Nitrogen-containing Drugs	Anticancer Activity	References
 22. Vincristine (IC_{50}= 52.5 μM against HepG2 cells; 4.4 nM against mouse leukaemia L1210 cells; 5 nM against mouse lymphoma S49 cells and 33 nM against mouse neuroblastoma cells)	Tubulin polymerization inhibition causes the anti-proliferative effect.	[63-65]
 23. Vinblastine(IC_{50} = 4.0 nM against mouse leukaemia L1210 cells; 3.5 nM against mouse lymphoma S49 cells and 15 nM against mouse neuroblastoma cells)		
 24. 4-Trypostatiin B	Tubulin polymerization inhibitors in oncology	[66]
 25. SK228 (IC50 = 0.27 μM against CL1-1 and 3.40 μM against A549)	Induction of ROS (reactive oxygen species) gives anti-proliferative activity	[67]

Table 2. Contd…

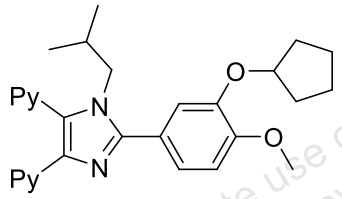
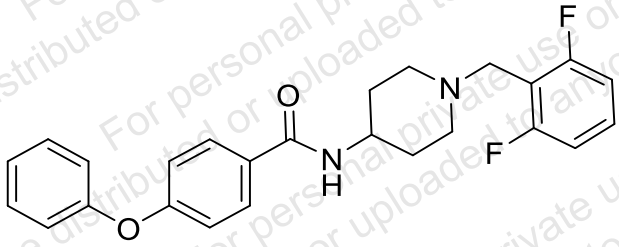
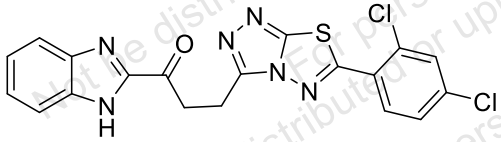
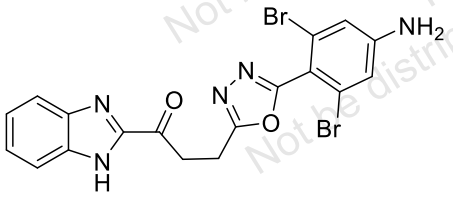
Nitrogen-containing Drugs	Anticancer Activity	References
 26. 2,2'-(2-(3-(cyclopentyloxy)-4-methoxyphenyl) -1-isobutyl-1*H*-imidazole-4,5-diyl)dipyridine (NSC 771432) (G2/M phase cycle arrest at 5 μM concentration)	Anti-proliferative activity against epithelial cancer cells through cell migration, cell proliferation, and anchorage-independent growth, inducing G2/M phase cycle arrest followed by activation of programmed cell death.	[68]
 27. *N*-(1-(2,6-difluorobenzyl)piperidin-4-yl)-4-phenoxybenzamide (IC_{50} = 0.25 μM against HepG2 cells)	Anti-proliferative activity within HepG2 cells by regulating AMPK (phospho-adenosine monophosphate-activated protein kinase) phosphorylation and inducing cell cycle arrest depending on p53/p21. It was also found to inhibit the expression of cyclin B1 and p-Rb and enhance Rb expression.	[69]
 28. 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-(6-(2,4-dichlorophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)propan-1-one (GI_{50} range = 0.20 to 2.58 μM)	Showed significant broad-spectrum cancer cell growth inhibition and superior selectivity for leukaemia cells	[70]
 29. 3-(5-(4-amino-2,6-dibromophenyl)-1,3,4-oxadiazol-2-yl)-1-(1*H*-benzo[*d*]imidazol-2-yl)propan-1-one (GI_{50}range=0.49 to 48.0 μM)	Showed broad spectrum anticancer effect and superior selectivity for cell lines of non-small cell lung cancer (NSCLC)	[71]

Table 3. FDA-approved oxygen-based heterocyclic anticancer drugs.

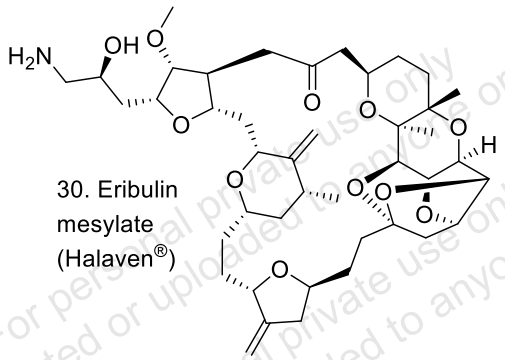
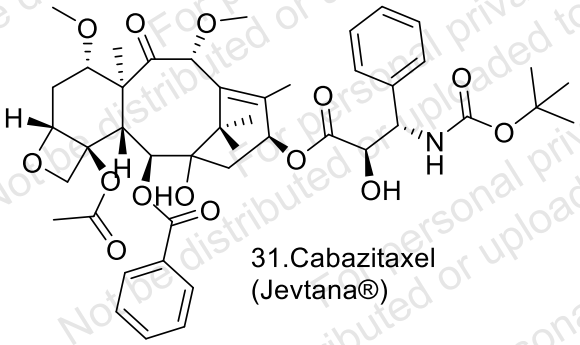
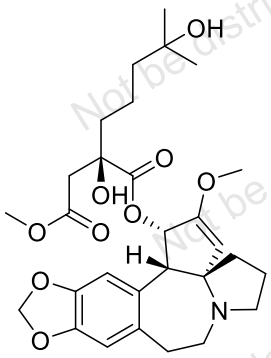
FDA Approved Drugs	Approved For	References
 30. Eribulin mesylate (Halaven®)	Metastatic prostate cancer	[72]
 31.Cabazitaxel (Jevtana®)	Metastatic prostate carcinoma	[73]
FDA Approved Nitrogen and Oxygen-Based Heterocyclic Drugs		
 32. Omacetaxine mepesuccinate (Synribo®)	Chronic myelogenous leukaemia	[74]

Table 3. Contd…

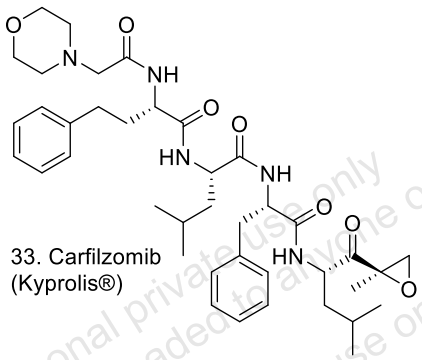
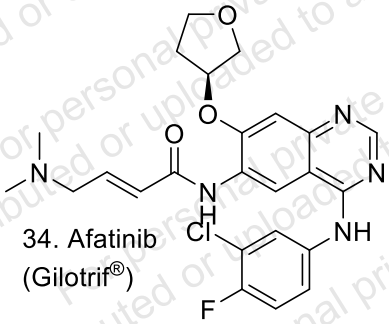
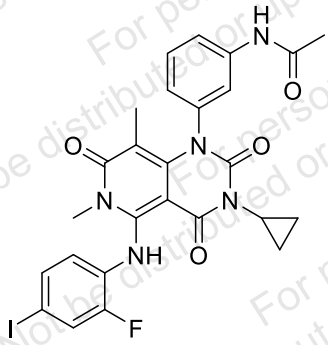
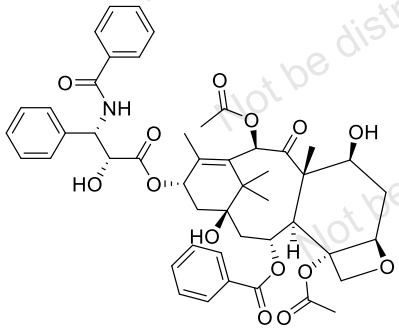
FDA Approved Drugs	Approved For	References
 33. Carfilzomib (Kyprolis®)	Multiple myeloma	[75]
 34. Afatinib (Gilotrif®)	Metastatic NSCLC (EGFR mutations)	[41]
 35. Trametinib (Mekinist®)	Tumours expressing gene mutations of BRAF V600E or V600K gene	[76]
 36. Paclitaxel (Taxol®)	One of the anticancer agents of the taxane class acts by stabilizing microtubules and selectively arresting the G2/M phase of the cell cycle. Finally provokes cytotoxicity depending on concentration and time. It was approved for the treatment of advanced ovarian cancer by US FDA.	[77]

Table 4. Oxygen-containing drugs under research.

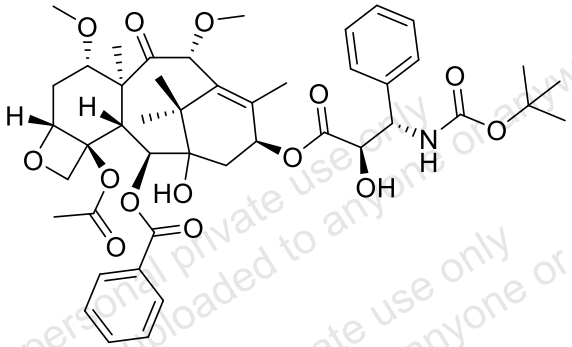
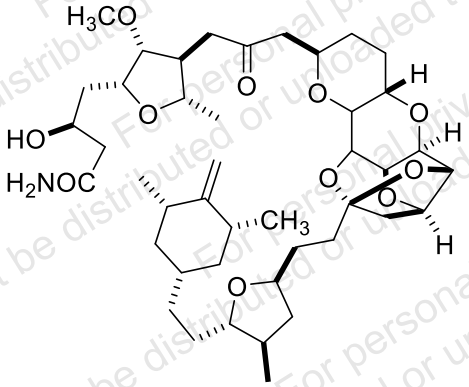
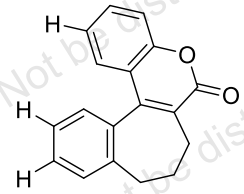
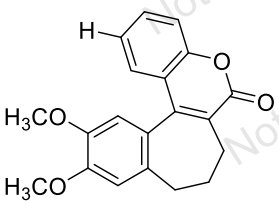
Oxygen-containing Drugs	Anticancer Activity	References
 37.Cabazitaxel (oxetane ring) (IC_{50} range: 0.013–0.414 μmol/L against various cancer cells)	It prevented cell division and proved effective in metastatic prostate carcinoma patients resistant to castrate.	[24]
 38. Eribulin(tetrahydrofuran and tetrahydropyran rings)	It was found in phase I-III trials to treat solid tumours as a non-taxane inhibitor of microtubule dynamics.	[78]
 39. 8,9-dihydrobenzo[3,4]cyclohepta[1,2-c]chromen-6(7H)-one (IC_{50} range: 3.35 to 16.79 μM against A549, HeLa, MCF-7 and MDA-MB-231cell lines)  40. 11,12-dimethoxy-8,9-dihydrobenzo[3,4] cyclohepta[1,2-c]chromen-6(7H)-one (IC_{50} = 6.72 μM against HeLa and 4.87 μM against MDA-MB-231cell lines)	Benzosuberone derivatives having coumarin moieties exhibited significant cytotoxicity against cervical, breast, and alveolar cell lines.	[79]

Table 4. Contd…

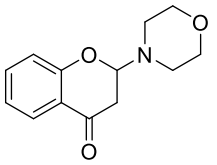
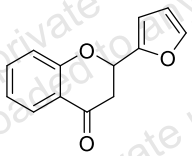
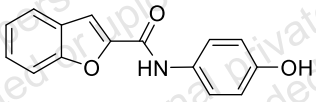
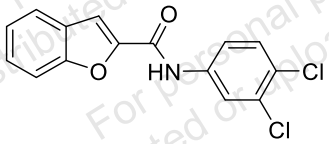
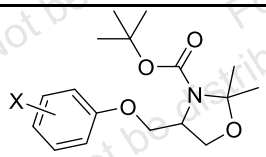
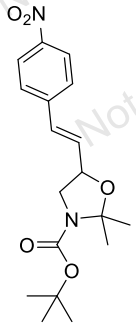
Oxygen-containing Drugs	Anticancer Activity	References
 41. 2-morpholinochroman-4-one [IC_{50} = 10.2±0.4 µg/ml (MCF7), 6.7±2.3 µg/ml (HT29),8.1±0.7 µg/ml (A498)]  42. 2-(furan-2-yl)chroman-4-one [IC_{50} = 7.3±0.3 µg/ml (MCF7), 4.9±0.5 µg/ml (HT29), 5.7±0.9 µg/ml (A498)]	The flavanone compounds showed effective anti-proliferative activity against HT29, A498and MCF7 cancer cell lines, and the furan ring was found crucial for the potent and optimum anticancer activity against all cell lines.	[80]
 43. N-(4-hydroxyphenyl)benzofuran-2-carboxamide (IC_{50} range = 2.20 to 5.86 µM against a variety of cancer cells)  44. N-(3,4-chlorophenyl)benzofuran-2-carboxamide (IC_{50} = 23.0 µM for NF-κB inhibition)	The benzofuran derivatives inhibited LPS-induced NF-κB transcriptional activity, thereby providing anticancer activity against the renal, colon, breast, gastric, lung, and prostate cancer cell lines.	[81]
 45. Substituted *tert*-butyl 2,2-dimethyl-4-(phenoxymethyl) oxazolidine-3-carboxylate X= NO2, COOCH3, OMe, COOH, H [IC_{50} = 28±2µM (HL60), 37±2 µM (MDA-MB-231)]  46. tert-butyl (E)-2,2-dimethyl-5-(4-nitrostyryl) oxazolidine-3-carboxylate [IC_{50} = 18±3 µM (HL60), 32±12 µM (MDA-MB-231), 27±1 µM (LNCaP), 42±9 µM (JURKAT)]	Chiral oxazolidine analogues provided an efficient anti-proliferative effect against JURKAT, HL60, LNCaP, and MDA-MB-231 cancer cell lines.	[82]

Table 5. FDA-approved nitrogen and sulfur-based heterocycle drugs.

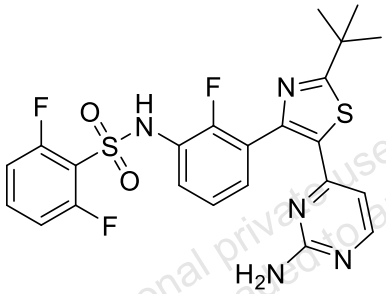
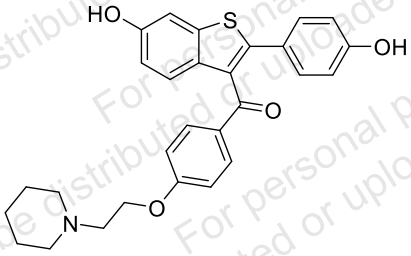
FDA Approved Drugs	Approved For	References
 47. Dabrafenib (Tafinlar®)	Melanoma expressing mutation for BRAF V600E gene	[86]
 48. Raloxifene (Evista®)	The US FDA approved raloxifene in 2007 to treat primary breast cancer in postmenopausal women.	[87]

Table 6. Sulphur-containing drugs under research.

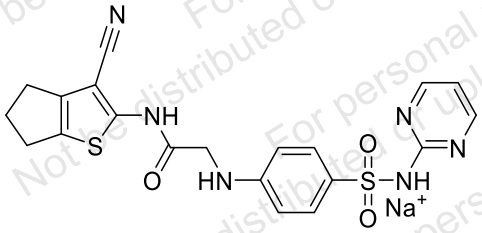
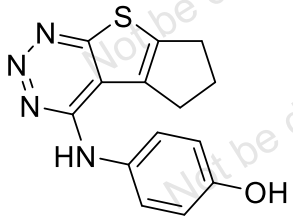
Sulphur Containing Drugs	Anticancer Property	References
 49. *N*-(3-cyano-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl)-2-((4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl)amino)acetamide, sodium salt (IC_{50} = 30.8 nM against human breast adenocarcinoma MCF7 cell line)  50. 4-((6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*][1,2,3]triazin-4-yl)amino)phenol (IC_{50} = 38.7 nM against MCF7 cell line)	Showed anti-proliferative activity against MCF7 by inhibiting ATP recognition binding sites of TKRs (tyrosine kinase receptors).	[88]

Table 6. Contd…

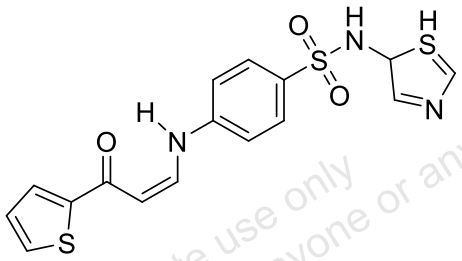
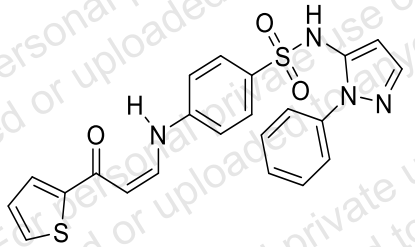
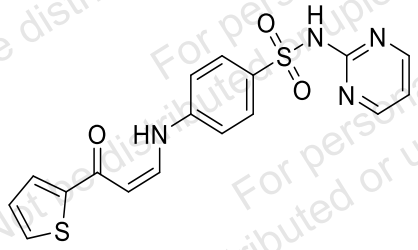
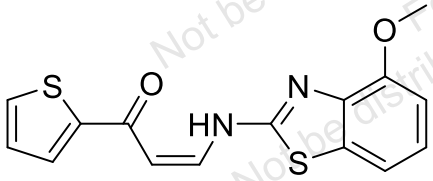
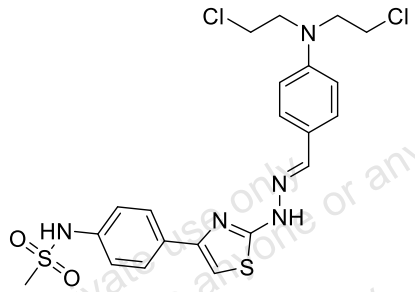
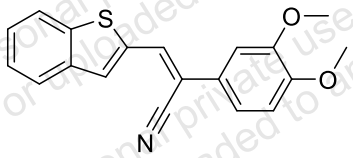
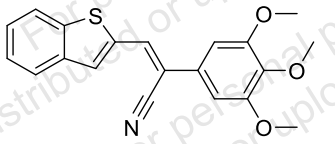
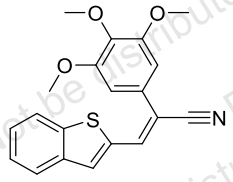
Sulphur Containing Drugs	Anticancer Property	References
 51. (Z)-4-((3-oxo-3-(thiophen-2-yl)prop-1-en-1-yl)amino) -N-(5H-1l4-thiazol-5-yl)benzenesulfonamide (IC_{50} = 10.25 μM against MCF7 cell line).		
 52. (*Z*)-4-((3-oxo-3-(thiophen-2-yl)prop-1-en-1-yl)amino)-*N*-(1-phenyl-1*H*-pyrazol-5-yl)benzenesulfonamide (IC_{50} = 9.70 μM against MCF7 cell line).	Showed good anti-proliferative activity against the MCF7 cell line.	[89]
 53. (*Z*)-4-((3-oxo-3-(thiophen-2-yl)prop-1-en-1-yl)amino)-*N*-(pyrimidin-2-yl)benzenesulfonamide (IC_{50} = 9.55 μM against MCF7 cell line).		
 54. (*Z*)-3-((4-methoxybenzo[*d*]thiazol-2-yl)amino)-1 -(thiophen-2-yl)prop-2-en-1-one (IC_{50} = 9.39 μM against MCF7 cell line)		

Table 6. Contd…

Sulphur Containing Drugs	Anticancer Property	References
 55. (*E*)-*N*-(4-(2-(2-(4-(bis(2-chloroethyl)amino) benzylidene)hydrazineyl)thiazol-4-yl)phenyl)methanesulfonamide (IC_{50} = 2.32 µg/ml and 2.81 µg/ml against MCF7 and HCT116 cell line)	Exhibited anti-proliferative effect against HCT116 and MCF7 cell lines.	[90]
 56. (*Z*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4-dimethoxyphenyl) acrylonitrile (GI_{50} ranges from 10 to 100 nM for a variety of carcinoma cell lines)  57. (*Z*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4,5-trimethoxyphenyl) acrylonitrile (GI_{50} ranges from 10 to 100 nM for a variety of carcinoma cell lines)  58. (*E*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4,5-trimethoxyphenyl) acrylonitrile (GI_{50} ranges from 10 to 100 nM for a variety of carcinoma cell lines)	Showed good anti-proliferative activity against various cancers, including leukaemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, and renal cancer.	[91]

3.2. Oxygen-Based Heterocyclic Compounds

Since 2010, around 8% of all FDA-approved anticancer heterocyclic drugs are oxygen-based heterocyclic agents, with eribulin and cabazitaxel being approved recently. Paclitaxel (Taxol®) with the oxetane ring holds a crucial position in carcinoma therapy. Coumarine-containing benzosuberone analogs have anticancer efficacy against the MCF7, A549, MDA-MB-231, and Hela cell lines Tables **3** and **4** [66, 72-82].

3.3. Sulphur-based Heterocyclic Compounds

Sulfur is one of the most biologically essential heteroatoms. The amino acids cysteine and methionine need sulphur to form the overall tertiary structure of the crucial bioelement proteins [83]. Sulfur is often found to form metal complexes, and covalently linked sulphur can be the determinant in various biological systems [84]. It is a vital element of many vitamin cofactors, nucleic acids, and sugars and crucial for the sulfuration of tRNA & thereby regulating

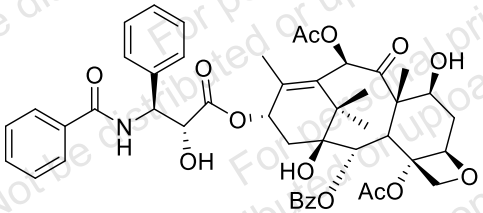
translation [83]. Heterocyclic incorporation of sulfur atoms leads to the changes in configurations of electrons, lone pair of electrons and finally, alteration of electro-negativity between carbon and hetero-atoms. This causes noteworthy changes in the molecular frame and thereby affecting physicochemical properties and reactivity Tables **5** and **6** [85-91].

4. HETEROCYCLIC COMPOUNDS ACTING ON TNBC

4.1. FDA-Approved Drug for TNBC

4.1.1. Atezolizumab and Abraxane Combination

Based on phase 3 IM passion 130 trial, for the treatment of TNBC, the target-specific FDA-approved drug consists of atezolizumab along with nab-paclitaxel in combination, which has been recommended for locally advanced or metastatic PD-L1-positive TNBC as frontline therapy. This combination is considered the first approved cancer immunotherapy treatment against breast cancer. It was observed that the addition of the inhibitor for programmed cell death-ligand 1 (PD-L1), Tecentriq to Abraxane diminished the risk of death and the progression of the disease by 40%, compared to sole Abraxane [92, 93].



59. Abraxane (nab-paclitaxel)

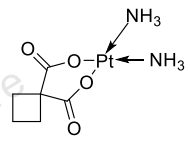
4.2. Mechanism of Action

TNBC was found to show high expression for PD-L1, which was inhibited by Atezolizumab. Atezolizumab also acts as an inhibitor of Programmed cell death protein 1(PD-1) and CD80 receptors (B7-1Rs) [94]. High expression of PD-L1 was found to reduce the activation of cytotoxic T-cells, in some tumours, thereby preventing them from recognizing and attacking the cancer cells. Atezolizumab inhibits PD-L1, and cytotoxic T-cells remain activated to provoke an anti-tumour response. "Immune checkpoint inhibition" is the strategy to block the signals inhibiting T-cell activation [95].

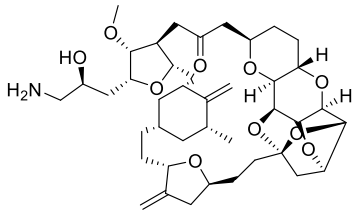
5. DRUGS UNDER CLINICAL TRIALS FOR TNBC

5.1. Combination of Carboplatin and Eribulin

An investigation was performed to evaluate the safety and efficacy of eribulin and carboplatin combination through neo-adjuvant therapy against early-stage TNBC. The biomarkers dependent on DNA expression profiles and proteins were analysed to predict response. The combination was found to be tolerant with grade 1 and 2 toxicities, and a PCR was obtained as 43% through prediction with an expression of CDK2 and homologous recombination (HR) deficiency status [96].



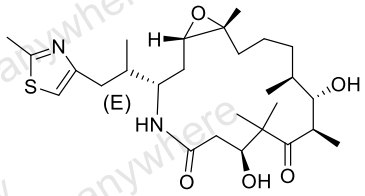
60. Carboplatin



61. Eribulin

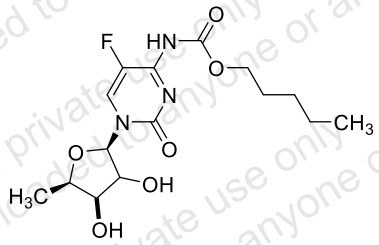
5.2. Ixabepilone

Ixabepilone (Ixempra, BMS-247550) was derived from epothilone B semi-synthetically. It is considered a microtubule-targeting drug through the isotypical alteration of microtubules. The βIII-tubulin expression suppressed the anticancer activity of ixabepilone. This concept suggested that βIII-tubulin could be responsible for developing ixabepilone resistance [97].



62. Ixabepilone

Ixabepilone was investigated for safety and efficacy in treating women with TNBC. The activity and toxicity data were interpreted in phase II studies through retrospective analysis against triple-negative subtypes. The drug candidate also was reviewed in phase III trials against TNBC *via* a prospective pooled analysis. Ixabepilone has shown promise as an anti-tumour agent for TNBC treatment in various settings. Ixabepilone and capecitabine in combination led to enhance median progression-free survival (PFS) about two-fold than capecitabine alone for the women with triple negativity than non-triple-negative tumours [25].



63.Capecitabine

6. RECENT ADVANCEMENTS IN HETEROCYCLIC COMPOUNDS AS ANTI-TNBC AGENTS

Recently, through an amide coupling reaction and hybridization strategy, tetrahydro-*β*-carboline-naphthalimide derivatives were synthesized and evaluated on estrogen-dependent and triple-negative breast cancer cells. The MTT assay on MCF7 and MDA-MB-231 cell lines revealed promising compounds with IC_{50} values less than 43 μM. Among them, compound **66** proved to be most efficient in the growth inhibition of breast cancer cells while providing a good safety profile for normal cells. The compound was also

suggested as a potential selective estrogen receptor modulator. The study showed the effectiveness of the hybridization strategy in cancer prevention by utilizing two distinct heterocyclic anticancer moieties [98].

In 2022, another series of compounds bearing fused benzimidazole-imidazole was reported to treat TNBC. Compound **67**, the most potent candidate from this series, was found to act through inhibition of autophagic flux along with nuclear p62 accumulation, thereby causing DNA damage and impairment of TNBC cell repair. Sequential p62 accumulation inhibited RNF168-mediated ubiquitination of chromatin. DNA damage response (DDR) regulatory HR-related protein degradation was also inhibited by this accumulation, resulting in the anti-TNBC effect. In the human TNBC cell lines, **67** exhibited excellent potential with the IC_{50} values of 8.3 μM (MDA-MB-231) and 6.0 μM (MDA-MB-468) [99].

In 2021, Madia *et al.* suggested the aminopyrimidine class of compounds as promising anti-proliferative agents against various cancer histotypes, including TNBC, glioblastoma, colon cancer, and oral cancer squamous cell carcinomas. The innovative anticancer agents **68** and **69** were able to reduce cell viability in all the carcinoma cell lines tested. New derivatives were obtained by substituting at the 6^{th} position of the pyrimidine core and on the 2-aniline ring of the previously established hit molecule, **68**. Different strategies like the replacement of Cl by electron-withdrawing groups, the introduction of the p-flurobenzyl ring, and substitution with varying alkyl amines were considered for optimization of **68**. Compound **69,** *N*-benzyl counterpart of **68,** exerted EC_{50}s in the range of 4 to 8 μM against various tumour cells and was found to be 4-13 fold more effective than **68** [100].

Considering the success and limitations of platinum-based compounds in the field of anticancer therapy, a study on ruthenium-based compounds was conducted. Compound **70** was found targeting mitochondria; thereby, the mitochondrial respiratory chain got impaired and production of mitochondrial superoxide anion was promoted, finally, mitochondrial membrane got depolarized. In addition, compound **70** showed dose-dependent cytotoxic activity through the misbalancing of cellular redox status. It proved itself efficient in the treatment of TNBC by mitochondrial malfunctioning and increasing oxidative stress [101].

Elena *et al*. conducted a one-pot three-component synthesis for potential anti-TNBC agents as spirooxindoles derivatives. The compounds **71**, **72,** and **73** having IC_{50} values of 6.70, 6.40 and 6.70 μM, respectively, against MDA-MB-231 cells, were the most potent derivatives. The cell apoptosis by **71** and **72** was caused by Bax up-regulation, Bcl-2 down-regulation, and promoting caspase-3 levels. Furthermore, compound **72** could elevate the percentage of annexin V-FITC-positive apoptotic cells from 1.34% to 44%. Compounds **72** and **73** also proved their ability as EGFR inhibitors with IC_{50} values of 120 and 150 nM, respectively. Of the three promising compounds, compound **72** was reported to have the potential to lead to anti-TNBC drug development [102].

Thienotriazolodiazepine compound **74** was estimated for TNBC treatment and was found to exhibit anticancer effects with less than 500 nM GI_{50} value. The compound inhibited the growth of proliferative cells by building up the assembly of G1 phase cells and reducing S phase cells, along with increasing CDKN1A (p 21) mRNA levels. Investigated mechanism of action includes down-regulation of c - Myc with n - Myc expressions in the cells. While in combination with everolimus **74** showed an additive anticancer effect on MDA - MB - 231 and HCC1937 cancer cells, alongside an antagonistic effect to the cell line of MDA- MB - MB - 468 in hypoxia and normoxia conditions was shown. The promising compound produced a synergistic effect against MDA - MB - 468 cell lines while combined with docetaxel in hypoxia and normoxia conditions [103].

On the cancer cells, the Phenylmethimazoles act through the principles of reducing the expression of interleukin-6(IL-6). In the treatment of TNBC, IL-6 inhibition is considered to be a crucial option. The Phenylmethimazole derivative **75** was optimized to obtain **76**. The promising derivatives were confirmed for inhibiting IL-6 secretion of MDA-MB-231 cells through ELISA (enzyme-linked immunosorbent assays). QRT-PCR (quantitative real-time polymerase chain reaction) demonstrated the inhibition of IL-6 mRNA within a panel of TNBC cells by **76**. The IC_{50} values for basal IL-6 secretion inhibition were 230 μM and 35 μM for compounds 75 and 76, respectively, while 76 could inhibit IL-6 mRNA with an IC_{50} of 61 μM. The most efficient compound **76** was reported to reduce NF-kB (p65/p50) DNA binding to provide an inhibitory effect [104].

Another novel drug series as multikinase inhibitors were evaluated for the treatment of TNBCs, and the lead was developed as **77** and found to potently inhibit KDR and Src with significant IC_{50} values of 0.032 μM and 0.003 μM, respectively. Compound **77** contained the ability to inhibit kinases, including MAPK signal transduction pathway kinases, DDR, RAF, and the P38 family of kinases. It was found to show precise selectivity during kinase profiling assay against 335 kinases and could completely suppress tumour growth at 40 mg/kg/q.d dose against MDA-MB-435 (IC_{50} = 0.030±0.006μM) and MDA-MB-231(IC_{50} = 0.008±0.002μM) xenograft models. The promising compound was found with a good pharmacokinetic profile, low acute toxicity, and less obvious hERG toxicity. For purpose of the anti-TNBC activity, **77** was proved more efficient than dasatinib, an Src inhibitor found in a clinical trial for TNBC [105].

Cannabinoids comprise a wide area of interest in cancer therapy through lack of studies due to their psychotropic effects by activating the expression of CB1 receptors in the brain. Quinine and cannabinoid combined pharmacophore containing chromenopyrazoledione compound **78** was reported to be selective to non-psychotropic CB2 receptors and induce apoptosis in human TNBC cells. The combination provides an anti-TNBC effect *in vivo* by activation of CB2 and production of ROS. The most potent derivative **78** showed tremendous efficacy against the TNBC cell lines - MDA-MB-231 (IC_{50} =2.8 ± 0.5μM), SUM149 (IC_{50} =4.6μM), SUM159(IC_{50} =4.1μM) and MDA-MB-468(IC_{50} =17.3μM). The capable derivatives investigated do not possess cytotoxicity to non-cancerous human mammary epithe-

lial cells and are recommended to be a novel therapeutic tool in the management of TNBC [106].

The combination of S-1(5-FU) and eribulin was evaluated against cell lines of TNBC (MDA-MB-468, MX-1, and MDA - MB-231). S-1, a fluoropyrimidine derivative, contains tegafur (1-(2-tetrahydrofuryl)-5-fluorouracil), gimeracil (5-chloro-2, 4-dihydroxypyrimidine) and oteracil (potassium oxonate). S-1 is used for gastric cancer and other cancers treatment in many countries. The combination provided a synergistic effect for all cell lines and proved more effective than individuals. The combination was found with a good rationale for metastatic breast cancer patients in clinical studies [107].

An investigation was performed to explore the anti-TNBC efficacy of noscapine **(79)** with or without a doxorubicin combination, and through the isobolographic method, index values were determined. The experiment results showed compound **79** was helpful in preventing the growth of MDA-MB-468 (IC_{50} =36.16±3.76μM) and MDA-MB-231(IC_{50} =42.7±4.3 μM) cancer cell lines. Noscapine and Doxorubicin proved strong synergistic interaction to provide marked raise in cell apoptosis when used against TNBC tumours. The combination was found to execute their apoptotic activity in two ways: anti-angiogenic pathways and NF-KB inactivation. For the TNBC with more aggressiveness, noscapine and Doxorubicin combination orally proved beneficial [108]. The structures mentioned above of recently developed anti-TNBC agents are depicted in Fig. (**2**).

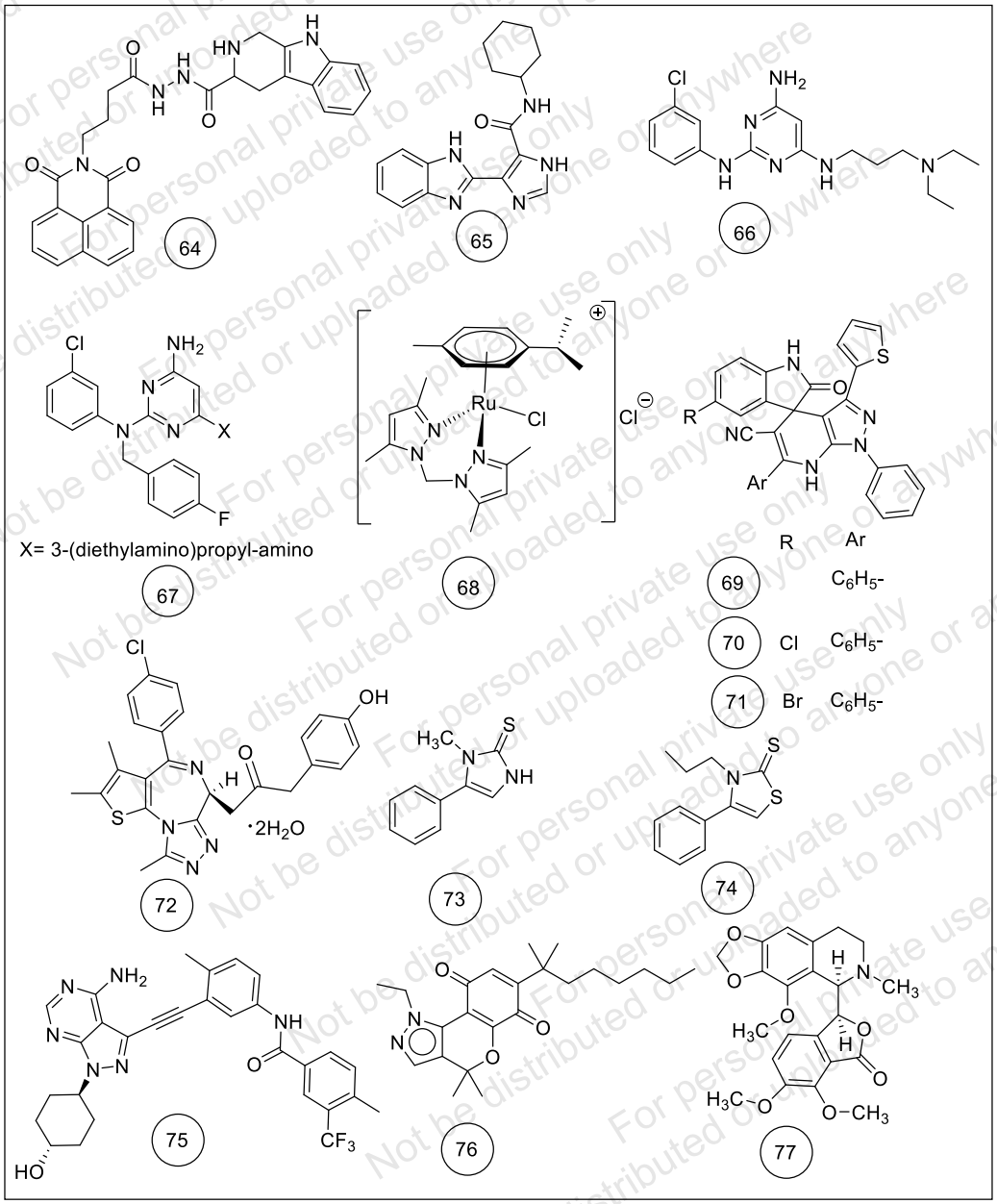


Fig. (2). Structures of recent heterocyclic compounds as anti-TNBC agents.

CONCLUSION

TNBC, a challenging and complex disease entity, is confusing and frustrating for researchers, physicians, and patients. In addition to exploring TNBC biology, the advancements in hetero-molecular approaches in the treatment have proved to be greatly efficient in TNBC therapy. A groundbreaking number of studies have been conducted on that event leading to the discovery of promising anti-TNBC agents, PARP inhibitors, and many TKs (Tyrosine kinases) that have moved to FDA-approved or as clinical trial candidates. Many heteroatom-heteroatom (N, O, S, P and Se) linkages in natural products have shown significant biological activity. The hydrogen bond acceptor ability generally helps increase the molecule's H-bond strength while performing drug design studies. The change in the energy of a topological hydrogen atom upon complexation [ΔE(H)] and the minimum electrostatic potential on the H-bond accepting site (V_{min}) are taken into consideration in many molecular scaffolds for finding out the most important, specific, and local interactions occurring in biological recognition processes. Through this thorough study concerning many anti-TNBC heterocyclic molecules, we conclude that incorporating hetero-core into the pharmacophores may lead to high protein-ligand interaction through a high amount of H-bonding and electrostatic interactions and, in some designs, improved target selectivity as well. Clinical trials are being conducted in a competitive race to develop anti-TNBC drugs. Thereby an extensive, thorough study of this field, including biology and heterocyclic drug developments, can bring a bright future in anti-TNBC research.

LIST OF ABBREVIATIONS

BC	=	Breast Cancer
BL1	=	Basal-Like 1
BL2	=	Basal-Like 2
BRCA1/2	=	Breast Cancer Type 1 and Type 2 Genes
DDR	=	DNA Damage Repair
ER	=	Estrogen Receptor
HER2	=	Human Epidermal Growth Factor Receptor 2
IM	=	Immunomodulatory
LAR	=	Luminal Androgen Receptor
MSL	=	Mesenchymal Stem-Like
PR	=	Progesterone Receptor
TNBC	=	Triple-Negative Breast Cancer

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Dr. Sudip Mandal is the Associate Editorial Board Member for the journal Current Cancer Therapy Reviews.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Roy A, Mandal SK, Ramadan MA. Prevention and treatment of cancer with alternative anticancer approach: Current scenario. Egypt J Chem 2020; 63(9): 3229-45.

[2] Ferlay J, Héry C, Autier P, *Sankaranarayanan R. Global burden of breast cancer.Breast cancer epidemiology*. New York, NY: Springer 2010; pp. 1-19. http://dx.doi.org/10.1007/978-1-4419-0685-4_1

[3] Allweis TM, Hermann N, Berenstein-Molho R, Guindy M. Personalized screening for breast cancer: Rationale, present practices, and future directions. Ann Surg Oncol 2021; 28(8): 4306-17. http://dx.doi.org/10.1245/s10434-020-09426-1 PMID: 33398646

[4] Sharma GN, Dave R, Sanadya J, Sharma P, Sharma KK. Various types and management of breast cancer: An overview. J Adv Pharm Technol Res 2010; 1(2): 109-26. PMID: 22247839

[5] Karki S, Shrestha A, Shrestha B. Adenolipoma of the breast: A case report. JNMA J Nepal Med Assoc 2021; 59(243): 1189-91. http://dx.doi.org/10.31729/jnma.6925 PMID: 35199756

[6] Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res 2017; 50(1): 33. http://dx.doi.org/10.1186/s40659-017-0140-9 PMID: 28969709

[7] Johnson RH, Anders CK, Litton JK, Ruddy KJ, Bleyer A. Breast cancer in adolescents and young adults. Pediatr Blood Cancer 2018; 65(12): e27397. http://dx.doi.org/10.1002/pbc.27397 PMID: 30156052

[8] Sudhakar A. History of cancer, ancient and modern treatment methods. J Cancer Sci Ther 2009; 1(2): i-iv. http://dx.doi.org/10.4172/1948-5956.100000e2 PMID: 20740081

[9] Krishnan CG, Theerthagiri P, Nishan A. Cancerous or non-cancerous cell detection on a field-programmable gate array medical image segmentation using xilinx system society 50 and the future of emerging computational technologies. CRC Press 2022; pp. 173-97.

[10] Das AK, Biswas SK, Bhattacharya A, Alam E. Introduction to breast cancer and awareness. 7th international conference on advanced computing and communication systems (ICACCS).

[11] Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer-Epidemiology, risk factors, classification, prognostic markers, and current treatment strategies-An updated review. Cancers (Basel) 2021; 13(17): 4287. http://dx.doi.org/10.3390/cancers13174287 PMID: 34503097

[12] Cao W, Li J, Hao Q, Vadgama JV, Wu Y. AMP-activated protein kinase: A potential therapeutic target for triple-negative breast cancer. Breast Cancer Res 2019; 21(1): 29. http://dx.doi.org/10.1186/s13058-019-1107-2 PMID: 30791936

[13] Dent R, Trudeau M, Pritchard KI, *et al.* Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res 2007; 13(15): 4429-34. http://dx.doi.org/10.1158/1078-0432.CCR-06-3045 PMID: 17671126

[14] Catalano A, Iacopetta D, Ceramella J, *et al.* New Achievements for the Treatment of Triple-Negative Breast Cancer. Appl Sci (Basel) 2022; 12(11): 5554. http://dx.doi.org/10.3390/app12115554

[15] Ismail-Khan R, Bui MM. A review of triple-negative breast cancer. Cancer Contr 2010; 17(3): 173-6. http://dx.doi.org/10.1177/107327481001700305 PMID: 20664514

[16] Anders CK, Abramson V, Tan T, Dent R. The evolution of triple-negative breast cancer: From biology to novel therapeutics. Am Soc Clin Oncol Educ Book 2016; 35(36): 34-42. http://dx.doi.org/10.1200/EDBK_159135 PMID: 27249684

[17] Yao Y, Chu Y, Xu B, Hu Q, Song Q. Risk factors for distant metastasis of patients with primary triple-negative breast cancer. Biosci Rep 2019; 39(6): BSR20190288. http://dx.doi.org/10.1042/BSR20190288 PMID: 31113872

[18] Oakman C, Viale G, Di Leo A. Management of triple negative breast cancer. Breast 2010; 19(5): 312-21. http://dx.doi.org/10.1016/j.breast.2010.03.026 PMID: 20382530

[19] Malhotra GK, Zhao X, Band H, Band V. Histological, molecular and functional subtypes of breast cancers. Cancer Biol Ther 2010; 10(10): 955-60. http://dx.doi.org/10.4161/cbt.10.10.13879 PMID: 21057215

[20] Herschkowitz JI, Simin K, Weigman VJ, *et al.* Identification of conserved gene expression features between murine mammary carcinoma models and human breast tumors. Genome Biol 2007; 8(5): R76. http://dx.doi.org/10.1186/gb-2007-8-5-r76 PMID: 17493263

[21] Perou C M, Sørlie T, Eisen M B, *et al.* Molecular portraits of human breast tumours. Nature 2000; 406(6797): 747-52.

[22] Prat A, Parker JS, Karginova O, *et al.* Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. Breast Cancer Res 2010; 12(5): R68. http://dx.doi.org/10.1186/bcr2635 PMID: 20813035

[23] Sørlie T, Tibshirani R, Parker J, *et al.* Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 2003; 100(14): 8418-23. http://dx.doi.org/10.1073/pnas.0932692100 PMID: 12829800

[24] Vrignaud P, Sémiond D, Lejeune P, *et al.* Preclinical antitumor activity of cabazitaxel, a semisynthetic taxane active in taxane-resistant tumors. Clin Cancer Res 2013; 19(11): 2973-83. http://dx.doi.org/10.1158/1078-0432.CCR-12-3146 PMID: 23589177

[25] Perez EA, Patel T, Moreno-Aspitia A. Efficacy of ixabepilone in ER/PR/HER2-negative (triple-negative) breast cancer. Breast Cancer Res Treat 2010; 121(2): 261-71. http://dx.doi.org/10.1007/s10549-010-0824-0 PMID: 20229176

[26] Yin L, Duan JJ, Bian XW, Yu S. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res 2020; 22(1): 61. http://dx.doi.org/10.1186/s13058-020-01296-5 PMID: 32517735

[27] Lehmann BD, Jovanović B, Chen X, *et al.* Refinement of triple-negative breast cancer molecular subtypes: Implications for neoadjuvant chemotherapy selection. PLoS One 2016; 11(6): e0157368. http://dx.doi.org/10.1371/journal.pone.0157368 PMID: 27310713

[28] Park JH, Ahn JH, Kim SB. How shall we treat early triple-negative breast cancer (TNBC): From the current standard to upcoming immuno-molecular strategies. ESMO Open 2018; 3(Suppl. 1): e000357. http://dx.doi.org/10.1136/esmoopen-2018-000357 PMID: 29765774

[29] Petrucelli N, Daly MB, Pal T. BRCA1-and BRCA2-associated hereditary breast and ovarian cancer. Gene Reviews 2016.

[30] Santana-Davila R, Perez EA. Treatment options for patients with triple-negative breast cancer. J Hematol Oncol 2010; 3(1): 42. http://dx.doi.org/10.1186/1756-8722-3-42 PMID: 20979652

[31] Rice JC, Ozcelik H, Maxeiner P, Andrulis I, Futscher BW. Methylation of the BRCA1 promoter is associated with decreased BRCA1 mRNA levels in clinical breast cancer specimens. Carcinogenesis 2000; 21(9): 1761-5. http://dx.doi.org/10.1093/carcin/21.9.1761 PMID: 10964110

[32] Young SR, Pilarski RT, Donenberg T, *et al.* The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer 2009; 9(1): 86. http://dx.doi.org/10.1186/1471-2407-9-86 PMID: 19298662

[33] Aysola K, Desai A, Welch C, *et al.* Triple-negative breast cancer-An overview. Hereditary genetics: Current research. Hereditary Genet 2013;2013(Suppl 2):001.

[34] Keam B, Im SA, Kim HJ, *et al.* Prognostic impact of clinicopathologic parameters in stage II/III breast cancer treated with neoadjuvant docetaxel and doxorubicin chemotherapy: Paradoxical features of the triple negative breast cancer. BMC Cancer 2007; 7(1): 203. http://dx.doi.org/10.1186/1471-2407-7-203 PMID: 17976237

[35] Banerjee S, Bose S, Mandal S C, *et al.* Pharmacological property of pentacyclic triterpenoids. Egypt J Chem 2019; 62(1): 13-35.

[36] Mandal S K, Das A, Dey S, *et al.* Bioactivities of Allicin and related organosulfur compounds from garlic: Overview of the literature since 2010. Egypt J Chem 2019; 62: 1-11.

[37] Mandal SK, Debnath U, Kumar A, *et al.* Natural sesquiterpene lactones in the prevention and treatment of inflammatory disorders and cancer: A systematic study of this emerging therapeutic approach based on chemical and pharmacological aspect. Lett Drug Des Discov 2020; 17(9): 1102-16. http://dx.doi.org/10.2174/1570180817999200421144007

[38] Sinha D, Sarkar N, Biswas J, Bishayee A. Resveratrol for breast cancer prevention and therapy: Preclinical evidence and molecular mechanisms. Semin Cancer Biol 2016; 40-41: 209-32. http://dx.doi.org/10.1016/j.semcancer.2015.11.001 PMID: 26774195

[39] Martins P, Jesus J, Santos S, *et al.* Heterocyclic anticancer compounds: recent advances and the paradigm shift towards the use of nanomedicine's tool box. Molecules 2015; 20(9): 16852-91.

[40] Most Frequent Rings in FDA Approved Drugs. Chemical Compounds 2015. Available from: http://www.click2drug.org/encyclopedia/chemistry/fda-based-rings.html

[41] Dungo RT, Keating GM. Afatinib: First global approval. Drugs 2013; 73(13): 1503-15. http://dx.doi.org/10.1007/s40265-013-0111-6 PMID: 23982599

[42] Massarelli E, Papadimitrakopoulou V. Ceritinib for the treatment of late-stage (metastatic) non-small cell lung cancer. Clin Cancer Res 2015; 21(4): 670-4. http://dx.doi.org/10.1158/1078-0432.CCR-14-1291 PMID: 25564153

[43] Quandt D, Fiedler E, Boettcher D, Marsch WC, Seliger B. B7-h4 expression in human melanoma: Its association with patients' survival and antitumor immune response. Clin Cancer Res 2011; 17(10): 3100-11. http://dx.doi.org/10.1158/1078-0432.CCR-10-2268 PMID: 21378130

[44] Flaherty KT, Yasothan U, Kirkpatrick P. Vemurafenib. Nat Rev Drug Discov 2011; 10(11): 811-2. http://dx.doi.org/10.1038/nrd3579 PMID: 22037033

[45] Sorensen S, Ellis L, Wu Y, Hutchins V, Linnehan JE, Senbetta M. Budgetary impact on a U.S. health plan adopting abiraterone acetate plus prednisone for the treatment of patients with metastatic castration-resistant prostate cancer. J Manag Care Pharm 2013; 19(9): 799-808. http://dx.doi.org/10.18553/jmcp.2013.19.9.799 PMID: 24156649

[46] Chau NG, Haddad RI. Vandetanib for the treatment of medullary thyroid cancer. Clin Cancer Res 2013; 19(3): 524-9. http://dx.doi.org/10.1158/1078-0432.CCR-12-2353 PMID: 23231950

[47] Frankfurt O, Licht JD. Ponatinib--a step forward in overcoming resistance in chronic myeloid leukemia. Clin Cancer Res 2013; 19(21): 5828-34. http://dx.doi.org/10.1158/1078-0432.CCR-13-0258 PMID: 23935038

[48] Viola D, Cappagli V, Elisei R. Cabozantinib (XL184) for the treatment of locally advanced or metastatic progressive medullary thyroid cancer. Future Oncol 2013; 9(8): 1083-92. http://dx.doi.org/10.2217/fon.13.128 PMID: 23902240

[49] Ettrich T J, Seufferlein T. Regorafenib. Small Mol Oncol 2018; 45-56.

[50] Amsberg GK, Schafhausen P. Bosutinib in the management of chronic myelogenous leukemia. Biologics 2013; 7: 115-22. PMID: 23674887

[51] Ramadan W, Kabbara W, Al Basiouni Al Masri H. Enzalutamide for patients with metastatic castration-resistant prostate cancer. OncoTargets Ther 2015; 8: 871-6. http://dx.doi.org/10.2147/OTT.S80488 PMID: 25945058

[52] Xue TM, Tao L, Zhang M, Xu G-C, Zhang J, Zhang P-J. miR-20b overexpression is predictive of poor prognosis in gastric cancer. OncoTargets Ther 2015; 8: 1871-6.

[53] Axelson M, Liu K, Jiang X, *et al.* U.S. Food and Drug Administration approval: Vismodegib for recurrent, locally advanced, or metastatic basal cell carcinoma. Clin Cancer Res 2013; 19(9): 2289-93. http://dx.doi.org/10.1158/1078-0432.CCR-12-1956 PMID: 23515405

[54] Tyler T. Axitinib: Newly approved for renal cell carcinoma. J Adv Pract Oncol 2012; 3(5): 333-5. PMID: 25031963

[55] Herrera AF, Jacobsen ED. Ibrutinib for the treatment of mantle cell lymphoma. Clin Cancer Res 2014; 20(21): 5365-71. http://dx.doi.org/10.1158/1078-0432.CCR-14-0010 PMID: 25361916

[56] Fouquet G, Bories C, Guidez S, *et al.* Pomalidomide for multiple myeloma. Expert Rev Hematol 2014; 7(6): 719-31. http://dx.doi.org/10.1586/17474086.2014.966074 PMID: 25265911

[57] Deeks ED. Olaparib: First global approval. Drugs 2015; 75(2): 231-40. http://dx.doi.org/10.1007/s40265-015-0345-6 PMID: 25616434

[58] Shah A, Mangaonkar A. Idelalisib. Ann Pharmacother 2015; 49(10): 1162-70. http://dx.doi.org/10.1177/1060028015594813 PMID: 26185276

[59] Khozin S, Blumenthal GM, Zhang L, *et al.* FDA approval: Ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. Clin Cancer Res 2015; 21(11): 2436-9. http://dx.doi.org/10.1158/1078-0432.CCR-14-3157 PMID: 25754348

[60] Laubach JP, Moreau P, San-Miguel JF, Richardson PG. Panobinostat for the treatment of multiple myeloma. Clin Cancer Res 2015; 21(21): 4767-73. http://dx.doi.org/10.1158/1078-0432.CCR-15-0530 PMID: 26362997

[61] Scott LJ. Lenvatinib: First global approval. Drugs 2015; 75(5): 553-60. http://dx.doi.org/10.1007/s40265-015-0383-0 PMID: 25795101

[62] Wedam S, Fashoyin-Aje L, Bloomquist E, *et al.* FDA approval summary: Palbociclib for male patients with metastatic breast cancer. Clin Cancer Res 2020; 26(6): 1208-12. http://dx.doi.org/10.1158/1078-0432.CCR-19-2580 PMID: 31649043

[63] Owellen RJ, Hartke CA, Dickerson RM, Hains FO. Inhibition of tubulin-microtubule polymerization by drugs of the Vinca alkaloid class. Cancer Res 1976; 36(4): 1499-502. PMID: 1260766

[64] Özdemir F, Akalın G, Şen M, *et al.* Towards novel anti-tumor strategies for hepatic cancer: Ɛ-viniferin in combination with vincristine displays pharmacodynamic synergy at lower doses in HepG2 cells. OMICS 2014; 18(5): 324-34. http://dx.doi.org/10.1089/omi.2013.0045 PMID: 24341688

[65] Ferguson PJ, Phillips JR, Selner M, Cass CE. Differential activity of vincristine and vinblastine against cultured cells. Cancer Res 1984; 44(8): 3307-12. PMID: 6744266

[66] Martins P, Jesus J, Santos S, *et al.* Heterocyclic anticancer compounds: Recent advances and the paradigm shift towards the use of nanomedicine's tool box. Molecules 2015; 20(9): 16852-91. http://dx.doi.org/10.3390/molecules200916852 PMID: 26389876

[67] Huang SM, Hsu PC, Chen MY, *et al.* The novel indole compound SK228 induces apoptosis and FAK/Paxillin disruption in tumor cell lines and inhibits growth of tumor graft in the nude mouse. Int J Cancer 2012; 131(3): 722-32. http://dx.doi.org/10.1002/ijc.26401 PMID: 22015944

[68] Sharma GVM, Ramesh A, Singh A, *et al.* Imidazole derivatives show anticancer potential by inducing apoptosis and cellular senescence. MedChemComm 2014; 5(11): 1751-60. http://dx.doi.org/10.1039/C4MD00277F

[69] Hou J, Zhao W, Huang ZN, *et al.* Evaluation of Novel *N* -(piperidine-4-yl)benzamide derivatives as potential cell cycle inhibitors in HepG2 Cells. Chem Biol Drug Des 2015; 86(2): 223-31. http://dx.doi.org/10.1111/cbdd.12484 PMID: 25430863

[70] Husain A, Rashid M, Shaharyar M, Siddiqui AA, Mishra R. Benzimidazole clubbed with triazolo-thiadiazoles and triazolo-thiadiazines: New anticancer agents. Eur J Med Chem 2013; 62: 785-98. http://dx.doi.org/10.1016/j.ejmech.2012.07.011 PMID: 23333063

[71] Husain A, Rashid M, Mishra R, Parveen S, Shin DS, Kumar D. Benzimidazole bearing oxadiazole and triazolo-thiadiazoles nucleus: Design and synthesis as anticancer agents. Bioorg Med Chem Lett 2012; 22(17): 5438-44. http://dx.doi.org/10.1016/j.bmcl.2012.07.038 PMID: 22840417

[72] Jain S, Vahdat LT. Eribulin mesylate. Clin Cancer Res 2011; 17(21): 6615-22. http://dx.doi.org/10.1158/1078-0432.CCR-11-1807 PMID: 21859830

[73] Galsky MD, Dritselis A, Kirkpatrick P, Oh WK. Cabazitaxel. Nat Rev Drug Discov 2010; 9(9): 677-8. http://dx.doi.org/10.1038/nrd3254 PMID: 20811375

[74] Nazha A, Kantarjian H, Cortes J, Quintás-Cardama A. Omacetaxine mepesuccinate (synribo) - newly launched in chronic myeloid leukemia. Expert Opin Pharmacother 2013; 14(14): 1977-86. http://dx.doi.org/10.1517/14656566.2013.821464 PMID: 23875628

[75] Herndon TM, Deisseroth A, Kaminskas E, *et al.* U.S. Food and Drug Administration approval: Carfilzomib for the treatment of multiple myeloma. Clin Cancer Res 2013; 19(17): 4559-63. http://dx.doi.org/10.1158/1078-0432.CCR-13-0755 PMID: 23775332

[76] Wright CJM, McCormack PL. Trametinib: First global approval. Drugs 2013; 73(11): 1245-54. http://dx.doi.org/10.1007/s40265-013-0096-1 PMID: 23846731

[77] Barbuti, A. M., & Chen, Z. S. (2015). Paclitaxel through the ages of anticancer therapy: exploring its role in chemoresistance and radiation therapy. *Cancers*, *7*(4), 2360-2371.

[78] Devriese, L. A., Mergui-Roelvink, M., Wanders, J., Jenner, A., Edwards, G., Reyderman, L., & Schellens, J. H. M. (2013). Eribulin mesylate pharmacokinetics in patients with solid tumors receiving repeated oral ketoconazole. *Investigational new drugs*, *31*(2), 381-389.

[79] Yadagiri, B., Holagunda, U. D., Bantu, R., Nagarapu, L., Kumar, C. G., Pombala, S., & Sridhar, B. (2014). Synthesis of novel building blocks of benzosuberone bearing coumarin moieties and their evaluation as potential anticancer agents. *Europ. J. Medi. Chem.*, *79*, 260-265.

[80] Murti, Y., & Mishra, P. (2014). Synthesis and evaluation of flavanones as anticancer agents. *Ind. J. pharmaceut. Sci.*, *76*(2), 163.

[81] Choi, M., Jo, H., Park, H. J., Kumar, A. S., Lee, J., Yun, J., & Lee, H. (2015). Design, synthesis, and biological evaluation of benzofuran-and 2, 3-dihydrobenzofuran-2-carboxylic acid N-(substituted) phenylamide derivatives as anticancer agents and inhibitors of NF-κB. *Bioorg. Medic. Chem. Let., 25*(12), 2545-2549.

[82] Andrade, S. F., Teixeira, C. S., Ramos, J. P., Lopes, M. S., Pádua, R. M., Oliveira, M. C., & Alves, R. J. (2014). Synthesis of a novel series of 2, 3, 4-trisubstituted oxazolidines designed by isosteric replacement or rigidification of the structure and cytotoxic evaluation. *Med. Chem. Comm,, 5*(11), 1693-1699.

[83] Toohey J, Cooper A. Thiosulfoxide (sulfane) sulfur: New chemistry and new regulatory roles in biology. Molecules 2014; 19(8): 12789-813. http://dx.doi.org/10.3390/molecules190812789 PMID: 25153879

[84] Makki MST, Abdel-Rahman RM, El-Shahawi MS. Synthesis of new bioactive sulfur compounds bearing heterocyclic moiety and their analytical applications. Int J Chem 2011; 3(1): 181-92. http://dx.doi.org/10.5539/ijc.v3n1p181

[85] García-Valverde M, Torroba T. Sulfur-nitrogen heterocycles. Molecules 2005; 10(2): 318-20. http://dx.doi.org/10.3390/10020318

[86] Ballantyne AD, Garnock-Jones KP. Dabrafenib: First global approval. Drugs 2013; 73(12): 1367-76. http://dx.doi.org/10.1007/s40265-013-0095-2 PMID: 23881668

[87] Waters EA, McNeel TS, Stevens WM, Freedman AN. Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. Breast Cancer Res Treat 2012; 134(2): 875-80. http://dx.doi.org/10.1007/s10549-012-2089-2 PMID: 22622807

[88] Said M, Elshihawy H. Synthesis, anticancer activity and structure-activity relationship of some anticancer agents based on cyclopenta (b) thiophene scaffold. Pak J Pharm Sci 2014; 27(4): 885-92. PMID: 25015456

[89] Ghorab MM, Bashandy MS, Alsaid MS. Novel thiophene derivatives with sulfonamide, isoxazole, benzothiazole, quinoline and anthracene moieties as potential anticancer agents. Acta Pharm 2014; 64(4): 419-31. http://dx.doi.org/10.2478/acph-2014-0035 PMID: 25531783

[90] Laczkowski Z. Synthesis and *in vitro* anti-proliferative activity of thiazole-based nitrogen mustards: The hydrogen bonding interaction between model systems and nucleobases. Anticancer Agents Med Chem 2014; 14(9): 1271-81.

[91] Penthala NR, Sonar VN, Horn J, Leggas M, Yadlapalli JSKB, Crooks PA. Synthesis and evaluation of a series of benzothiophene acrylonitrile analogs as anticancer agents. MedChemComm 2013; 4(7): 1073-8. http://dx.doi.org/10.1039/c3md00130j PMID: 23956835

[92] Reddy SM, Carroll E, Nanda R. Atezolizumab for the treatment of breast cancer. Expert Rev Anticancer Ther 2020; 20(3): 151-8. http://dx.doi.org/10.1080/14737140.2020.1732211 PMID: 32067545

[93] FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer. 2019. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm633065.htm (Accessed on: 08 March, 2019).

[94] Heimes AS, Schmidt M. Atezolizumab for the treatment of triple-negative breast cancer. Expert Opin Investig Drugs 2019; 28(1): 1-5. http://dx.doi.org/10.1080/13543784.2019.1552255 PMID: 30474425

[95] Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune checkpoint targeting. Lancet Oncol 2017; 18(12): e731-41. http://dx.doi.org/10.1016/S1470-2045(17)30607-1 PMID: 29208439

[96] Kaklamani VG, Jeruss JS, Hughes E, *et al.* Phase II neoadjuvant clinical trial of carboplatin and eribulin in women with triple negative early-stage breast cancer (NCT01372579). Breast Cancer Res Treat 2015; 151(3): 629-38. http://dx.doi.org/10.1007/s10549-015-3435-y PMID: 26006067

[97] Lopus M, Smiyun G, Miller H, Oroudjev E, Wilson L, Jordan MA. Mechanism of action of ixabepilone and its interactions with the βIII-tubulin isotype. Cancer Chemother Pharmacol 2015; 76(5): 1013-24. http://dx.doi.org/10.1007/s00280-015-2863-z PMID: 26416565

[98] Shalini, Lata S, Saha ST, *et al.* Tetrahydro-β-carboline-naphthalimide hybrids: Synthesis and anti-proliferative evaluation on estrogen-dependent and triple-negative breast cancer cells. J Mol Struct 2022; 1262: 133053. http://dx.doi.org/10.1016/j.molstruc.2022.133053

[99] Yang DL, Zhang YJ, Lei J, *et al.* Discovery of fused benzimidazole-imidazole autophagic flux inhibitors for treatment of triple-negative breast cancer. Eur J Med Chem 2022; 240: 114565. http://dx.doi.org/10.1016/j.ejmech.2022.114565 PMID: 35797901

[100] Madia VN, Nicolai A, Messore A, *et al.* Design, synthesis and biological evaluation of new pyrimidine derivatives as anticancer agents. Molecules 2021; 26(3): 771. http://dx.doi.org/10.3390/molecules26030771 PMID: 33540875

[101] Silvestri S, Cirilli I, Marcheggiani F, *et al.* Evaluation of anticancer role of a novel ruthenium(II)-based compound compared with NAMI-A and cisplatin in impairing mitochondrial functionality and promoting oxidative stress in triple negative breast cancer models. Mitochondrion 2021; 56: 25-34. http://dx.doi.org/10.1016/j.mito.2020.11.004 PMID: 33220497

[102] Eldehna WM, EL-Naggar DH, Hamed AR, Ibrahim HS, Ghabbour HA, Abdel-Aziz HA. One-pot three-component synthesis of novel spirooxindoles with potential cytotoxic activity against triple-negative breast cancer MDA-MB-231 cells. J Enzyme Inhib Med Chem 2018; 33(1): 309-18. http://dx.doi.org/10.1080/14756366.2017.1417276 PMID: 29281924

[103] Noel K, D'incalci M. Method of treating triple-negative breast cancer using thienotriazolodiazepine compounds: Google Patents. 2017.

[104] Noori MS, O'Brien JD, Champa ZJ, *et al.* Phenylmethimazole and a thiazole derivative of phenylmethimazole inhibit IL-6 expression by triple negative breast cancer cells. Eur J Pharmacol 2017; 803: 130-7. http://dx.doi.org/10.1016/j.ejphar.2017.03.049 PMID: 28343970

[105] Zhang CH, Chen K, Jiao Y, *et al.* From lead to drug candidate: Optimization of 3-(Phenylethynyl)-1 *H* -pyrazolo[3,4- *d*]pyrimidin-4-amine derivatives as agents for the treatment of triple negative breast cancer. J Med Chem 2016; 59(21): 9788-805. http://dx.doi.org/10.1021/acs.jmedchem.6b00943 PMID: 27739679

[106] Morales P, Blasco-Benito S, Andradas C, *et al.* Selective, nontoxic CB(2) cannabinoid o-quinone with *in vivo* activity against triple-negative breast cancer. J Med Chem 2015; 58(5): 2256-64. http://dx.doi.org/10.1021/acs.jmedchem.5b00078 PMID: 25671648

[107] Terashima M, Sakai K, Togashi Y, *et al.* Synergistic antitumor effects of S-1 with eribulin *in vitro* and *in vivo* for triple-negative breast cancer cell lines. Springerplus 2014; 3(1): 417. http://dx.doi.org/10.1186/2193-1801-3-417 PMID: 25140293

[108] Chougule MB, Patel AR, Jackson T, Singh M. Antitumor activity of Noscapine in combination with Doxorubicin in triple negative breast cancer. PLoS One 2011; 6(3): e17733. http://dx.doi.org/10.1371/journal.pone.0017733 PMID: 21423660