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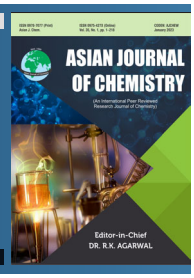

REVIEW

N-Heterocyclic Analogs: A New Prospect in Cancer Therapy

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One of the serious problems in the healthcare industry is cancer. In today's scenario, a lot of anticancer medications are available in the market, but they are not specific for specific cancer or have poor safety value, adverse effects and high resistance. Therefore, the designing of safer and more focused anticancer medications is essential. In today's situation, more than 85% of all medications with good physiological activity are heterocyclic compounds with one or more heteroatoms in the aromatic structure. The most common aromatic moieties that have the highest prevalence in anticancer medication are nitrogen-containing heterocycles. The information about the synthesis and anticancer activity of various *N*-containing derivatives, such as pyridine, pyrimidine, carbazole, indole, imidazole, benzimidazole, quinoline, isatin, pyrazole and triazole, has been summarized which directly indicates their anticancer potentiality against different types of cancer. The study also showed that in contrast to other substituents, the substitution of electron-withdrawing groups on the heterocyclic *N*-containing moiety has greater anticancer action. The information in this work might serve as a model for future investigations into the production and anticancer properties of novel *N*-containing heterocyclic compounds.

Keywords: Nitrogen-containing heterocycles, Anticancer, Biological activity, MTT assay.

INTRODUCTION

The abnormal cell division in the normal cells is the major cause of cancer that normally divide away from their original margins and easily enters surrounding areas and broaden to other organs and resulting in metastasis, which is the frequent reason for malignancy causing mortality, the second highest recurrent reason of mortality across the world [1-7]. An average of ten million fatalities associated with cancer and 19.3 million latest cancer cases were estimated by 2020 internationally. Around 25% of cancer cases are originated from those diseases which are cancer-causing like hepatitis as well as human papilloma-virus infections.In recent years, it is observed that the most frequent malignancies in both males and females are lung, liver, breast, thyroid, ovarian, prostate and colorectal cancer. As per the report by the WHO, approximately 400,000 children develop cancer every year. The occurrence of cancer is expanding globally as years pass which would badly affect patients and families emotionally and financially too [8-11].

Reported cases of different types of cancer in last 2 years are ductal, colorectal, prostatic intraepithelial and gastric carcinoma among which bronchogenic carcinoma is reported to have the highest mortality rate with cases of 2,210,000 value [12]. In affluent and opulent countries, carcinoma is the leading cause of fatality. Mutation in the DNA can be an important cause of cancer development, which may be of heredity or adoption, genetic and epigenetic both factors concerned [13-16]. There are hormonal and many different epigenetic factors responsible for the promotion of malignancy and even alteration by the suppression of the oncogenes for the proliferation of cancer cells [17-20]. Proliferation is the most important factor in the development of cancer cells growth in comparison to normal cell growth. Malignant cells propagate without control and changes occur in growth factors and the proteins, angiogenesis related to tumors and intracellular pathways which control apoptosis and cell cycles [21-24]. Current approaches suffer from the limitations of toxic effects and drug resistance so sustained research for novel and imp-

regnable antiproliferative agents remains desperately vital [25-30].

Heterocyclic chemistry plays a prominent role in the advancement of pharmacologically active compounds, contributing to approximately one-third of the overall scientific publications in this field [31-36]. Heterocyclic moieties show their pharmacologically potent activity in various applications as anticancer, antimalarial, antiviral, anti-inflammatory, hypnotics, analgesics and antidepressant agents [37-41]. Heterochemistry started with the medicinal compounds having heteroatoms in their moieties like oxygen, sulfur and nitrogen by replacing their carbon atom [42-44]. The alteration in the heterocyclic compounds affects the size and existence of the moiety in the parent molecule and enhances the chemical and physical parameters [45-48].

These alterations in the heterocyclic moiety can influence the antibacterial, antiproliferative, antiviral and antifungal, antibacterial characteristics [49-51]. These *N*-containing compounds are extensively present in nature and show different actions as alkaloids, hormones, agrochemical dyes, vitamins, antibiotics and many others. Frequently, they serve as an essential component within numerous pharmacological formulations [55-55].

These nitrogen atoms enhance the strength of the complex by making a hydrogen bond with DNA. The reaction between compounds with the deoxyriboucleic acid usually starts with reducing the progression of cancer. In such moieties where one or more than one nitrogen heteroatom occurs having a highly polarized nature and optimal interaction with proteins [56-62]. The genetic material, which consists of base pairs comprising pyrimidine and purine, is derived from compounds that are heterocycles containing nitrogen [63-65]. These *N*-containing heterocycles show different qualities and wide applications and have found eminence in speedily growing areas of synthetic and medicinal chemistry [66-68].

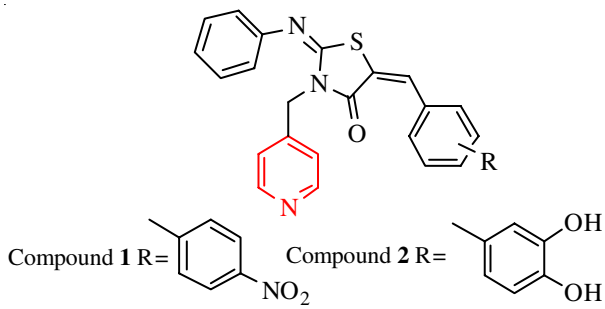
The *N*-containing heterocycle has electron rich property and creates some weaker interactions, *e.g*. some of them are intermolecular forces like hydrogen-bonds, dipole-dipole interaction, hydrophobic interaction and van der Waal forces augmented the significance of nitrogen-containing heterocycles in the organic chemistry field and encourage to fused with various types of enzymes and receptors in a biological system having greater similarity because to their enhanced solubility [69,70]. Classification of these compounds is based on the number of nitrogen atoms found inside the ring at C-3, C-4, C-5 and C-6 [71,72].

Examples of the five-membered single nitrogen containing compounds are pyrrole and azole while pyrazole and imidazole are two nitrogen-containing five-membered heterocyclic rings.

Pyridine is the most prevalent example of a six-membered heterocyclic ring containing a sole nitrogen atom, while pyrimidine is the most typical case of such a ring having a double nitrogen atom [73,74]. Over the last decade, nitrogen containing heterocycles are paying attention in front of scientists due to their biological significance and variation in structure. In this study, the focus is to cover the recent developments of nitrogen containing heterocycles as potent anticancer chemotherapeutics. This review provides insight into certain hetero-compounds that have been documented for their potential anticancer properties. This information certainly will help researchers in their search of other hetero base analogs exhibiting anticancer activity. Numerous examples of different *N*-heterocyclic compounds with anticancer activities synthesized by the researchers in last 10 years are discussed below:

Pyridine moiety: Pyridine is a heterocyclic moiety and shows the structural similarity to benzene with the replacement of one carbon by a nitrogen atom. It contains a conjugated system of six delocalized electrons located around the heterocyclic ring [75]. It shows potent antipsychotic properties against cancerous cells because of the presence of nitrogen atoms at *ortho*-position and also the effect of methyl group attachment on the 4 or 5 positions of pyridine ring.

Ansari *et al.* [76] studied the anti-proliferative screening by designing some novel pyridine substituted thiazolidine dione derivatives (Fig. 1) and were tested against the human carbonic anhydrase inhibitors-IX (CAIX) and human embryonic kidney cells-293 (HEK-293), michigan cancer foundation-7 (MCF-7) and human liver cancer cell line (HepG2) cell lines. Compound with nitro substitution on the benzene ring (**1**) with dihydroxyl substitution on the benzene ring (**2**) showed the maximum binding energy with targets (MCF-7, Hep-2 cell lines) with half maximum inhibitory concentration (IC_{50} value) 13.2 ± 2.28 with 19.2 and 12.4 ± 1.39 with 18.5 in comparison to standard drug doxorubicin 18.5 ± 1.59 with 8.0. Based on the molecular modeling studies, it was observed that these compounds exhibited a robust affinity for the active site residues of CAIX. Thus, these compounds hold promise as significant advancements in the pursuit of combating hypoxia-induced cancer in forthcoming investigations.



Compound with nitrosubstitution on benzene ring (compound **1**) showed high receptor affinity due to nitro substitution while compound with dihydroxyl substitution on benzene ring (compound **2**) demonstrate high affinity with receptor

Fig. 1. General structure of pyridine substituted thiazolidine dione derivatives

Gomha *et al*. [77] synthesized a novel pyridinylacetohydrazide compound (Fig. 2) and utilized this intermediate to synthesize novel pyridine-based heterocyclic compounds. The researchers further investigated the potential carcinogenic effects of these compounds on the human liver cancer cell line (HepG2 cell line), with doxorubicin serving as a reference agent. In this study, the highly effective derivative was compound **3** with an IC_{50} value of 0.97 μM for the HepG2 cell lines. The positive control showed a maximum inhibitory concentration value of 0.74 μM.

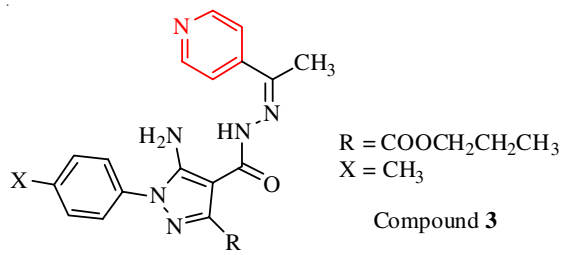
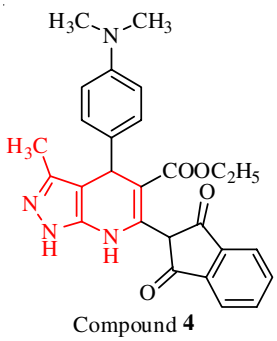
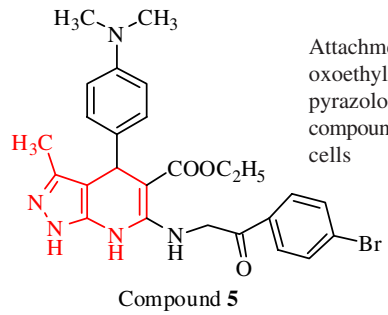


Fig. 2. General structure of substituted pyridinyl acetohydrazide derivatives

El-Gohary *et al.* [78] designed from molecular modeling and synthesized new pyrazole pyridine derivatives and determined the anticancer potential of these derivatives. The *in vitro* study of the synthesized compounds against henrietta lacks cell line (Hela), MCF-7 and HepG2 cell lines compounds **4** and **5** (Fig. 3) give high affinity against cancer cells. Compound **4** showed the maximum inhibitory concentration of 3.11, 4.91 and 3.63 µM against the carcinoma cell lines MCF-7, Hela and HepG2 while compound **5** provided the maximum inhibitory concentration of 4.24, 4.06 and 4.22 µM against the cell lines HepG2, MCF-7 and Hela in comparison to standard having maximum inhibitory concentrations 4.3, 3.97 and 5.17 µM. Even studying two non-cancerous cells with these derivatives. Compounds **4** and **5** exhibit IC_{50} values of 64.58, 53.96 and 55.61, 60.31 against WISH and W138 normal cells, respectively, when compared to doxorubicin, which demonstrates IC_{50} values of 8.14 and 6.68. Molecular modeling studies also yield information regarding the highly effective binding of these two chemicals with DNA. This determination showed these two compounds as propitious pharmacophores for future determination in the formation of new antisarcomaagents.



Attachment of 1,3-dioxoisoindoline-2-yl at 6 position of pyrozolopy-ridine skeletol provide the compound with good receptor bindng property and highly effective anticancer property.

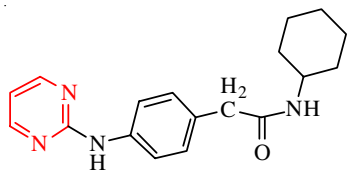


Attachment of 2-(4-bromo phenyl 2-oxoethyl amino group at 6-position of pyrazolo pyridine skeletol) made the compound highly reactive for cancerous cells

Fig. 3. General structure of pyrazole-pyridine derivatives

Pyrimidine moiety: Pyrimidine is a very effective heterocyclic moiety that exhibits a broad range of pharmacological and biological activities. It consists of substituted benzene having 1,3-diazine aromatic structure having nitrogen at its 1 and 3 positions and present in various naturally occurring compounds like vitamins, co-enzymes, uric acid and genetic material also. This extensive behaviour of pyridimine moiety may be due to its presence in the structure of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). The first analogue of the pyrimidine structure involves the replacement at the 5-position with the incorporation of a halogen moiety. Zidovudine, minoxidil, methotrexate, trimethoprim, phenobarbital and sulfamethazine are some of the important drugs with different uses having pyrimidine in their nucleus [79-81]. Pyrimidine has electron-rich nitrogen atoms in its structure and replacement can occur in carbon at different positions [82,83].

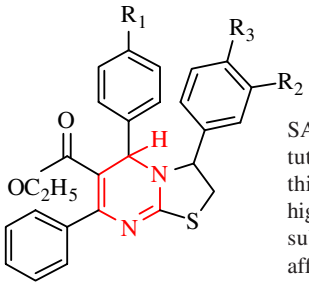
Yu *et al.* [84] developed some novel disubstituted pyridine and screened them for carcinogenic activity with positive control VX-680 against aurora kinase and a group of adenocarcinomic cell line 549 (A549), MCF-7 and human colorectal carcinoma cell line-116 (HCT-116). Compound **6** (Fig. 4) showed maximum inhibitory concentration against sarcoma cells (A549-12.05 µM), (MCF-7-20.53 µM) and (HCT-116-1.31 µM). Compound **6** showed Aurora-A and Aurora-B reducing activity having maximum inhibitory concentrations of 309 nM and 293 nM. Furthermore, it should be emphasized that it induced apoptosis in hematocrit (HCT) cells by boosting the susceptibility of the pro-apoptotic protein Bax and decreasing the presence of the anti-apoptotic protein BCl-XL. The derivative under investigation had favourable drug-like properties as determined by the analysis of molecular modeling data utilizing SwissADME software. The provided information suggests that the examined derivative holds potential as a viable alternative to current medications for further advancement in its role as an inhibitor of Aurora kinase.



SAR study of compound **6** is when benzene is replace by cyclohexyl ring shows greater potency and replacement of one NH in urea with CH_2 group gives good activity.

Fig. 4. General structure of substituted 2,4 disubstituted pyridine derivatives

Nemr *et al.* [85] reported the latest series of thiazolopyrimidine hydrobromides as well as triazolopyrimidines that work on topoisomerase-II and screened for antiproliferative action against more than 50 human cancer cell lines mostly targeting blood, hepatocellular, colorectal, skin, prostate, kidney, breast as well as ovarian cancers. After determination, it is found that compound **7** (Fig. 5) showed selective cell growth inhibition of more than 90% against kidney cell A498 (maximum inhibitory concentration 3.5 µM) and has remarkable inhibition against leukemia cell line (K-562) and prostate cell line (PC-3). This compound exhibited stoppage of the cell cycle at the interface of cell division (G2/M phase) ending with stoppage of increasing cell division and induction of cell death. The



SAR study showed that chloro substitution at both the benzene ring gives thiazolopyrimidine derivative showed highly reactive and comparison to other substituents a good receptor binding affinity

R_1 = Cl, R_2 = H, R_3 = Cl

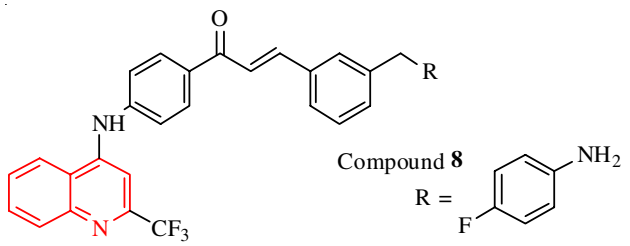
Compound **7**

Fig. 5. General structure of substituted thiazolopyrimidine and triazolopyrimidines derivatives

compound also exhibits remarkable potency against topoisomerase II with (a maximum inhibitory concentration of 2.89 µM) in comparison to the positive control (standard) (maximum inhibitory concentration of 2.67 µM).

Quinoline moiety: Quinoline, often known as benzopyridine, is a one of the significant heterocyclic moiety with a chemical formula of C_9H_7. This ring system contains a bicyclic ring where one benzene is fused with pyridine moiety causing the structure as a significant moiety in synthetic chemistry. Quinoline is a 3º amine base in the chemical mean and showed electrophilic and nucleophilic substitution reactions [86-89]. It gives reactions similar to benzene and pyridine. One of the prominent example within this classification is the naturally occurring compound identified as cinchona alkaloids [90-92].

Patel *et al.* [93] designed novel phenyl halogen substituted quinoline derivatives and screened their antiproliferative activity against the MCF-7, ductal carcinoma cells by sulforhodamine B (SRB) assay method. After determining neoplasmic activity derivative **8** exhibited good potency against breast cancer. Adriamycin is used as a reference compound. Derivative **8** (Fig. 6) showed potent carcinogenic activity against MCF-7 cells (maximum inhibitory concentration 0.004 µM).

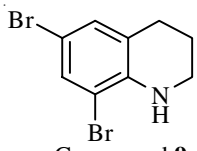


3-Phenyltrifluromethyl quinoline derivatives

*SAR studies showed that 2-thione group position of 3-phenyltriflurometyl quinoline moiety and substituion of electronegative atom at phenyl ring at R gives compound potent anticychotic agent.

Fig. 6. General structure of substituted 3-phenyltrifluoromethyl quinoline derivatives

Koprulu *et al.* [94] investigated the antiproliferative and cytotoxic activity of novel substituted quinolines and tetrahydroquinolines against human adenocarcinoma (HT29), mouse GBM cells (C6) and Henrietta Lacks (HeLa) cancer cell line. The docking study also revealed that compound **9** (Fig. 7) was most effective for the treatment of metastatic carcinoma



Compound **9**

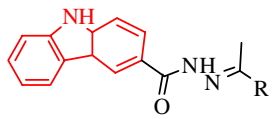
*SAR studies showed that attachment of two bromo substitution at 6 and 8 position of quinoline ring inhibits the proliferation of cancerous cells

Fig. 7. General structure of substituted 3-phenyltrifluoromethyl quinoline derivatives

because of its binding likeness with phospholipase C gamma-1 (PLCγ1). Compound **9** with IC_{50} values against HeLa, C6 and HT29 were 144.8, 100 and 117.6 µM in comparison to reference drug 5-fluorouracil with IC_{50} values of 163, 469.6 and 501.2 µM.

Carbazole moiety: Carbazole is a polycyclic aromatic heterocyclic compound that has two benzene rings used in the middle with a nitrogen-containing 5-membered ring. This nitrogen atom exhibits the delocalization of electrons [95-97]. In last few years, carbazole hybrid in combination with other moieties has been recognized as the advanced and better quality chemical structure to influencenumerous drug targets for carcinoma simultaneously [98,99]. Many kinds of cancer cell pathways could be activated by some approved anticancer agents with carbazole moieties like alectinib, ellipticine and celiptium signifying the potency of this moiety as an antiproliferative agent [100].

Huang *et al.* [101] synthesized novel substituted carbazole derivatives (Fig. 8) and determined their antiproliferative activities against three cancer cells *e.g.* melanoma sarcoma cell (A875), HepG2 and African green monkey kidney cell line subclone (MARC145) by tetrazolium salt assay method using 5-florouracil as positive control. Two compounds exhibit the excellent results for all cancerous cells in comparison to standard drugs. In contrast to 5-fluorouracil, these two compounds had very little effect on normal cell lines.



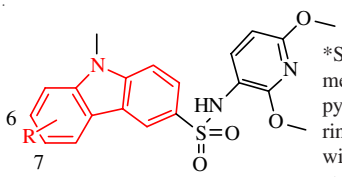
Compound **9** R = 3,4-OCH_2OPh
Compound **10** R = 4-ClPh

* SAR studies demonstrate that electron withdrawing group on *m* and *p* positions of phenyl ring of carbazole acylhydrazones showed potent cytotoxicity.

Fig. 8. General structure of substituted carbazole derivatives

Compound **9** showed IC_{50} values for (A875) and (HepG2) cell lines was 7.65 and 8.16 while compound **10** exhibited IC_{50} values against (A875) and (HepG2) was 11.44 an 12.24, respectively. Both exhibited IC_{50} values for the normal cell line (MARC145) was > 105 in comparison to standard drug maximum inhibitory concentration of 72.33 and 81.94 with normal cell 77.56. This data demonstrated that these scaffolds might be developed as a potential pharmacophore in future anticancer drug agents.

Sun *et al.* [102] designed and synthesized novel carbazole sulfonamide derivatives (Fig. 9) and evaluated their antiproliferative potency against different cell lines by SRB assay. The positive control used for the study is podophyllotoxin. The maximum inhibitory concentration of compound **11** observed



*SAR studies revealed that 3,4,5-trimethoxyphenyl with 2,6-dimethoxylpyridine, the B ring with a carbazole ring and presence of sulfonamide group with adding polor or ionizable group at 6 or 7 position of the carbazole ring gives high aquous solublity.

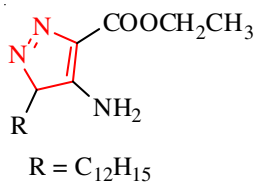
Compound **11** R = 7-OH
Compound **12** R = 7-NH_2

Fig. 9. General structure of substituted carbazole sulfonamide derivatives

was 0.012, 0.051, 0.014 and 0.056 µm. The maximum inhibitory concentration of compound **12** against hepatic and breast cancer cells were 0.070, 0.092, 0.036 in comparison to podophyllotoxin against the same cancer cells were 0.003, 0.012, 0.020, 0.016 and 0.18. These results exhibit these two compounds for future enhancement of new possible cytotoxic drug molecules.

Imidazole moiety: Imidazole is another important cyclic molecule consisting of a five-membered aromatic ring. It exhibits high polarity due to the presence of two nitrogen atoms within the ring, permitting it to function as both an acid and a base. In absence of N1 substitution, imidazole exhibits hydrogen bonding capabilities as a hydrogen bond donor and can also coordinate with metal ions [103]. Imidazole participates in hydrogen bonding, coordination, van der Waal interactions, π-π stacking, cation–π interactions as well as some other interactions too [104]. The importance of this moiety in various drug interactions is because of its existence in purine bases and histidine amino acids [105,106].

Ruzi, *et al.* [107] designed building blocks of substituted imidazole-4-carboxylate derivatives (Fig. 10) and evaluated carcinogenic activity against HeLa, HT-29 and ductus carcinoma cells MDA-MB-231 in which one compound showed good potency against cancerous cells with IC_{50} 0.81, 1.77 and 5.48 in comparison to positive control doxorubicin 0.1, 0.03, 1.1, 0.27 and 0.51. This investigation confirmed that the compound can be a potential pharmacophore for more cytotoxic drug advancement.

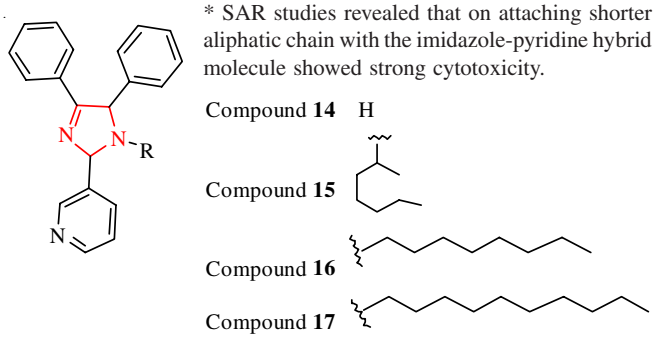


*SAR studies revealed that attachment of larger alkyl chain from 12-15 carbon atom at N-1 position of imidazole ring demonstrates potential inhibition on development and proliferation of selected cell

$R = C_{12}H_{15}$

Fig. 10. General structure of substituted-imidazole-4-carboxylate derivatives

Aruchamy *et al.* [108] prepared novel imidazole-pyridine molecules (Fig. 11) and tested them against Alexander Hepatoma cell line (PLC/PRF/5), liver (HepG2, Human Hepatoma derived cell line (HUH-7), colon cell line (HCT116) and lung carcinoma cell line (H1299) sarcoma cells. Compounds **14**, **15**, **16**, **17** showed good potential against these cancerous cells. IC_{50} of compounds **14**, **15**, **16** and **17** for cell lines PLC/PRF/5, HepG2, HUH-7, H1299, HCT116 were (29.00, 22.49, 31.5, 24.17, 20.40) (9.66, 16.46, 15.50, 29.58, 13.70) (16.74, 17.19, 18.89, 21.59, 9.10) and 19.51, 21.08, 20.73, 16.43, 10.12 as compared to reference compound 5-flurouracil with 29.93,



* SAR studies revealed that on attaching shorter aliphatic chain with the imidazole-pyridine hybrid molecule showed strong cytotoxicity.

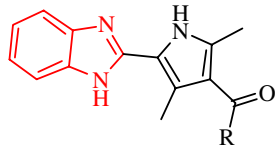
Compound **14** H
Compound **15**
Compound **16**
Compound **17**

Fig. 11. General structure of substituted imidazole-pyridine derivatives

32.73, 19.33, 6.51, 22.30. This study showed that an imidazole-pyridine hybrid moiety may be developed as a selective GSK-3β inhibitor for further anticancer agents.

Benzimidazole moiety: When benzene fused with the imidazole ring at the 4- and 5-positions is structured as benzimidazole moiety. This moiety is completely planer and the proton at N-1 which rapidly exchange the –NH and =N- nitrogen atoms and forms two tautomeric forms. This tautomerism performs as an intermolecular process with two or more benzimidazole rings [109-111].

Rasal *et al.* [112] designed 2,4-dimethyl-1*H*-pyrrole-3-carboxamide derivatives bearing benzimidazole moiety by molecular hybridization approach and investigated the cytotoxic activity of these synthesized derivatives against ovarian, renal, prostate, breast, colon, lung and melanoma cancer lines with an only 10 µm dose. In the determination of cytotoxic activity of these derivatives, compound **13** (Fig. 12) showed prominent activity against many cell lines. This pharmacophore would be delivered as a potential antiproliferative agent in the coming future.



* SAR studies revealed that attachment of substituents at amide linkage enhance anticancer activity also ethyl amine substitution with aliphatic cyclic ring potentiate the antiproliferative activity

Compound **13** R =

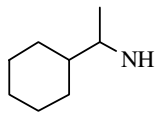
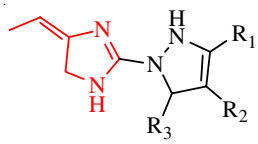


Fig. 12. General structure of substitutedcarboxamide derivatives bearing benzimidazole moiety

Carter *et al.* [113] optimized a benzimidazole pyrazole based scaffold (Fig. 13), which is also known as a Jumonji domain containing lysine demethylase (KDM) enzymes inhibitor and investigated against prostate cancer and after attachment of non-polar substituent to improve antiproliferative property, which will provide compound **14** to 10 times more antiproliferative action against various cell lines and non-cancerous cell (HuPrEC) and having the GI_{50} value in between of 8-26 µM.

Indole moiety: Indole is alternatively referred to as benzopyrrole and its structure consist of benzene atom attached to the 2,3-position of pyrrole moiety. Due to the presence of



* SAR studies revealed that non polor substitution at R_2 postion hances the potency and also attachment with receptor also enhanced

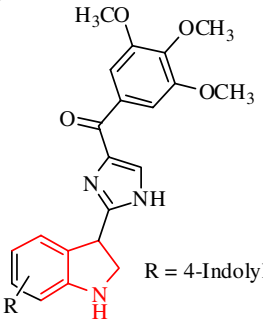
Compound **14**

$R_1 = CH_3$
R_2 = Phenyl ring
$R_3 = OH$

Fig. 13. General structure of substituted benzimidazole pyrazole derivatives

electrons in its pyrrole ring, the structure of this nitrogenous aromatic non-basic heterocyclic ring is benzene as a result of electrophilic substitution. The indole moiety is present in a wide variety of biological compounds, including tryptophan, somatostatin (5-HT) as a neurotransmitter, sumatriptan and melatonin [114-119].

Wang *et al.* [120] designed indole-imidazole molecules (Fig. 14) and investigate their carcinogenic activity as potent tubulin inhibitors, resulting in the development of two highly reactive derivatives compounds having IC_{50} values against A375, M14 and metastatic human melanoma cell line 164 (WM164) are 3.6, 3.7 and 1.6 µm, which is around 2-3 times more potency as compared to positive control colchicine having IC_{50} value 14.1, 16.6 and 10.8. This study recommends the use of this scaffold in future anticancer investigations.

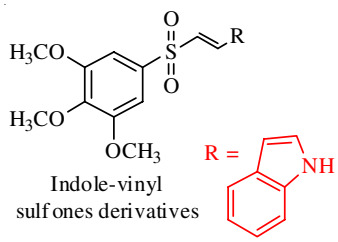


*SAR study demonstrats that on addition of indolyl ring at C-4 of the indole affects the potency of the compound as it reduces the tumor cell growth upto 83% and reduces weight of tumor by 62%

R = 4-Indolyl

Fig. 14. General structure of substitutedindole-imidazole derivatives

Li *et al.* [121] investigated and designed novel indole-vinyl sulphonate (Fig. 15) and evaluate their anticancer activity as novel tubulin polymerization inhibitors against various cancer cells having the standard drug colchicine. Compound **16** showed good potency (IC_{50} value = 3.09 µM) in comparison to standard (2.17 µM). It specifically reduces microtubule polymerization by acting on the tubulin. Also, the selectivity inhibits the microtubule polymerization by attaching tubulin, which blocks the microtubule network and causes the arrest of the cell cycle G2/M phase, promoting programmed cell demise in myelogenous leukemia cell line (K562) cells.



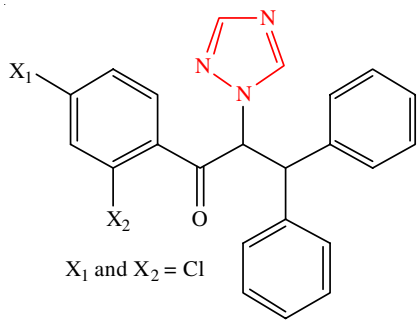
* SAR studies revealed that on attachment of indole ring at R gives highly potent compound with least toxicity as compared to parent molecule.

Indole-vinyl sulfones derivatives

Fig. 15. General structure of substituted indole-vinyl sulphonate derivatives

Triazole moiety: Triazole is a five-membered three nitrogen containing heterocycle ring moiety. This ring system consists two carbon atoms and three nitrogen atoms with three hydrogen atoms in the structure. There are two possibilities of arrangement of nitrogen and the moiety namely 1,2,4-triazole and 1,2,3-triazole. Both arrangements have two tautomers in which the derivatives with 1,2,3-triazole are non-aromatic and hence not useful for biological identification. The existence of three nitrogen atoms in the ring makes 1,2,4 triazole an energy-rich heterocycles. In the biological system, triazole moiety can form weak non-bonding interactions with the various enzymes and receptor proteins and produces the moiety a key pharmacophore for various pharmacological actions [122,123].

Emami *et al.* [124] investigated and designed novel 1,2,4-triazole derivatives and determined their antiproliferative properties against human cancer cell lines MCF-7, Hela and A549 with positive control cisplatin by using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium chloride (MTT) assay method. Compound 1-(2,4-chlorophenyl)-3,3-diphenyl-2-(1*H*-1,2,4-triazol-1-yl)propane-1-one (Fig. 16) and showed good potency against MCF-7, Hela and A549 the cell line with minimum inhibitory concentration (IC_{50}) 4.7, 2.9, 9.4 and normal human fetal lung fibroblast cell line (MRC-5) with IC_{50} 27.8 in comparison to cisplatin with (IC_{50}) 36.5, 12.5, 14.8 and MRC-5 with IC_{50} 45.2. The outcomes of the study indicated that the active derivative can be a lead molecule in the future for searching good anticancer agents.



*SAR study demonstrates that the presence of carbonyl group and on addition of electronegative substitutents at phenyl ring results in inceasing the cytotoxicity of the synthesized compounds

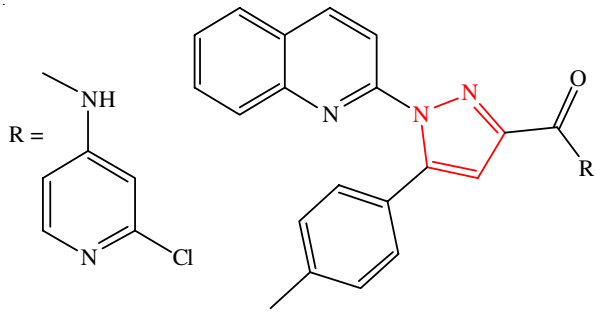
X_1 and X_2 = Cl

1-(Substituted phenyl)-3,3-diphenyl-2-(1*H*-1,2,4-triazol-1-yl)propan-1-one

Fig. 16. General structure of substituted 1,2,4-triazole derivatives

Pyrazole moiety: Pyrazole is a heterocyclic compound characterized by a five-membered ring structure containing two nitrogen atoms and three neighboring carbon positions having chemical formula is $C_3H_4N_2$ [125]. Two nitrogen atoms in an adjacent position make its structure more versatile and highly potent [126].

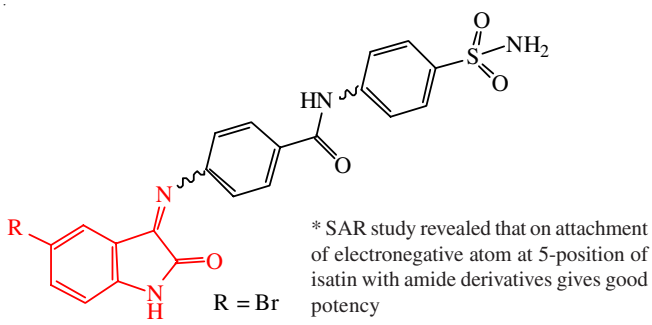
Cancara *et al.* [127] designed and synthesized a series of novel quinoline-containing pyrazole derivatives and evaluated their antiproliferative property against three human cancer cell lines Huh7, MCF7 and HCT116 by sulforhodamine B. One compound having 2-chloro-4-pyridinyl at amide group (Fig. 17) shows good activity with minimum inhibitory concentration (IC_{50}) 1.6, 3.3 and 1.1 in comparison to positive control camptothecin with minimum inhibitory concentration (IC_{50}) 0.04, 0.06 and 0.0015. These results indicated that after some



5-(*p*-Tolyl)-1-(quinolin-2-yl)pyrazole-3-carboxylic acid derivative

*SAR study demonstrates that on attachment of electronegative atom at pyridinyl ring gives high potency to synthesized compounds.

Fig. 17. General structure of amide substituted pyrazole derivatives



Substituted isatin drivatives

* SAR study revealed that on attachment of electronegative atom at 5-position of isatin with amide derivatives gives good potency

Fig. 18. General structure of amide substituted isatin derivatives

modifications in the structure, this drug can be a good anticancer agent in the future.

Isatin moiety: Isatin is also known as indenedione or indole quinine. In its structure, one nitrogen atom present in at position 1 and having two carbonyl groups at positions 2 and 3 (1*H*-indole-2,3-dione). This moiety has two rings one is an aromatic six-membered ring and the other is anti aromatic five-membered and both the rings are planer in nature [128].

Eldehna *et al.* [129] synthesized two series of amido and ureido substituted isatin moiety incorporated with benzenesulphonamide derivatives (Fig. 18) derived from molecular hybridization technique and evaluated against anticancer activity against hCA I, II and XII isoforms. One derivative with bromo substitution 4-(5-bromo-2-oxoindolin-3-ylideneamino)-N-(4-sulfamoylphenyl)benzamide showed potent activity against these isoforms with IC_{50} values 7.9, 7.5, 0.58 in comparison to acetazolamide 250, 12, 5.7. This study revealed that amide-substituted isatin derivatives would be a milestone in the future for the development of new anticancer agents.

Some more examples of *N*-hetero fused compounds that are approved by the Food and Drug Administration (FDA) in the last 8 years for cancer are reported in Table-1.

Conclusion

The information summarized in this article reveals that the nitrogen-containing heterocyclic compounds (pyrimidine, pyridine, carbazole, indole, imidazole, benzimidazole and quinoline) are very important scaffolds and versatile against a variety of cancer. The range of nitrogen-containing heterocyclic compounds is increasing day by day and a lot of analogs recommend a promising route for the discovery of medicines with extensive pharmaceutical applications. This study also reveals that reported nitrogen-containing heterocyclic compounds may be synthesized using innovative synthetic strategies that target different types of cancer. Novel potential derivatives of nitrogen containing heterocycles with additional new plausible targets may be discovered *via* the use of several synthetic techniques that have been shown to be effective against a wide range of cancers.

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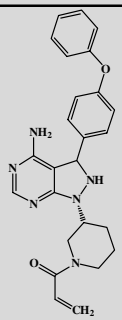
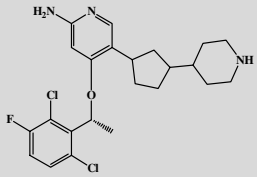
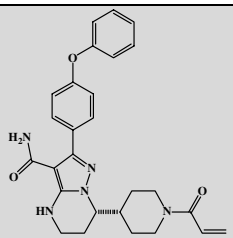
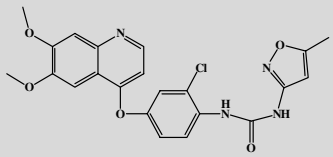
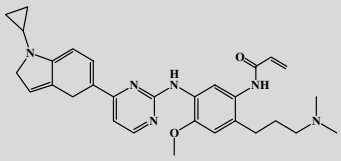
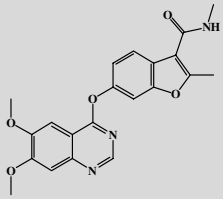
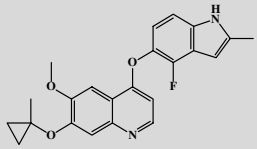
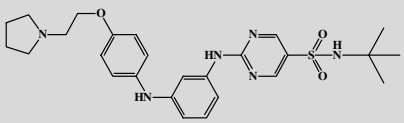
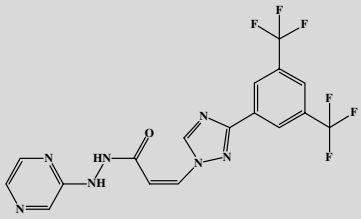
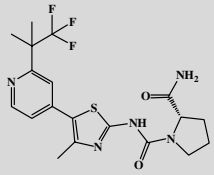
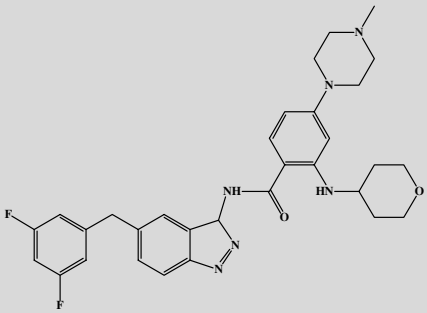
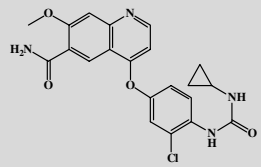
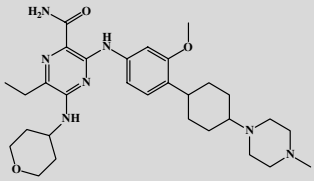
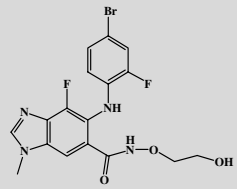
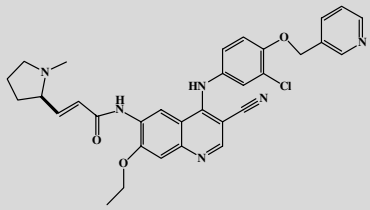
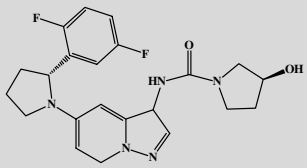
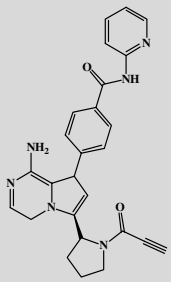
CONFLICT OF INTEREST

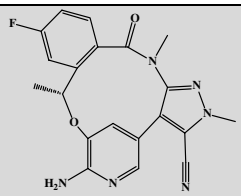
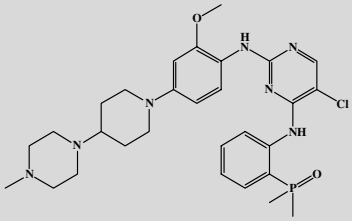
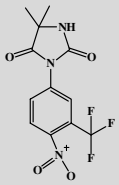
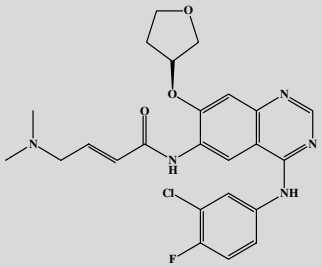
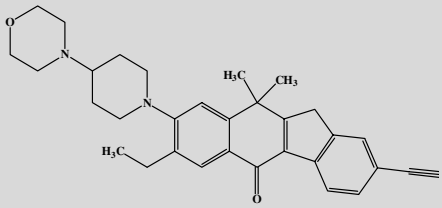
The authors declare that there is no conflict of interests regarding the publication of this article.

TABLE-1
FDA-APPROVED *N*-CONTAINING HETEROCYCLIC DRUGS

Name	Structure	Drug target	Mode of action	Brand name	Year	Ref.
Ibrutinib		Tyrosine kinase	Interact with the target residue (CYs-481) of the enzyme thus obstructing the action of the kinase enzyme	Imbruvicaamong	2022	[130,131]
Crizotinib		An ALK (anaplastic lymphoma kinase) and c-ros oncogene1 (ROS1)	Inhibits the activation of the oncogene proliferation and proteins	Xalkori	2022	[132,133]

Zanubrutinib		A selective Bruton tyrosine kinase inhibitor	Obstruct the formation and development of carcinoma cells and lessens the tumor area	Brukinsa	2021	[134,135]
Tivozanib		Selective vascular endothelial growth factor (VEGF) inhibitors	Inhibits phosphorylation of endothelial growth factor-1,2 and 3 and inhibits tumor growth and progression by stopping the action of platelet-derived growth factor - β (PDGFR β)	Fotivda	2021	[136,137]
Almonertinib		Epidermal growth factor receptor inhibitor (EGFR) tyrosine kinase	Blockstyrosine kinase by targeting T790M resistance mutation and EGFR-sensitizing cells	Ameile	2020	[138,139]
Fruquintinib		Vascular endothelial growth factor (VEGF)-1,2,3	Selectively blocks tubule sprouting and endothelial cell proliferation thus preventing tumor angiogenesis	Elunate	2019	[140,141]
Anlotinib		Vascular endothelial growth factor	Mostly hinder the elongation of tumor cells, enhances apoptosis by seizing the cell cycle by inactivating the VEGF pathway by reducing the phosphorylation levels of all the kinases	Focus V	2020	[142,143]
Fedratinib		Janus Associated Kinase-2 (JAK2) and tyrosine kinase-3	Block phosphorylation and increases apoptotic cell death	Inrebic	2019	[144,145]
Selinexor		Exportin-1 (XPO1)	Binds with suppressing XPO1-protein-Ran-GTP complex formation in carcinoma to suppress the cancer development and enhanceapoptosis in cancerous cells	Xpovio	2019	[146,147]
Alpelisib		P110-α isoform-selective phosphatidylinositol-3-kinase (PI3K)	Blocks Phosphorylation of phosphatidylinositol-3-kinase-α (PI3K-α) and blocks tumor growth and proliferation	Piqray	2019	[148,149]

Entrectinib		ATP competitor and selective inhibitor of tropomyosin tyrosine kinase Trk A B C, Activin-like kinase (ALK), proto-oncogene tyrosine-protein kinase (ROS-1)	Blocks the enzyme and control the proliferation of tumor and apoptosis	Rozlytrek	2019	[150,151]
Lenvatinib		Multiple selective tyrosine kinase inhibitors	Inhibits the activity of VEGF receptor and inhibits cancer progression	Lenvima	2018	[152,153]
Gilteritinib		Selective tyrosine kinase inhibits several kinases such as FLT-3, AXL and ALK	Induces apoptosis in the cancer cells and inhibits unrestricted down streamed signaling and cell proliferation [88]	Xospata	2018	[154,155]
Binimetinib		Mitogen-activated kinase 1 & 2	Blocks phosphorylation of extracellular signal-related kinase (ERK) and also inhibits phosphorylation of BRAF-mutant human melanoma cell lines	Mektovi	2018	[156,157]
Pyrotinib		Irreversible EGFR	Covalently binds with ATP binding sites to block the generation of homogenous/ heterogeneous/ and auto phosphorylation of HER family and blocks tumor development in cancerous cells	Irene	2018	[158,159]
Larotrectinib		Tropomyosin receptor kinase (TRK) kinase inhibitor	Blocks TRK proteins and demonstrates inhibition of cell lines containing genesNTRK1,2 & 3 genes thus blocking cell proliferation causes enhancement in apoptosis [94]	Vitrakvi	2017	[160,161]
Acalabrutinib		Bruton tyrosine kinase	Covalently binds with cysteine residue and decreases BTK action which results in blockage of cell elongation and division in cancerous cells	Calquence	2017	[162,163]

Lorlatinib		Anaplastic lymphoma kinase	Demonstrates cytotoxic action to mutant forms of the ALK enzymes and inhibits phospho-rylation of ALK	Lorbrena	2017	[164,165]
Brigatini		Janus kinase 1 and 2	Blocks phosphorylation of JK-1 and 2 and inhibits signal transduction and activation of transcription (STATs)	Alunbrig	2017	[166,167]
Nilutamide		Androgen receptor	Blocks androgenic receptor and inhibits effects of testosterone and prevents normal androgenic effect in patients [102]	Niandron	2016	[168]
Afatinib		Second-generation tyrosine kinase inhibitor	Inhibits autophosphorylation of tyrosine kinase and results in prevention of regression and growth of tumor	Gilotrif	2016	[169]
Alectinib		Highly selective ALK and RET Tadyrosine kinase inhibitor	Blocks tyrosine kinase and blocks signaling pathway together with STAT-3 and PI3K/AKT and increases tumor cell death	Alecensa	2015	[170,171]

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