Ind. J. Pharm. Edu. Res., 2024; 58(1s):s26-s39.
https://www.ijper.org

Review Article

Heterocyclic Compounds and their Derivatives with Potential Anticancer Activity

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ABSTRACT

Cancer is the second leading cause of the death worldwide. As per the reports published by WHO, the cases of cancer in the world will increase to 22 million by 2030. Many resources are investigated all around the world for developing preventive, diagnostic and therapeutic strategies for cancer. Malignant cells display metabolic changes because of genetic and epigenetic alterations as compared to normal cell. Heterocycles are the key structural feature of many anti-cancer drugs present in the market. Between 2010 to 2015, FDA approved anticancer drugs also contain heterocyclic rings in their structures. Their presence in anti-cancer drugs can be credited to their being extremely common in nature, with enormous cellular processes and mechanisms. This review throws light on several heterocyclic compounds containing nitrogen, sulphur and oxygen in their rings, possessing anticancer activity on different cell lines. A compiled data of heterocyclic rings will help in providing a new way towards future development of new compound for treatment of cancer.

Keywords: Heterocyclic compounds, Anticancer activity, Cell lines, Cytotoxicity, Natural product, FDA.

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Received: 24-01-2023;
Revised: 27-05-2023;
Accepted: 29-08-2023.

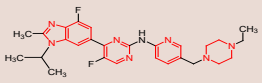
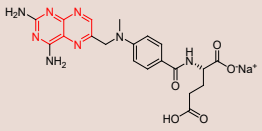
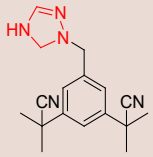
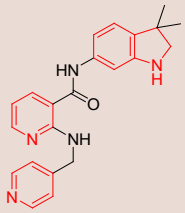
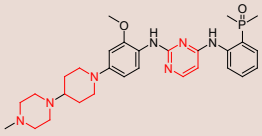
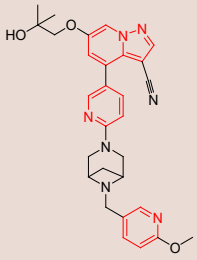
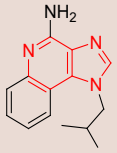
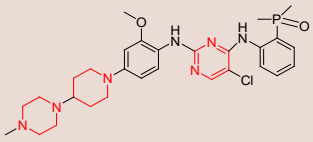
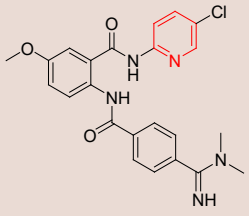
INTRODUCTION

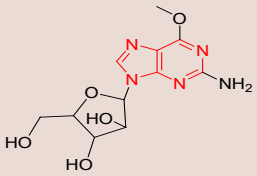
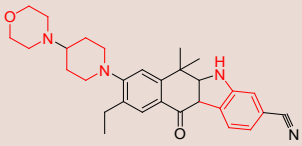
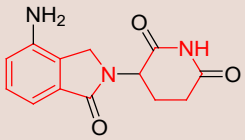
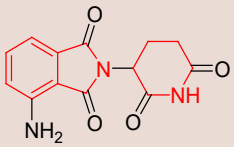
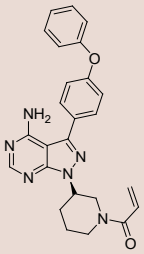
Heterocyclic containing compounds constitutes diverse family of organic compounds. They are the cyclic compounds which constitute at least one or more hetero atoms.[1] Nitrogen, oxygen and sulphur are the most communal hetero atoms which are widely known whereas other heterocyclic rings containing other heteroatom are also of great importance.[2] Heterocyclic compounds are reviewed as one of the essential classes of organic compounds that are employed in various biological fields due to its activity in multiple diseases.[3-7] Heterocyclic compounds occur widely in nature and in diversity of non-naturally occurring compounds. Large number of heterocyclic compounds are essential to life.[8] Numerous compounds including vitamins, amino acids, antibiotics, alkaloids, hormones, hemoglobin and huge quantity of synthetic compounds and dyes contain heterocyclic ring in their structure.[9-13] Many heterocyclic compounds have wide application in common diseases.[14-16] Heterocycles bearing nitrogen atoms in their ring structure are considered as vital class of compounds among physiologically active complexes, natural products and chemicals that are extensively used in medicinal chemistry.[17-19] Nitrogen bearing compounds like indole,[20] imidazole,[21] pyrrole,[22] triazole,[23] piperazine[24] have acquire importance in many research sectors including synthesis and medicine.[24-29] Whereas, oxygen containing compounds covers hefty portion of FDA approved drugs and therapeutically important structures.[30] The sulphur containing compounds like benzthiazole, thiophene have been proven to exert anticancer,[31,32] antimicrobial,[33] antiviral,[34] anti-inflammatory[35] and many other biological activities. In addition to it, sulphur containing compounds are used to flavour food products.[36] Numerous FDA approved drugs include nitrogen and sulphur heterocycles such as anastrazole, ademaciclib, anastrazole, tamoxifen, 5-flourouracil, clopidogrel, raloxifene etc are used to cure breast cancer, diabetes and many other diseases (Table 1).[37]

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells, which leads to death if not treated at the right time.[38] It is one of the most important health concern for human being with highest fatality rate.[39] Many substances may be natural, biological, chemical are the causing agents of cancer.[40] Many drugs are used to cure this disease but they possess their own toxic effects. Therefore, lot of research is required to synthesize new entities with better selectivity, least side

DOI: 10.5530/ijper.58.1s.3

Table 1: Clinically approved drugs containing heterocyclic compounds.

Drug	Brand name	Structure	Heterocyclic ring involved	Clinical indication
Abemaciclib	Verzenio		Piperazine, Pyrimidine, Benzimidazole, Pyridine.	CDK 4/6 inhibitor, use for treatment of breast cancer.
Methotrexate sodium	Trexall, Xatmep		Pyrazine, Pyrimidine.	Acute lymphoblastic leukaemia, breast cancer, lung cancer.
Anastrozole	Arimidex		Triazole.	Breast cancer in menopausal women.
Ramucirumab	Cyramza		Indole, Pyrimidine.	Colorectal cancer, hepatocellular carcinoma, stomach adenocarcinoma.
Nivolumab	Opdivo		Piperazine, pyridine, pyrimidine.	Classic Hodgkin lymphoma.
Selparcatinib	Retevmo		Pyrazole, pyrimidine.	Non-small cell lung cancer, Medullary thyroid cancer, Thyroid cancer.
Imiquimod	Aldara Zyclara		Imidazole, Pyridine.	Actinic keratosis, Basal cell carcinoma, Genital warts
Brigatinib	Alunbrig		Pipetazine, piperidine, pyrimidine.	Lung carcinoma.
Durvalumab	Imfinzi		Pyridine.	Use in adults with Phase III non-small lung cancer that cannot be remove by surgery.

Drug	Brand name	Structure	Heterocyclic ring involved	Clinical indication
Nelarabine	Arranon		Imidazole, pyrimidine.	Use to treat children 1 year or above with T-cell lymphoblastic leukemia.
Acletinib	Alecensa		Morpholino, piperidine, indole.	Receptor tyrosine kinase anaplastic lymphoma kinase.
Lenalidomide	Revlimid		Indole, Piperidine.	Follicular lymphoma, multiple myeloma, marginal zone lymphoma.
Pomalidomide	Pomalyst		Indole, piperidine.	Use to treat Kaposi sarcoma and multiple myeloma.
Ibrutinib	Imbruvica		Imidazole, pyrimidine, piperidine.	Chronic lymphocytic leukemia, small lymphocytic leukemia.

effects and minimum dosages for the cure of cancer. Discovery of newer drugs involves use of heterocyclic chemistry.[41,42] In this review an effort has been made to study different heterocyclic compounds containing nitrogen, sulphur, and oxygen in their ring, having anti-cancerous activity (Figure 1). The combined data from all the recent articles will help in providing a new way for future research in developing new compounds for the treatment of cancer.

Benzoxazole

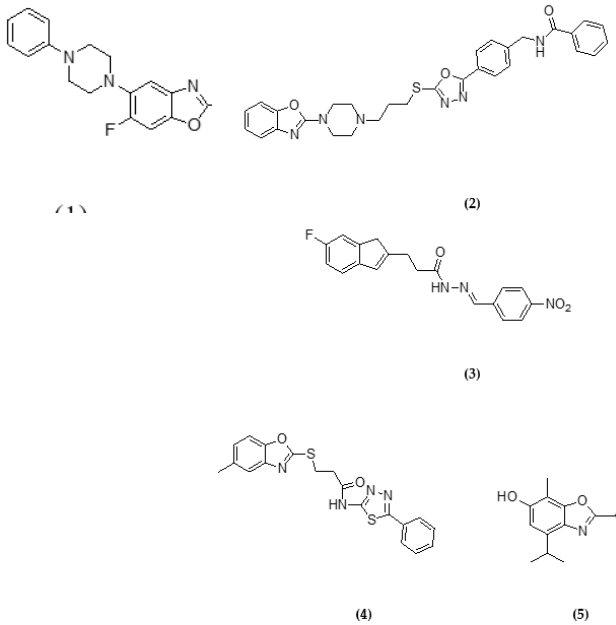
Al-Harthy *et al.*, synthesized benzoxazole derivatives linked to the piperazine and fluorine group. These benzoxazole clubbed piperazine hybrids were prepared by nitration and piperazinylation followed by *in situ* reductive cyclization. The prepared compounds were evaluated against human lung cancer epithelial cells A549. The cytotoxicity study was measured using CellTitre-Glo luminescent cell proliferation assay and it was observed that some intermediates (1) showed promising activity and cell dependent toxicity. Whereas, the initial results obtained were too low owing to the low solubility of aryl-piperazine.[43]

Murty *et al.*, synthesized benzoxazole derivatives coupled with piperazine ring (2) and evaluated their cytotoxic potential towards five distinct human cancer cell lines of various origins viz. Hela (cervical), MCF-7 (Breast), A431 (skin), HepG2 (liver) and A549 (lung). All the synthesized compounds displayed IC_{50} value lesser than 100 in MCF-7. cell line. The compounds possessing amide linkage showed increased cytotoxicity against A431 cell line as compared to other cell lines.[44]

Altintop *et al.*, reported newer benzoxazole hydrazone derivatives and reported *in vitro* cytotoxicity studies on rat glioma and NIH/3T3 mouse embryonic fibroblast cell lines using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay shadowed by apoptosis in C6 cell line. From the studies it was reported that the compound N'-(1,1'-Biphenyl-4-yl-methylene)-2-[(5-fluorobenzoxazole.-2-yl) thio] acetohydrazide (3) was found to be more active on C6 cell line with IC_{50}=4.30±0.28 µg/mL in comparison to mitoxantrone with IC_{50}=4.56±1.24 µg/mL. Increased in SI value of (3) compound indicates selective

anti-glioma activity. In comparison to results, it was observed that this compound causes dose-dependent late apoptosis.[45]

El-Helby *et al.*, prepared a series of sulphamide linked benzoxazole derivatives and evaluated them for their ability to inhibit VEGFR-2 as well as their anti-tumor activity against MCF-7 (breast cancer), HepG2 (hepatocellular carcinoma) and HCT-16 cell lines. The compounds prepared contain essential pharmacophoric groups having substituted and unsubstituted hydrophobic moieties linked through spacers and linkers which interact as hydrogen bond donor and -NH linked to carboxylate of essential amino acid. Among the prepared series, compound N-(4-(N-(cyclohexylcarbomoyl) sulfamoylphenyl)-3-((5-methylbenz-oxazol-2-yl) thio) propenamide (4) was most potent and had appreciable activity against all three cell lines. This compound was further examined for VEGFR-2 inhibitory activity. Results obtained showed that in comparison to sorafenib (standard) (IC_{50}=0.1±0.02 μM): synthesized compound (4) strongly inhibited VEGFR-2 with lower IC_{50} values.[46,47]



(1) (2) (3) (4) (5)

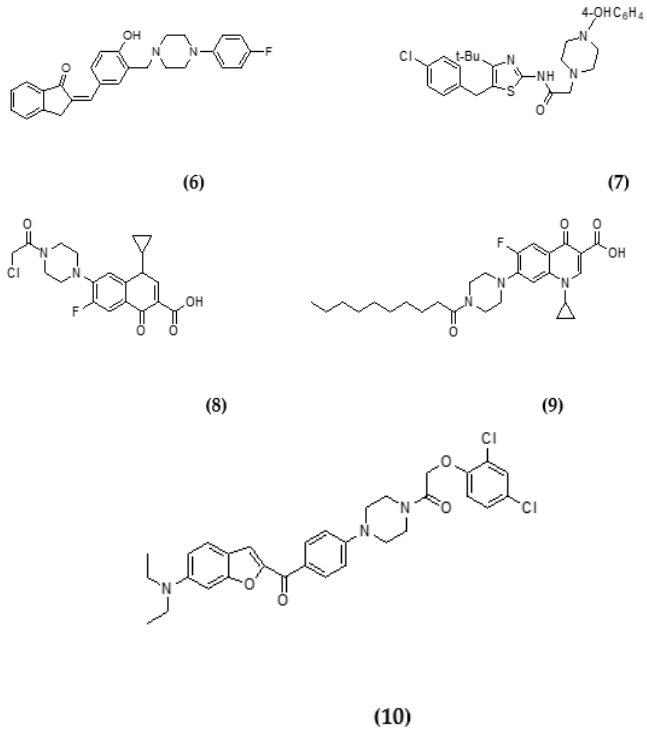
Piperazine

A new series of mono mannich bases containing piperazine scaffold were prepared and their cytotoxicity and inhibitory activity against carbonic anhydrase I (hCAI) and carbonic anhydrase II isozymes (hCAII) were tested *in vitro*. All compounds showed good inhibition towards hCAI with Ki value in range of 29.6-58.4 nM and 38.1-69.7 nM. Among the series, compound 4-fluorophenyl piperazine (6) had highest tumor selectivity value (TS: 59.6) by causing cell death.[48,49]

Wu and Ding *et al.*, synthesized a set of piperazine clubbed acetamide derivatives. All the prepared compounds were characterized by ^{1}H NMR,^{13}C NMR, elemental analyses and further evaluated against different cancer cell lines. Compound N-(5-benzyl-4-(tert-butyl) thiazol-2-yl)-2-(piperazin-1-yl) acetamides (7) showed appreciable cytotoxicity against. HeLa cancer cells with IC_{50} value ranging from 1.6±0.8μM. Further Wu. and co-workers also stated that this compound stopped G1 phase cell cycle, which causes cell apoptosis.[50]

Ciprofloxacin is an antibiotic having apoptotic and antiproliferative activity. Considering the importance of ciprofloxacin Azema *et al.*, reported set of piperazine compounds linked to ciprofloxacin derivatives of varying lipophilicities and tested them against different cancer lines. Among the synthesized compound 7-(4-2-chloroacetyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydr0-4-oxoquinoline-3-car boxylic acid (8) and 7-(4-decanoylpiperazin-1-yl)-1- cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (9) was the most potent with their IC_{50} values in the range ≤10 μM in cancer cell lines.[51]

In an extension. of the work piperazine analogues linked with benzofuran were prepared by Mao and co-workers and assessed them against four tumor cell lines (Hela, A549, MCF-7, SGC7901) using MTT assay. Among the prepared analogues 2-(2,4-dichlorophenoxy)-1-(4-(4-(6-(diethylamino) benzofuran-2-carbonyl) piperazin-1-yl) ethenone (10) was most effective compound against four strains of tumor cell lines and was also found to be more actives than standard cisplatin, and exhibited cytotoxicity selectively against HeLa.[52]

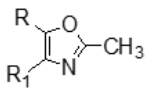


(6) (7) (8) (9) (10)

Oxazole

Romagnoli *et al.*, prepared new 2-methyl- 4,5 -disubstituted oxazole derivative and screened them for anti-cancerous activity against series of seven human tumor cell lines in comparison to standard combrestatin-4 with IC_{50}=0.8-3100 nM. Compound 11a and 11b was found to be most active having IC_{50} value 0.35-4.6 nM and 0.5-20.2 nM respectively. SAR studies revealed that compounds having 3,4,5-trimethoxyphenyl moiety at C-4 with respect to oxazole was beneficial for showing anticancer activity. Whereas, presence of electron releasing group placed at para position to phenyl ring showed increase in the activity and when placed on meta position was found to be detrimental for the activity.[53]

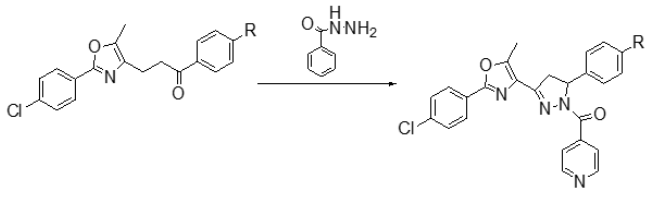
Katariya *et al.*, synthesized some biologically active heterocyclic ring containing propenones (12a-12e) and methadone (13a-13e) derivatives clubbed with biologically active heterocyclic rings including oxazole, pyridine and pyrazoline. All the compounds prepared were further screened for *in vitro* anticancer activity against sixty cancer cell lines at NCI, USA. Based on the bio-activity results, SAR studies revealed that the chalcone with floro substitution showed poor inhibition in comparison to other prepared chalcones derivatives. Whereas, compound 12d with bromo substitution showed highest potency among all the prepared compound with inhibition of 55%, 52% and 50% against T47D (breast cancer), OVCAR-4(ovarian cancer) and RPMI-8226 (leukemia) respectively.[54]



(11)

11a =R = 4'-OMe, 3'-F-C_6H_3, R1 = $(OMe)_3Ph$

11b =R = OEt-C_6H_4, R1 =$(OMe)_3Ph$



(12 a- 12e) **(13a- 13e)**

12a/13a R = H
12b/13b R = CH_3
12c/13c R = Cl
12d/13d R = Br
12e/13e R = F

Indole

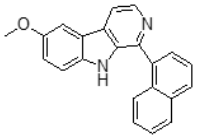
For a search of new scaffold for anti-cancer activity Patil. *et al.*, prepared series of pyrido[3,4-b] indole derivatives and screened them for anti-proliferative. activity against panel of human cancer cell lines, containing HCT116 colon, MIA, HPAC, MCF-7, PaCa-2, Panc-1 pancreatic and MDA-MB-468 breast, WM164 and A375 melanoma, A549 lung, and LNCaP, DU145 and PC3 prostate cancer lines.1-Napthyl group at first carbon clubbed with methoxy group at sixth carbon (1-naphthyl-6-methoxy-9H-pyrido [3,4-b] indole) (14) showed the highest anticancer. and highest potency.[55]

In addition to above research, indole-based imidazo[2,1-b][1,3,4] thiadiazole compounds (15) were synthesized by Casciofero *et al.,* and evaluated for anticancer efficacy on series of Pancreatic Ductal Adenocarcinoma Cells (PDAC) including Panc-1, Capan-1, and SUIT-2. From the result it was observed that compound 15 significantly inhibited the release of Capan-1 cells and SUIT-2 in wound healing assay and showed appreciable *in vitro* anti-cancer activity on all three preclinical models with IC_{50} ranging from 5.11 -10.80 µM.[56]

A new series of heterocyclic compound was prepared by *Lotify et al.,* indole derivatives was prepared by condensing L-proline and dicarbonyl compound isatin, with dipolar groups containing spiro-oxindole and pyrrolidine rings. Further the prepared analogues were screened for breast cancer cell lines (MCF-7) and leukemia (K562). Among the prepared series, (1R, 5'R)-3-(E) -4-bromobenzylidiene)-7',7a-dihydro-1'H,3'H disp iro[cyclohexane-1,6'pyrrolo[1,2-c]thiazole-5'3"indoline]-2,2"-dione (17) was recognized as the most effective compound with IC_{50} values of 15.49 ± 0.04 µM, against breast cancer cell lines (MCF-7) comparison to standard drug 5-florouracil (IC_{50}=78.28 ± 0.2 µM).[57]

Islam et al., synthesized in high yields a series of functionalized 3-acylindole linked with spiro-oxindole. Chalcones obtained from 3-acetyl indole was used as a starting material. These spiro-oxindole hybrids screened *in vitro* for their anticancer effect counter to colon cancer (HCT-116), hepatocellular carcinoma (HepG2) and prostate cancer (PC-3). Compound (17) found to have high selectivity and cytotoxicity against HCT-116.[58]

By condensation of nitro indole with diazotized *p*-aminoacetophenone and different heteroaromatic amines Kaur *at al.*, prepared a series of indole linked diazinyl compounds and screened them for cytotoxicity against breast cancer (MDAMB231), human lung carcinoma (HCT-116), leukemic and normal (K562 and HEK293) cell lines using MTT assay kit and doxorubicin as standard. Two compounds (18, 19) found to be active against human colon and breast carcinoma having IC_{50}=19-65 µg/mL.[59]



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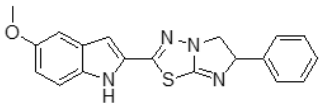

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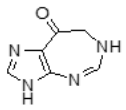

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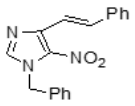

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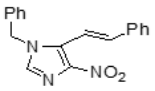

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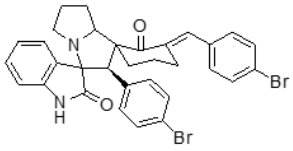

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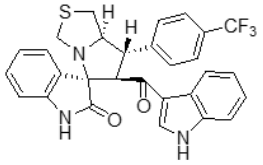

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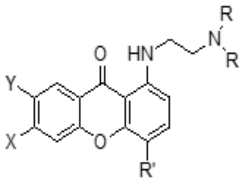
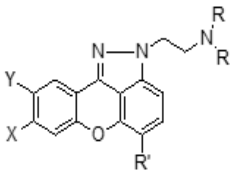


X, Y = H, C_4H_4

R= Me, Et

R'= NO_2, $NHCOCH_2NRR$

(23)



X, Y = H, C_4H_4

R = Me, Et

R'= NO_2, $NHCOCH_2NRR$

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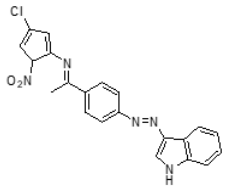

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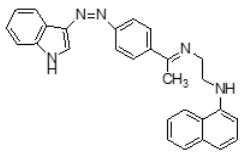
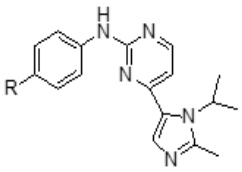


(19)



R

(25) SO_2Me

(26) $CONH_2$

(27) CONHMe

(28) $CONHMe_2$

(29) CONHPr

(30) $CONHC_2H_4OH$

(25-30)

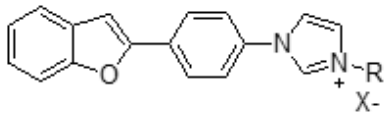
Imidazole

In a search for a new lead, Chen *et al.*, carried out reaction of 1-benzyl-5-nitroimidazole with carbanion produced tert-butoxide to synthesize benzyl-dichloromethyl-nitroimidazole derivative (20-22) and screened their anticancer activity. All the derivative compounds were biologically active compounds and showed prominent action against cancer cells.[60]

In addition, Kostakis *et al.*, reported a series of substituted amino xantheno imidazole derivatives (23-24) and screened their anticancer activity against human breast MDA-MB-231 cell line. A series of synthesized test compounds having two side chains exhibited maximum antiproliferative activity at higher dose while increase in the size of substituent and increase in basicity of alkyl substituent causes increase in anticancer activity.[61]

Whereas, Jones *et al.,* synthesized a set of imidazole linked pyrimidine amides (25-30) as CDK inhibitors (cyclin-dependent kinase). All synthesized compounds exhibited better activity against CDK enzymes as anti-proliferative agents.[62]

Further series of derivatives was synthesized by Yang *et al.*, they prepared hybrid between 2-phenylbenzofuran and imidazole (31-42) and tested for their *in vitro* anti-tumor activity on different tumor cell lines. Results revealed that imidazolyl group placed at third position with bromophenacyl (42) or naphthylacyl (43) group was essential for modifying anticancer activity. Among all the twelve synthesized derivatives, compound (43) showed remarkable activity against four different strains of human tumor cell lines.[63]



R

(31) -

(32) Benzyl

(33) 2-Bromobenzyl

(34) Allyl

(35) Butyl

(36) Phenacyl

(37) 4-Hydroxyphenacyl

(38) 4-Methoxyphenacyl

(39) 4-Fluorophenacyl

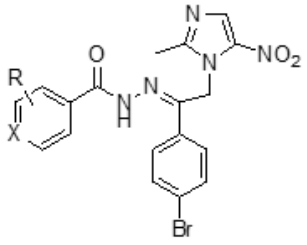
(40) 4-Bromophenacyl

(41) Naphthylacyl

(42) 2'-Phenyl-phenacyl

(31-42)

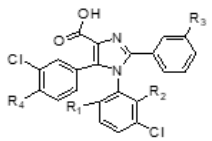
In addition to above research, Makawana *et al.*, synthesized new Schiff base derivatives of imidazolyl ethanones with benzo hydrazides (43-49) and tested for inhibition of Epidermal Growth Factor Receptor (EGFR) as anti-cancer agents. Among the compounds studied, compounds 46, 49 and 50 inhibited epidermal growth factor receptor and compounds 44, 45, 47 and 49 exhibited effective antibacterial activity. Compound 50 shows effective inhibition against EGFR receptor.[64]



	R	X
(43)	H	C
(44)	4-CH_3	C
(45)	4-Cl	C
(46)	2-OH	C
(47)	2-NH_2	C
(48)	4-OH	C
(49)	4-NH_2	C
(50)	H	N

(43-50)

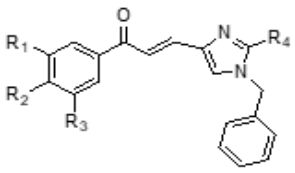
Vaupel *et al.*, synthesized few new classes of inhibitors based on tetra substituted imidazole scaffold. They showed considerable antiproliferative activity on a p53-dependent MDM2 amplified cell line. All the derivatized compounds showed significant anti-cancerous activity towards p53 dependent MDM2 amplified cell line.[65]



	R_1	R_2	R_3	R_4
(51)	H	H	H	H
(52)	Me	H	H	H
(53)	H	F	H	H
(54)	Me	H	Me	H
(55)	H	F	H	F

(51-55)

In an effort to identify anticancer agent, Oskuei *et al.*, synthesisized novel imidazole based chalcone derivatives as polymerization inhibitors on tubulin protein. Anticancer activity of imidazole based chalcone derivatives (56-65) was evaluated and tested on some human cancer cell lines including adenocarcinoma human alveolar basal epithelial cells (A549), mitoxantrone resistant human breast cancer cell (MCF-7/MX), Human hepatocellular carcinoma cells (HEPG2). Compound (63) and (65) exhibited significant cytotoxicity activity with IC_{50} against all four human cancer cells.[66]



(56): R1=R3=H, R2=Br, R4=SMe
(57): R1=R3=H, R2=F, R4=SMe
(58): R1=R3=H, R2=Cl, R4=SMe
(59): R1=R3=H, R2=NO_2, R4=SMe
(60): R1=R3=H, R2=OPh, R4=SMe
(61): R1=R3=H, R2=CH_3, R4=SMe
(62): R1&R2=Ph, R3=H, R4=SMe
(63): R1=R3=H, R2=Ph, R4=SMe
(64): R1=R3=H, R2=OCH_3, R4=SMe
(65): R1=R2=R3=OCH_3, R4=SMe

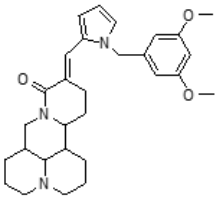
(56-65)

Pyrrole

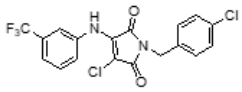
Bavadi *et al.*, in search of new derivative synthesize some novel pyrrole derivatives incorporating sulphonamides and screened against different cancer cell lines MCF-7, MOLT-4 and HL-60. Among the synthesized compounds, the compound (66) possessing morpholine group clubbed with pyrrole derivative was found to be more effective against these cell lines. Docking study reveals seven hydrogen bonds between the active site and pyrrole derivatives.[67]

To study mechanism of action of pyrrole derivatives with EGFR and VEGFR. Kuznietsova and co-workers synthesized pyrrole derivatives: chloro-1-(4-chlorobenzyl)-4-((3-(trifluoromethyl)-phenyl)-amino)-1H-pyrrole-2,5-dione (67a) and

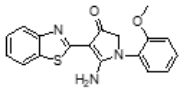
5-amino-4-(1,3-benzothyazol-2-yn)-1-(3-methoxyphenyl)-1,2-dihydro-3H-pyrrole-3-one (67b) and screened them against various EGFR and VEGFR like protein kinase. From the results it was obtained that pyrrole derivative bind with VEGFR and EGFR and form stable complex by forming electrostatic interaction with polar group of phospholipids in cell membrane.[68]



(66)



(67a)

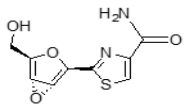


(67b)

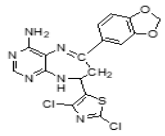
Thiazole

Siddiqui *et al.*, synthesized thiazole containing derivatives 2-((1R,2R,4S,5R)-4-(hydroxymethyl)- 3,6-dioxabicyclo [3.1.0] hexan-2-yl)thiazole-4- carboxamide (68) and screened for its anti-tumour activity against K562 malignant cells. This synthetic compound showed potent cytotoxic activity with low IC_{50} value.[69]

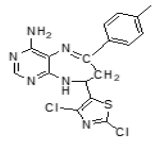
Ramirez *et al.*, derivatized a series of thiazole derivatives and screened for anti-tumour activity by US NCI (National cancer Institute) against sixty different human cancer cell lines which are derived from nine cancer types: ovary, renal, colon, CNS, leukaemia, lung, melanoma, breast and prostate cancers. From the results it was obtained that two compounds (E)-6-(benzo[d] [1,3] dioxol-5-yl)-8-(2,4-dichlorothiazol-5-yl)-8,9-dihydro-7H-pyrimido[5,4-b] [1,4] diazepin-4-amine (69) and (E)-8-(2,4-dichlorothiazol-5-yl)-6-p-tolyl-8,9-dihydro-7H-pyri mido[5,4-b] [1,4] diazepin-4-amine (70) have potent cytostatic activity. The compound (69) possesses cytostatic activity against K-562 of leukaemia, SND-75 of CNS cancer, MDA-MB-435 of melanoma and A498 of renal cancer, whereas compound (70) found to be more active against K-562 of leukaemia and MDA-MB-435 of melanoma. This compound has also shown its viability against HCT-15 of colon cancer, SNB-75 of CNS cancer, RXF393 of renal cancer and MDA-MB-468 of breast cancer cell lines.[70]



(68)

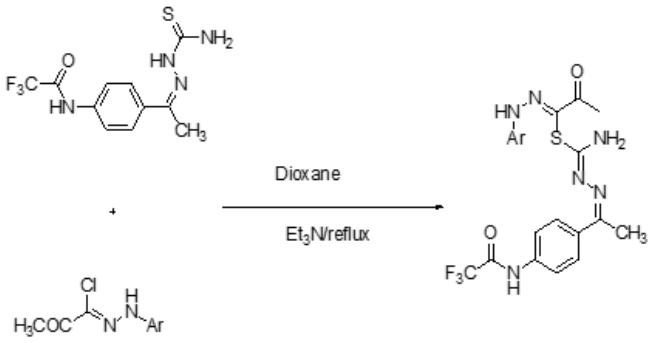


(69)



(70)

Alsaedi *et al.*, synthesized novel nano sized fluorinated thiazoles and evaluated their antiproliferative activity. They prepared trifluoro methylated thiosemicarbazone (73a- 73f) by reacting with thiosemicarbazone in acidic solution of ethanol. They found that nanosized thiazole derivative was found more active than standard cisplatin. And also found two thiazole derivatives exhibited good activity with IC_{50} value 13.4 and 14.9 µg/mL.[71]

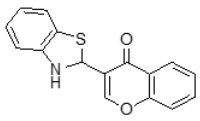


a) Ar = 4-$CH_3C_6H_4$
b) $CH_3C_6H_4$
c) 4-$CH_3OC_6H_4$
d) 3-ClC_6H_4
e) 2-$NO_2C_6H_4$
f) 3-$NO_2C_6H_4$

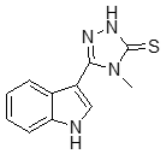
(71 a-71f)

Haribabu *et al.*, in a search of new compound synthesized heterocyclic azole containing compounds, 3-(2,3-dihydrobenzo [d]thiazol-2-yl)-4H-chromen-4-one (72) and 5-(1H-indol-3-yl) -4-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thione(73) which were synthesized from 2-aminothiophenol and 4-oxo-4H-chromene-3-carbaldehyde, and (E)-2-((1H-indol-3- yl) meth ylene)-N-methylhydrazine-1-carbothioamide in the presence of anhydrous ferric chloride, respectively. They assessed compounds 72, 73 and cisplatin as standard for their cytotoxic study against a series of three cancer cells of human such as HepG-2 (hepatic carcinoma), T24 (bladder) and EAHy 926 (endothelial) cells by using MTT assay. The results exhibited that compound (75) has

significant cytotoxicity against HepG-2 and EAHy926 cells with the IC_{50} values of 33.8 μM.[72]



(72)

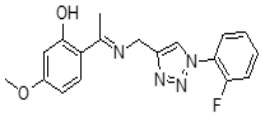


(73)

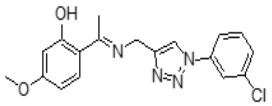
Jiang *et al.*, synthesized some new Schiff base linked 1,2,3-triazole derivatives and screened them for human cancer cell line A549 using paeonol as a standard. Compounds (E)-2-[1-{[1-(3-fluorophenyl)-1H -1,2,3-triazol-4-yl]methyl}imino)ethyl]-5-methoxyphenol (74) and (E)- 2-[1-{[1-(3-chloroophenyl)-1H -1,2,3-triazol-4-yl]methyl}imino)ethyl]-5-methoxyphenol (75) showed cytotoxicity with IC_{50} value of 45.1μM and 78.9 μM respectively in comparison to standard having IC_{50} of 883.0 μM.[73]

Narsimha *et al.*, synthesized novel coumarin based 1,2,3-triazole derivatives (76) and observed potent cytotoxic activity with IC_{50} 3.12 and 2.77 μM against HeLa and MCF-7 cancer cell lines in parallel to standard Doxorubicin having IC_{50} 0.23 μM in HeLa and 2.67 μM in MCF-7. SAR studies revealed that introducing 7-hydroxycoumarin, 7-hydroxy-4-methylcoumarin, 8-hydroxy quinoline and 2-mercaptobenzoxazole derivatives at the fourth position of 1,2,3-triazole ring affect the cytotoxicity.[74]

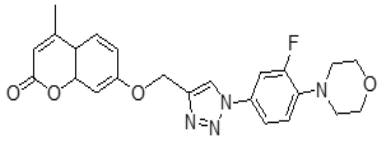
Tubulins play an important role in several cellular life processes. Tubulin polymerase inhibitors are agents that interfere with the tubulin system. Du and co-workers synthesized some triazole derivatives as tubulin polymerase inhibitors. Compound 5-(2-Chlorophenyl)-4-[4-(3,5-dimethoxyphenyl)piperazine-1-carbonyl]-2H-1,2,3-triazole (77) which showed strong cytotoxic effect on A549 and taxol resistant cells which inhibit polymerization by arresting G2/M phase.[75]



(74)



(75)



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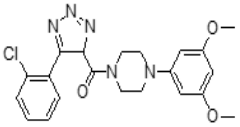
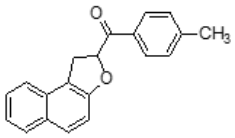


(77)

Furan

In search of new compound as anticancer agent, Islam and co-workers synthesized furan derivatives by cyclizing 1-(aryl/alkyl(arylthio)methyl)-naphthalen-2-ol and pyridinium bromides in the presence of 1,8- diazabicyclo[5.4.0] undec-7-ene (DBU) in good yield. The compound was evaluated against triple negative MCF-7 breast cancer cell line, MDA-MB-468 and non-cancerous lung fibroblast cell line FI-38 cells using MTT assay. The prepared furan derivatives, (1,2-dihydronaphtho[2,1-b] furan-2-yl)(p-tolyl) methanone (78) considered to have best anti-cancer activity from the series of prepared compounds.[76]



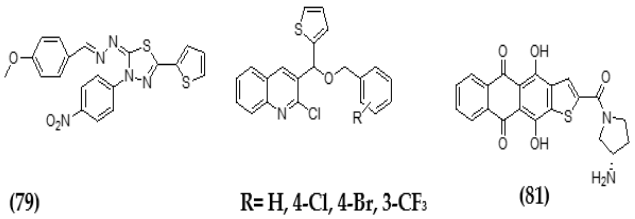
(78)

Thiophene

Gomha *et al.*, synthesize 5-(thiophen-2-yl)-1, 3, 4-thiadiazole derivatives (79) as potential antiproliferative compounds. By cyclization of N-(4-nitrophenyl) thiophene-2-carbohydrazonoyl chloride with arylidene thiosemicarbazones, the 1,3,4-thiadiazoles derivatives was prepared. The compound exhibited potent activity against human lung cancer A-549 and human hepatocellular carcinoma (HepG-2) using cisplatin as a standard. From the SAR (structure activity relationship) analysis, it was observed that introducing electron donating methoxy group on aryl moiety showed promising anticancer activity. Whereas, on replacing methoxy group with chlorine does not show appreciable activity as that was observed with methoxy group.[77]

Othmana *et al.*, derivatised a series of thiophene compounds and screened their anticancer activity against four cancer cell lines HeLa, HepG2, MCF-7 and HCT-116 and result displayed that benzyloxy derivatives exhibited good anticancer activity against MCF-7 with IC_{50} value=28.36 μM. Structure activity relationship studies (SAR) showed that presence of lipophilic group (benzyloxy) increases the antiproliferative activity in comparison to other synthesized derivatives. In addition, introduction of substituent's like fluoro, trifluoromethyl, chloro group at fourth position of benzene ring causes increase in the anticancer activity. This compound (80) also showed effective inhibition against EGFR-TK enzyme having IC_{50}=3.66 μM, which indicated this inhibition activity of the compounds may be due to strong interaction with EGFR-TK enzyme.[78]

Volodina *et al.*, synthesized thiophene-2-carboxamide derivatives of anthraquinone. This anthraquinones since ages known as a source of efficacious antitumour drugs. Various chemical modifications in the side chain of the compound yielded the compound with various anti-tumour activities. Among the prepared anthraquinone derivatives, anthra[2,3b] thiophene-2-carboxamide (81) was found to be potent against variety of human tumour cell lines. Sub micromolar or low molecular concentration of the prepared compound was effective against chronic myelogenous leukaemia K562.[79]



(79) R= H, 4-Cl, 4-Br, 3-CF_3 (80) (81)

Targeted receptor for anti-cancer drug

Protein kinase

They are the enzymes that modify the shape of proteins by phosphorylating certain amino acids with ATP to control functions of protein. This mechanism activates intracellular signaling pathway through gene expression via cell proliferation, growth and apoptosis.[80,81] Protein kinase are often considered as oncogenic and essential for the survival and spread of the cancerous cells. Other kinase targets include tyrosine Kinase (TKs) and cyclin-dependent kinase (CDKs). TKs is crucial for controlling the survival and cell growth of cancer cells (Figure 2).[82] Conversely, CDKs are in charge of cellular transcription and the advancement of the cell cycle.[83] Tyrosine kinase consist of around thirty different families including VEGFR, EGFR and NGF. Genome of human consists of 90 tyrosine kinase and 43 tyrosine like genes. Stimulation of TKs causes activation of number of signaling pathways. These pathways in turn are responsible for cell movement and reorganization which causes metastasis of tumour.[82] Hence, protein kinases emerged as an attractive group of targets for the anti-cancer drug development.

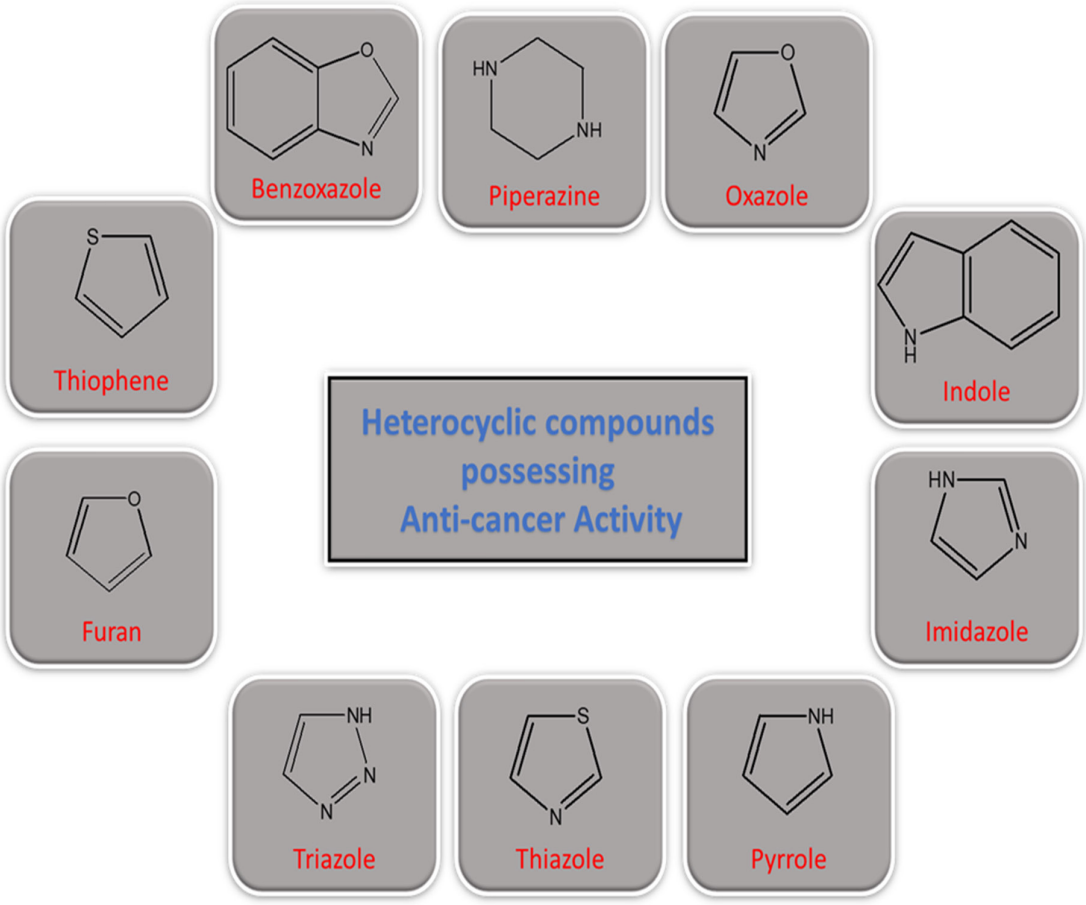


Figure 1: Heterocyclic scaffolds containing anticancer activity.

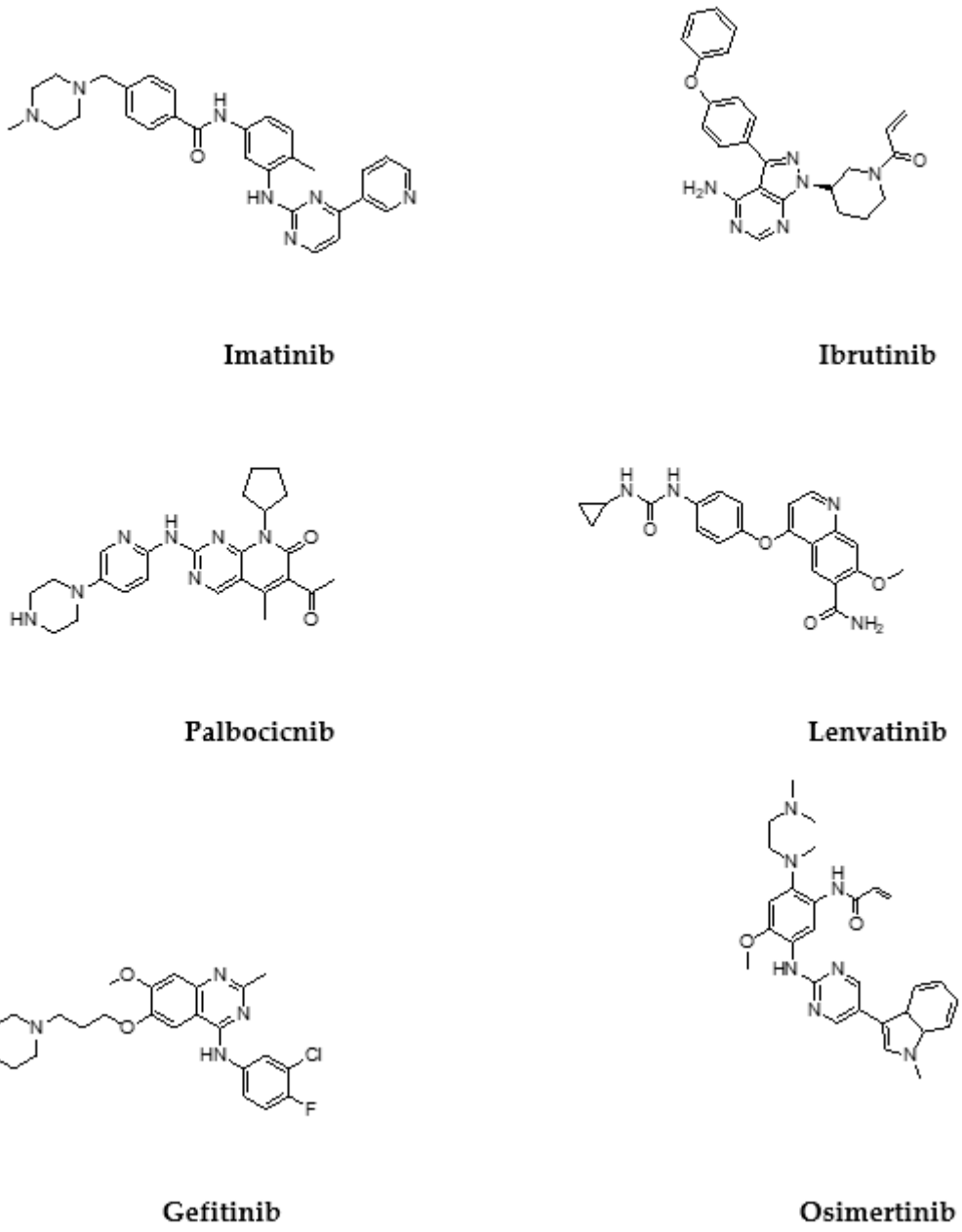


Figure 2: Kinase inhibitors approved for the treatment of cancer.

Apoptosis inducers

Apoptosis also known as "cellular suicide". It is a form of programmed cell death in which infected cells or cancerous cells are removed from the body. Cells generally try to repair the damaged DNA but when the damaged DNA is beyond repair then apoptosis takes place and remove this damage cells. When this damage DNA does not undergo apoptosis then it may lead to cancer.[84]

Topoisomerase

DNA topoisomerase I and topoisomerase II are the nuclear enzymes that play an important role in replication, recombination as well as repair and transcription of DNA. These enzymes cause transient breaks in DNA molecule by slicing one strand or both the strands of DNA, thereby relieving the topological tensions and relaxing DNA helices. Hence topoisomerase I and II are considered as important target for the anticancer drug design.[85,86]

Microtubules

They are cytoskeletal structures that are formed by association of two subunits i.e., α and β. These microtubules play an important role in providing shape and rigidity to the cell. They are also involved in the process of cell division, cell reproduction; cell signalling and cellular movement.[87] Two types of microtubules such as stabilising and destabilizing agent are the important

target for the anticancer drugs. Microtubule Stabilizing Agent (MSA) act by binding to tubulin in the polymeric tubular form. and stop the process of depolymerization. These MSA bind with one of the two binding site that promote stabilization and prevent depolymerizations. As a result, cell cycle arrest takes place at G2/M stage.[88]

Whereas, microtubule destabilising agent act by binding to colchicine and vinca domain thereby destabilizing microtubules and prevent tubulin polymerisation process. Tubulin emerged as an important target for anticancer drug development.[89]

Cancer stem cells

These are the cells which are present within the tumor. Cancer stem Cells (CSC) produces daughter cells and reproduces very fastly for a short period of time. These types of cells further segregate and produce cell in the tumor mass that are non-cancer stem cells. CSC's play role in development of tumors and maintenance of population of cells that proliferate rapidly.[90] According to the study, cancer stem cells are present in variety of tumors[91] including those of prostate,[92-94] brain,[95-98] ovarian,[99-100] colon,[101] lung[102] and in chronic leukemia.[103,104] Therefore, it is believed that different types of cancer contain subset of stem like tumor cells. So, targeting cancer stem cells are essential for an effective anticancer drug development.

CONCLUSION

This review is focused on recent development of heterocyclic ring containing synthesized derivatives having anticancer properties which mainly focused on development of target based anticancer drugs. Heterocyclic moieties play an important role as they are present in majority of drugs which improves both pharmacokinetic and pharmacodynamics properties of the anticancer agents. About 30% of FDA approved anticancer drugs have one or more heterocyclic rings containing oxygen, nitrogen and sulphur. Heterocyclic moieties play a vital role in metabolism of all living creatures approximately through many biochemical processes necessary to sustain life. Their involvement of about two thirds of anticancer drugs approved by FDA in the first half of decade to highlight their ongoing importance in cancer research play a center role to fight against cancer. Moreover, efforts have been made to provide recent advances in heterocyclic compounds as anticancer agents and a new way in developing new compounds for the treatment of cancer.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

FDA: Food drug administration; **MTT:** (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide); **CSC:** Cancer stem cells; **HeLa:** Henrietta Lacks **SAR:** Structure activity relationship; **IC_{50}:** Half maximal inhibitory concentration; **TK:** Tyrosine kinase; **hCAI:** Human carbonic anhydrase I; **hCAII:** Human carbonic anhydrase II; **CDK:** Cyclin dependent kinase; **CSC:** Cancer stem cells; **MSA:** Microtubule stabilising agent **VEGFR:** Vascular endothelial growth factor; **HPAC:** Human pancreatic cancer; **Hep:** Hepatoblastoma; **PDAC:** Pancreatic ductal adenocarcinoma; **MCF:** Michigan cancer foundation; **MDM2:** Murine double minute.

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Cite this article: Kaur A, Shakya AK, Singh R, Badhwar R, Sawhney SK. Heterocyclic Compounds and their Derivatives with Potential Anticancer Activity. Indian J of Pharmaceutical Education and Research. 2024;58(1s):s26-s39.