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A Review on Azole Derivatives as Potent Anticancer Agents

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Abstract : Cancer a disease where anomalous cells divide irrepressibly and abolish body tissue with potential to invade or extent to other parts of the body which acknowledged as metastasis. Although substantial advancement in chemotherapy, but the delinquent of drug resistance enforced the search of new class of drugs with more efficacy. Azoles are five-membered heterocyclic system displayed numerous pharmacological activity proved the future prospective in pharmaceutical industry. This review summarizes the latest development of azoles as novel chemotherapeutic agents with improved therapeutic competency.
Keywords : Azole, Heterocyclic, anticancer, chemotherapeutic.

1. Introduction

The term cancer exemplifies the uninhibited progression of abnormal cells, conquering into the adjacent tissues, prominent to their obliteration and sometimes metastasis. Currently cancer is the second most lethal disease leading to death in both developing and developed countries[1-2]. Different types of cancers like breast, lung, liver, colorectal and stomach cancers are amongst utmost collective cause of deaths[3]. The use of tobacco led to augmented death above 20% with major risk cause universally around 70% lung cancer death statistics. Within the next few decades, it is expected that figure of yearly deaths due to cancer will raise from 14 million in 2014 to 22 million[4]. Drugs that are presently existing for the treatment of cancer embrace bio-alkylating agents [5,6], antimetabolic agents (fluorouracil) [7,8], antibiotics as anticancer [9],besides complexes from plants and their derivatives[10]. Though, appropriate dosages of anticancer medications to eradicate tumor cells are often lethal to normal tissues, consequently prominent to numerous side effects, which confines the treatment efficiency. Extensive term efficacy is repeatedly limited by dose-related cumulative cardiotoxicity and advancement of acquired drug resistance[11-13]. There is sustained scuffle to exploration of chemotherapeutic agents with new-fangled pharmacological activity, these anticancer agents are still the significant ones in cancer treatment apart from irradiation and surgical possibilities[14]. Progression of new therapeutic agents in treatment of cancer which are more dynamic with fewer side effects with vital proximately. Foremost percentage of all anticancer drugs permitted internationally are either a natural product or their analogues mostly established on the basis of the acquaintance of the pre-existing knowledge of drugs [15]. Recent researches have highlighted the active role of various azole derivatives in the field of anticancer research[16-22]. It has been evidenced that heterocycles possess azole pharmacophore found privileged structure in medicinal chemistry as well as

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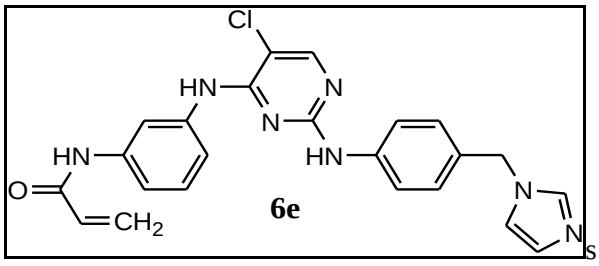
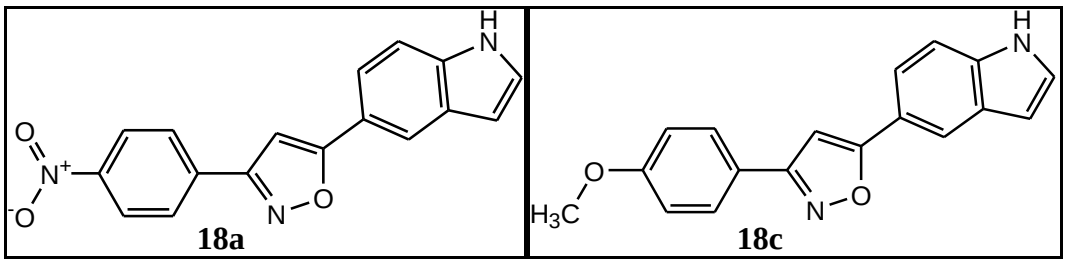
pharmaceutical industry[23-27].Aromatic heterocycles are present in numerous molecules of chemical or biological interest, as well as in organic materials for different applications[28]. On the basis of the existing synthetic approaches and anticancer properties of such heterocycles, this field of research has opened doors for biologists and chemists to design some novel entities with better efficacy through chemical transformations and development of new moieties having broad spectrum therapeutic implications[29-34]. In this review, we highlight some areas of current interest in context to azoles and their derivatives as potent chemotherapeutic agents. An azole is a class of five-membered nitrogen containing heterocyclic compounds with electron-rich property[35]. This distinctive structure and their derivatives effortlessly bind the target proteins and receptors in organisms through non-covalent forces such as van der Waals, electrostatic, hydrogen bonds, coordination bonds and hydrophobic interactions, thus holding several applications in drug discovery[36]. A percentage of chemotherapeutic agents and anticancer therapeutic methodologies are unceasingly in the practice in order to decipher novel drug candidates interacting with the molecular target of various cellular progressions during tumor progression [37-44]. The escalating trend in prevalence different types cancers, the operative therapies are immediately needed to regulate the human malignancies. The discovery of several novel anticancer agents modulates the cancer-specific molecular targets which contributes most in the treatment of cancer patients. Though, virtually most of chemotherapeutic drugs presently in the market roots severe side effects. On the bases of these facts, the designing of novel anticancer agents requires the simulation of a suitable bioactive pharmacophore that should have essential potency and also safer on normal cell than on tumor cells. In existing environment, the main attention of research is to discover new drugs that could be effortlessly accessible, with minor side effects and price effective[45-54]. Azoles and their derivatives fulfill such criteria of broad range of curing numerous diseases[55-60]. Overall, this review paper summaries the recent advancement of background in the cancer with an emphasis on structure activity relationship (SAR) studies which helps to improve the potency of upcoming new moieties. Azoles exemplify vastly resourceful class of heterocyclic compounds that have been widely studied for the credentials of potential anticancer drugs. Some recent developments are highlighted here.Zhendong and coworkers [61] reported a series of novel azole-diphenylpyrimidine derivatives and biologically evaluated as potent $EGFR^{T790M}$ inhibitors, Azoles, particularly the bioisosteric 1,3,4- oxadiazoles, 1,2,4-triazoles, and 1,3,4-thiadiazoles, exhibited successful interactions with particular receptors on enzyme active sites through polar interactions. The most active inhibitor 6e not only displayed high activity against $EGFR^{T790M/L858R}$ kinase (IC_{50} = 3.3 nM), but also was able to repress the replication of H1975 cells harboring $EGFR^{T790M}$ mutation at a concentration of 0.118 lmol/L. In contrast to the lead compound rociletinib, 6e slightly reduces the key $EGFR^{T790M}$-minduced drug resistance. Significantly, inhibitor 6e demonstrates high selectivity (SI = 299.3) for T790M-containing EGFR mutants over wild type EGFR, hinting that it will cause less side effects. The structure activity relationship revealed that compound 6f (IC_{50} = 0.152 lM), which has a fluorine atom at the C-5 position of pyrimidine core, was the most potent inhibitor within this class of inhibitors. When replacing the fluorine atom in compound 6f with a chlorine substituent, the molecule 6e yielded a 5 times increased activity, with an IC_{50} value of 0.733 lM. It was apparent that the most active inhibitors were 6e and 6f, which displayed stronger potency than references against the A431 cells, this exploration provided a promising DPPY derivative 6e featuring a novel azole functionality with enhanced anticancer activity.



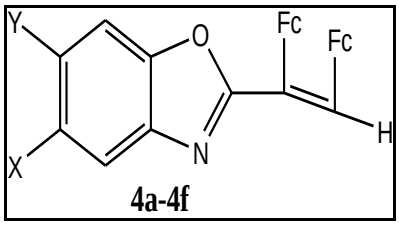
6e

In 2012 Ghani and co-worker[62] reported The solid Pd(II) and Pt(II) complexes of the benzimidazole compound (L) (X ¼Cl, Br, I, SCN and NO3). These complexes showed higher activity against the studied cell lines, especially HepG2. The IC_{50} (the concentration that inhibited in 50% of the cellular proliferation) of these compounds and cis-platin were determined. The palladium complexes are slightly affected by the nature of the anion and the inhibitory activity was found to be in decreasing order as follows: Cl (1) ¼ Br (2) > SCN (4) > I (3) > NO3 (5). It was found that the PdeL (1) complex possesses a moderate antitumor activity and is more toxic than the platinum complex (6). The higher toxicity of PdeL (1) complex than PteL (6) happens because the ligand-exchange behavior of platinum compound is quite slow, which gives them a high kinetic stability and results in ligand-exchange reactions of minutes to days, rather than microseconds to seconds for many other

coordination compounds. In addition, another unusual phenomenon deals with the preferred ligands for platinum ions is that Pt(II) has a strong thermodynamic preference for binding to Sdonor ligands and for this reason, one would predict that platinum compounds would perhaps never reach DNA, with many cellular platinophiles (S-donor ligands, such as glutathione, methionine) as competing ligands in the cytosol. The studied compounds have the capacity of inhibiting the metabolic growth of the investigated bacteria to different extents. In addition, the complexes are toxic against three cell lines of different origin and represent an interesting class of new compounds from the viewpoint of their physicochemical and structural properties. The IC_{50} (mg/ml) values were always twice those of the cis-platin.Tohid and coworkers[63] identified a series of novel indole-containing diarylisoxazoles and the assessment of the in vitro growth inhibitory activity of the new isoxazoles against the Colo320 (colon) and Calu-3 (lung) human cancer cell lines has been carried out using the WST-1 assay. The overall exposure of the cells to a number of compounds from the present series resulted in dose-dependent decrease in cell viability with IC_{50}'s in the low micromolar concentration range. Those with IC_{50} mean values >100 mM were considered to be inactive. The most active compounds were the 5-(1H-indol-5-yl)-3- phenylisoxazoles 18a (R ¼ 4-NO2), 18c (R ¼ 4-OCH3), 18d (R ¼ 4-F), and 18e (R ¼ 3,4,5-tri-OCH3) with growth inhibitory activity similar to that observed for 5-fluorouracil in the Colo320 cells. The cell line data indicated a clear preference for activity in the 5- substituted indole series, with the exception of compound 18b (containing an ester substituent at the phenyl 4-position), which was found to be inactive. It is noteworthy that activity (low micromolar IC_{50}) within the indol-5-yl series appeared to be tolerant of both electron-withdrawing (e.g. nitro) and electrondonating (e.g. methoxy) substituents. Of the 2-substituted indole series, only the 3-(indol-2-yl)-5-phenylisoxazaoles (7f and 14a; containing a methoxyphenyl substituent) showed moderate growth inhibitory activity, particularly in the Calu-3 cell line. Remaining compounds of the 2-substituted indole series were found to be inactive in test assays. The indol-5-yl substituted compounds 18a and 18c were the most active compounds in this assay, with IC_{50} values in the low micromolar range. The 5-substituted indole compounds were furthermore able to induce expression (2-4 fold over controls) of the apoptotic effector enzymes caspase-3 and caspase-7. Further studies on human bronchial smooth muscle cells (BSMC), indicated that the 5-(1H-indol-5-yl)-3-(methoxyphenyl) isoxazoles 18c and 18e had little or no effect on cell viability in this normal cell line control, suggestive of selective pro-apoptotic antitumour effects.

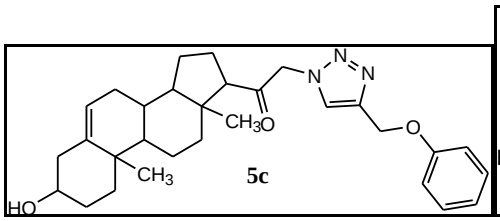


García and coworker [64]reported A novel 2-(Z,E-1,2-diferrocenylvinyl)arenooxazoles 4a-f and 5a-e,3-ferrocenyl-2-ferrocenylmethyl-2-morpholino-2H-areno[1,4]oxazines 7a-f, 20,30-diferrocenyl- 3H-spiro[areno[d]oxazole-2,10-cycloprop[2]ene] 6-f, 2-ferrocenylarenooxazoles 3a-e (4e6%), and 3,4-diferrocenyl-8-hydroxyquinolines 8d-f (ca ~25e30%), they were tested in vitro against six human tumor cell lines: U-251 (glioma), PC-3 (prostate cancer), K-562 (leukemia), HCT-15 (colon cancer), MCF-7 (breast cancer) and SKLU-1 (lung cancer). Primary screening at a fixed concentration showed cytotoxicity against the six tested human tumor cell lines Bicalutamide at the same concentration was used as the positive control. The compounds were used as 50 mM solutions in DMSO. Compounds 4a/5a and 4e/5e which contain the benzoxazole moiety, appeared to be the most active against three human tumor cell lines: K-562, MCF-7, SKLU-1. Compound 4a/5a, 4e/5e and 6a exhibited the highest activity against the HCT-15 and SKLU-1 tumor cell lines vs. bicalutamide, which was used as reference. These results identified diferrocenyl(areno)oxazoles as new possible candidates for antitumor chemotherapy. Our study suggests that further exploration of the potential of these candidates is required in order to discover and develop better and safer therapeutic antitumor agents. The reactions described in this study will be of interest to synthetic, theoretical and experimental organic chemists looking to obtained a variety of functionalized ferrocenyl compounds.

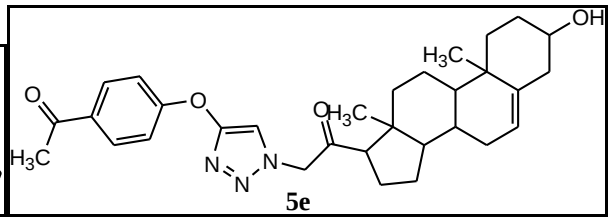


4a-4f

Bandaya and coworkers[65] reported the synthesis of a series of novel D-ring substituted 1,2,3-triazolyl 20-keto pregnenane, All the compounds were assayed for in vitro cytotoxicity against a panel of seven human cancer cell lines including DU-145, PC-3 (prostrate), SF-295 (CNS), HCT-15, 502713 (colon), HEP-2 (liver) and A-549 (lung) using Sulforhodamine B. From the IC_{50} values, it is clear that all the compounds have significant cytotoxic activity against prostrate, CNS, colon and liver derived cancer cell lines. However, it may be noted that these compounds showed comparatively highest activity against DU-145 and PC-3, both prostrate derived cancer cell lines. Compound 5e, with p-methoxy-substitution on benzene part, showed significant cytotoxicity against DU-145, PC-3, SF-295, HCT-15 and 502713 cell lines but it was found to be the most active against PC-3 cell line with IC_{50} value 0.03 at 106Mconcentration. Compounds such as 5a, 5b, 5c, 5g and 5h were also found to have promising activity against the above mentioned cell lines. From the IC_{50} values, it is clear that steroid derivatives with basic nitrogenous heterocycles are potential antitumor agents with profound activity against prostate cancer cell lines. The compound 5e was found to be the most active in this study especially against DU-145 and PC-3 cell lines.

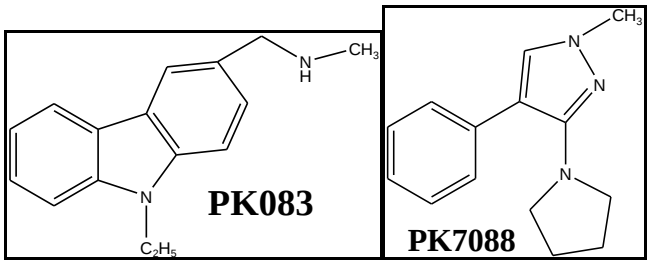


5c

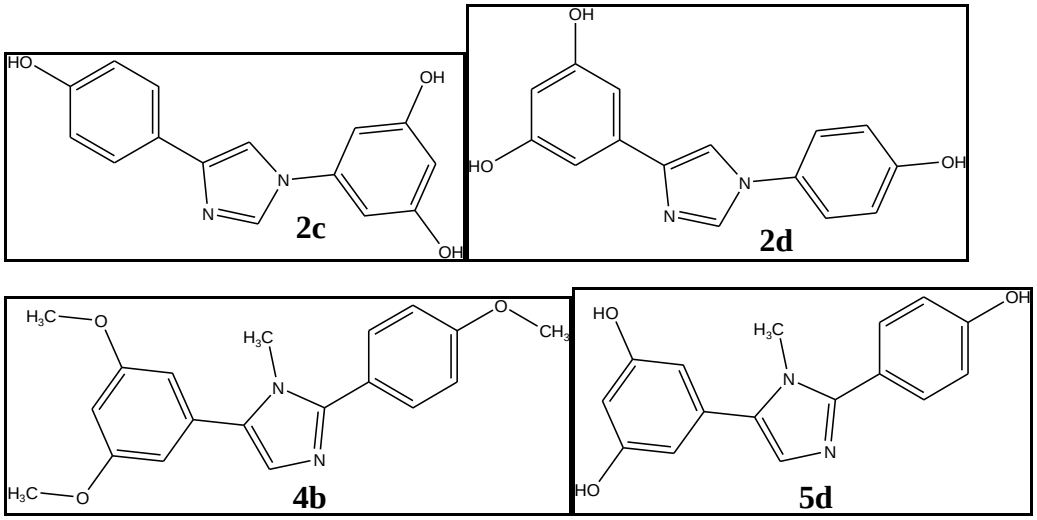


5e

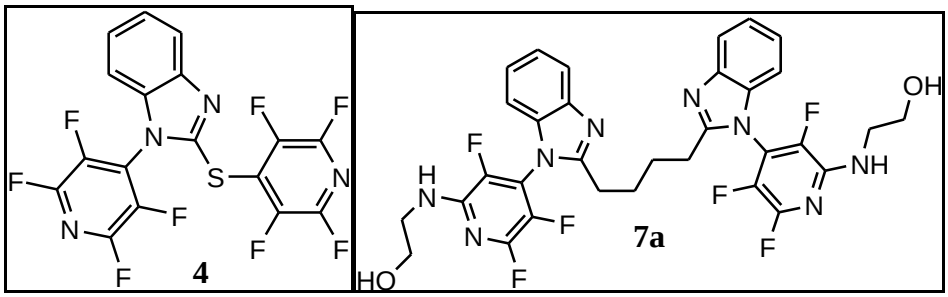
Baud and coworker[66] reported anticancer activity of aminobenzothiazole derivatives, the experiment was performed on cancer cell lines containing p53 WT (NUGC4, HUH-6), mutant p53 (NUGC3,HUH-7, SW1088, BXPC-3), and a non-cancerous fibroblast cell line (WI38). The N-ethylcarbazole derivative PK083 (1) binds to the Y220C pocket with a dissociation constant (Kd) of 140 μM, increases the thermos stability of the mutant protein and slows down its aggregation in vitro. The pyrrole-substituted pyrazole derivative PK7088 (2) binds with a similar affinity and displays promising cellular activity in cancer cell lines carrying the Y220C mutation, e.g., induction of caspases and upregulation of p53 target genes PUMA and NOXA. However, relatively high concentrations of the compound (up to 200 μM) are required to observe these effects, and the possibility of off-target effects contributing to the observed response cannot be ruled out completely. A biophysical screen of a halogen enriched fragment library identified the 2-iodophenol moiety as a potent scaffold to target the Y220C pocket. Binding of 3 and other iodophenol derivatives is driven by a strong halogen bond between the iodine atom and the carbonyl oxygen of Leu145.33 Targeting additional subsites of the binding pocket led to the development of PK5196 (3), which displays a Kd of 10 μM and raises the Tm of the protein by almost 4 °C under saturating conditions. Although compounds 1-3 and derivatives stabilize Y220C, their modest affinities as well as issues of stability or toxicity (e.g., flatness or relatively unstable acetylene groups) have hampered biological studies and their potential use as drug candidates. Improving the affinity of future lead compounds, in addition to tuning of their physicochemical properties, will therefore be crucial for fully exploiting the therapeutic potential of small-molecule stabilizers of Y220C in cancer cells. The aminobenzothiazole derivative selectively reduced viability of Y220C-mutated cell lines, NUGC3, BXPC-3 and HUH-7, which correlated with selective upregulation of proapoptotic and cell cycle arrest p53 target genes BTG2, p21, PUMA, FAS, TNF, and TNFRSF10B in NUGC3.



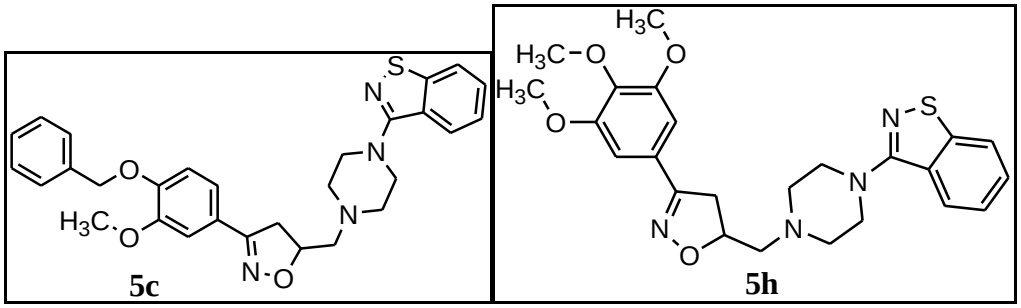
Bellinaa and coworker[67] reported the syntheses of 1,4-, 2,4- and 2-5-diarylimidazoles, in which the two aryl moieties are linked to the heteroaromatic core in a 1,3 fashion in order to preserve the trans stereochemistry, have been successfully carried out by regioselective sequential transition metal-catalyzed arylations of simple, commercially available imidazole precursors. The anticancer activity of selected analogues has been evaluated in vitro against the NCI 60 human tumor cell lines panel. the chemical structures of compounds 2a-d, 3a-d, and 4a-d were screened for different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. The bioisosteric replacement with an imidazole core of the double bond of resveratrol provides a means to increase the anticancer activity in vitro against the NCI 60 human cell lines panel, but also that this improvement deeply depends on the relative position of the two aryl rings on the azole scaffold. the 1,4-diaryl substituted imidazole 2d had higher cytotoxic activity against all the nine types of human tumor cells significantly more potent than its regioisomer 2c. Moreover, we also found that the presence of the 4-hydroxyphenyl and 3,5-dihydroxyphenyl moieties is, on its own, not enough to secure a good bioactivity. This is clearly evidenced by a comparison of the results scored by compounds 4d and 4b.



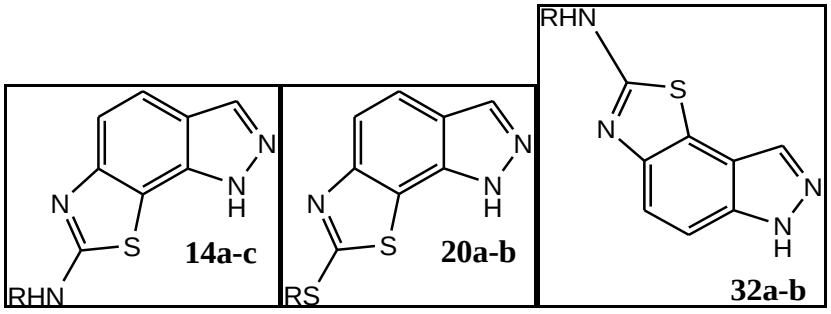
Bhambra and coworker[68] reported the synthesis of fluoroaryl benzimidazoles. The anticancer activities of all new compounds were determined against several breast carcinoma MCF-7 and leukemia K562 cell lines after 72 h of incubation using the Calcein assay, and the CDK inhibitor, roscovitine, as a control compound. Compounds 4, 6, 7d and 8a display cytotoxicity in which IC_{50} values reached low micromolar ranges. These four compounds were further screened against melanoma G361 and osteosarcoma HOS cell lines to expand information about selectivity towards various types of cancers. Concentration-dependent activity was observed in all cases with these four compounds. Three of the active compounds contained the tetramethylene bis-benzimidazole linker group 5 with tri- or tetrafluorinated pyridine rings, whilst the smaller molecule 4 also contains two fluorinated pyridine rings, separated by the benzimidazole ring. This suggeststhat two fluorinated pyridine rings separated between 4-6 Å is desirable for activity. Initial studies have shown possible interaction with double-stranded DNA.



Byrappa and coworker[69] reported the Synthesis of 3-(4-((3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl)piperazin-1-yl)benzoisothiazole derivatives (5a-i), which constitute a new class of isoxazolines, has been accomplished in regio-selective manner. These derivatives have been prepared by employing the reaction between substituted aldoximes (4a-i) and 3-(4-Allylpiperazin-1-yl) benzoisothiazole in presence of chloramine-T which afforded in good yields. In our present study, four out of nine compounds showed potent pro-apoptotic activity in the EAT tumor model, which was assessed by both trypan blue dye exclusion assay and AO/EtBr dual staining, which was on par or better than the rTRAIL induced apoptosis. In terms of the identification of potent and selective activity in MDA MB 231 breast cancer cell lines, the compounds 5c, 5g and 5e exhibited high cytoxicity. Compounds 5b, 5d and 5a showed intermediate activity and compounds 5f, 5i and 5h were weakly cytotoxic. From the experimental results it is evident that compound 5f and 5i show negligible cytotoxic activity and compounds 5c, 5b, 5e and 5g are cytotoxic and induce apoptosis and this may be due to the substitution of benzyloxy group at the para position as in 5b, which shows good apoptotic activity and by inclusion of methoxy group at meta position with benzyloxy group as in 5c, results in increased rate of apoptosis compared to 5b. When the benzyloxy group is replaced to Meta position (5e), we observed a decrease in the activity compared to 5b and 5c. But in the absence of benzyloxy group's compounds (5a, 5f, 5d and 5h) lose their apoptosis inducing ability and the presence of fluorine group (5i) at para position decreases the activity drastically.

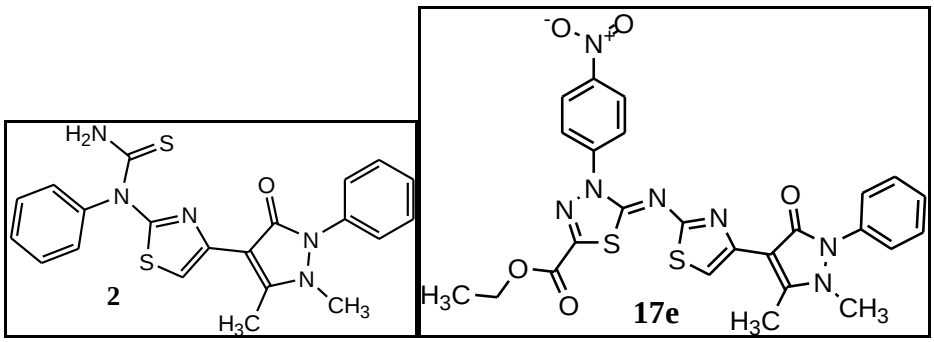


Chakrabarty and coworker[70] reported the synthesis of novel 2-alkylamino- and 2-alkylthiothiazolo[5,4-e]- and -[4,5-g]indazoles and their 6-alkyl and 8-alkyl derivatives. Seven thiazole indazoles, viz. 5a,14a–c,18a and 30a,bwere tested at 25, 50 and 100 mmol solutions in DMSO for anticancer activity against human lung carcinoma A549 cell line at using the methyl thiazolyl tetrazolium bromide assay (MTT).25 The experiments were done in triplicate. The results (Table 1) revealed that at 25 mmol concentrations, the screened products showed weak to moderate (ca. 29–72%) inhibition with respect to control, i.e., DMSO. Of these, 14c appeared to be more effective.

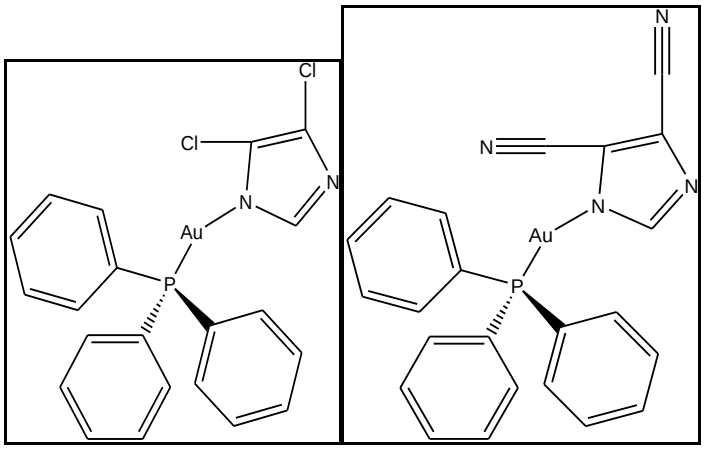


Dawood and coworker[71] reported the Synthesis of Some New Pyrazole-based 1,3-Thiazoles and 1,3,4-Thiadiazoles as Anticancer agents. N-(4-(Pyrazol-4-yl)thiazol-2-yl)-N´-phenylthiourea derivative 2 was

synthesized and then treated with variety of hydrazonoyl chlorides under basic condition at reflux to afford the corresponding 2- (4-(pyrazol-4-yl)thiazol-2-ylimino)-1,3,4-thiadiazole derivatives 6, 10a-e and 17a-e. Reaction of 2 with ethyl chloroacetate and with 3-chloro-2,4-pentanedione gave the thiazolidin-4-one 22 and 1,3-thiazole 25 derivatives, respectively. Condensation of thiazolidin-4-one 22 with aldehydes gave their 5-arylidene derivatives 23a-f. Most of the synthesized compounds were tested for anticancer activity against human hepatocelluar carcinoma HepG2, human breast cancer MCF-7 and human lung cancer A549. Their SAR was studied and variously affected by the electronic factor of electron donating and withdrawing groups. Compounds 2, 6, 10a-e, 17a-e, 22 and 23a-f were tested for their in-vitro antitumor activity against human hepatocellular carcinoma cell (HepG2), human breast cancer cells (MCF-7) and human lung cancer cells (A549). Doxorubicin was used as a reference standard and among the test compounds, compounds 2 and 17e were the most potent pyrazole derivatives, displaying IC50 values of 8.438 and 8.107 uM respectively compared to reference standard. Concomitantly, thiazolylpyrazole derivatives 17d and 23d showed equipotent anticancer activity against HepG2 of IC50 values 12.91 and 13.17 uM, respectively. Also, compound 23f exerted appreciated activity of IC50 16.65 uM. Further, 10c and 10d displayed pronounced activity, affording IC50 31.66 and 41.25 uM respectively. On the other hand, pyrazole derivatives 10a, 22 and 23a showed mild activity against HepG2 (IC50; 67.11, 70.49 and 63.42 uM, respectively). Finally, human hepatocellular carcinoma cells, HepG2 showed resistance for the rest of the test compounds.

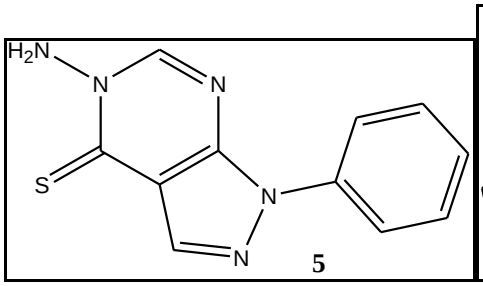


Recently Gambini and coworker [72] reported the In vitro and in vivo studies of gold(I) azolate/phosphane complexes for the treatment of basal like breast cancer. seven gold(I) azolate/phosphane compounds were evaluated in vitro by MTT tests in human MDA-MB-231, human mammary epithelial HMLE cells overexpressing FoxQ1, and murine A17 cells as models of BLBC. Two compounds, (4,5- dichloro-1H-imidazolate-1-yl)-(triphenylphosphane)-gold(I) 1 and (4,5-dicyano-1H-imidazolate-1-yl)-(triphenylphosphane)-gold(I) 2 were found very active and chosen for an in vivo study in A17 tumors transplanted in syngeneic mice. The compounds resulted to be more active than cisplatin, less nephrotoxic and generally more tolerated by the mice. This study also provides evidence that both gold(I) complexes inhibited the 19S proteasome-associated deubiquitinase USP14 and induced apoptosis, while compound 1's mechanism of action depends also on its ability to down-regulate key molecules governing cancer growth and progression, such as STAT3 and Cox-2.



Compound 1 **Compound 2**

Ghorab and coworker [73] studied anticancer activity of pyrazolo[3,4-d]pyrimidines. A new series of pyrazolo[3,4-d]pyrimidine derivatives were synthesized and tested for in-vitro anticancer activity against Ehrlich Ascites Carcinoma (EAC) cell line. Moreover, one of the target products was evaluated for in-vivo radioprotective activity. Doxorubicin, the reference drug used in this study, is one of the most effective antitumor agents used to produce regressions in acute leukemias, Hodgkin's disease and other lymphomas. The relationship between surviving ratio and drug concentration was plotted to obtain the survival curve of Ehrlich Ascites Carcinoma (EAC) cell line. The response parameter calculated was IC_{50} value which corresponds to the compound concentration causing 50% mortality in net cells.



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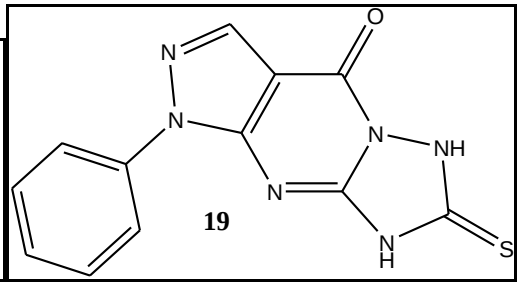
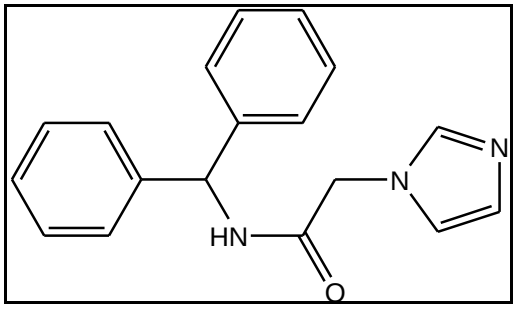


19

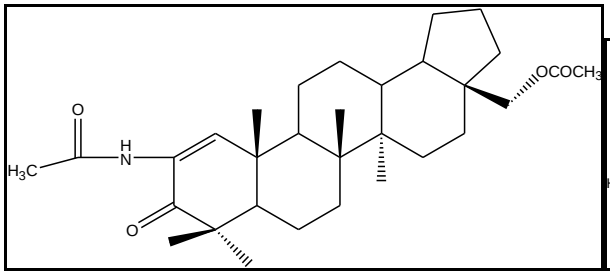
Greish and coworker [74] reported a new azole-based HO-1 inhibitors was reported, using compound 1 as a lead compound, in which an imidazole moiety is linked to a hydrophobic group by means of an ethanolic spacer. compounds 2–4, and the in vitro anticancer activity profile of a previous compound synthesizedcompound 1. Differently to molecule 1, which is one of the most potent/selective HO-1 inhibitors known to date with sub-micromolar inhibitory activity against HO-1 and moderate activity against HO-2 (HO-1 IC_{50} = 0.4 M, HO-2 IC_{50} = 32.0 M), the new compounds 2–4 were still active but possess IC50 values in the micromolar range, IC_{50} = 80, 28.8, and 67.6 M, respectively. Compound 1 showed the most interesting results for melanoma (B16 IC_{50} = 42 M) and hormone-sensitive cell lines (MCF-7 IC_{50} = 52.55 M) when compared to hormone-resistant (MDA-MB-231 IC_{50} = 82.60 M) and showed certain selectivity towards normal cells. Moreover, combination of compound 1 and doxorubicin give synergistic activity in melanoma cell lines. Finally, considering the micelles formulation as an efficient way to solubilize/carry hydrophobic drugs and an elegant example of supramolecular structures for its use in drug delivery and as smart systems for efficient targeting, a nanomicellar formulation was synthesized for compound 1. The formulation was also tested for its cytotoxicity with reduced cytotoxic activity.



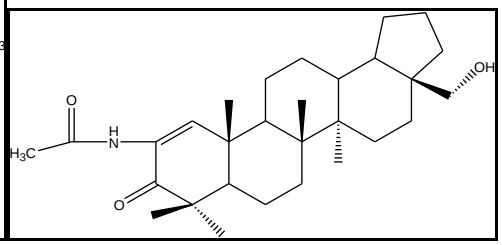
3

Grishko [75] reported novel ring-A fused heterocyclic derivatives of botulin to betulone used as the key compound to synthesize the substituted azoles such as C(2)-C(3)-fused 1,2,3-triazoles, oxazoles and 1,2,4-triazine, as well as C(1)-C(2)-fused isoxazoles. The semi-synthetic compounds were screened for their cytotoxic activity against human cancer cell lines A549, HCT 116, HEp-2, MS and RD TE32 with use of the photometric MTT assays. Among the tested compounds, N-acetyltriazole of botulin (10) displayed impressive cytotoxic activity with IC_{50} 2.3e7.5 mM against HCT 116, HEp-2, MS and RD TE32 cell lines as well as 3-methyl-4-oxido-1,2,4-triazine-derivative of betulonic acid (12) that was active against HCT 116 and HEp-2 cell lines with IC_{50} 1.4 and 1.5 mM, respectively. Comparative experiments showed triazole (10) to have a lower cytotoxicity to normal epithelial cells, in comparison with compound (12). In accord with the in vivo acute toxicity test, the LD_{50} of triazole (10) exceeded 600 mg/kg. The ability of the most potent active triazole (10) to trigger apoptotic cell death was explored in the Annexin V-FITC test and by analyzing of caspase activity and morphological alterations in mitochondria and nuclei of HCT 116 cells. According to the SAR analysis, heterocyclic

triterpenoids with C(2)-C(3)-fused N-acetyltriazole fragment associated with 28-hydroxyl or 28-carboxyl moiety were more toxic against tested human cancer cell lines among the synthesized azoles, whereas HCT 116 cells were more sensitive to the synthesized compounds. By the example of N-acetyltriazole of betulin (10) featured by most cytotoxic activity against tested cancer cell cultures, the ability of lupane triazoles to induce early apoptosis in cancer cells by activation of caspases 8 and 3/7 was shown. Despite a lack of detectable caspase-9 activity, morphological alterations in the mitochondria of HCT 116 cells were registered.

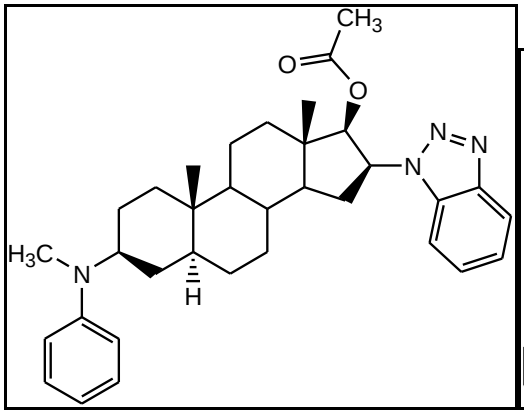


3

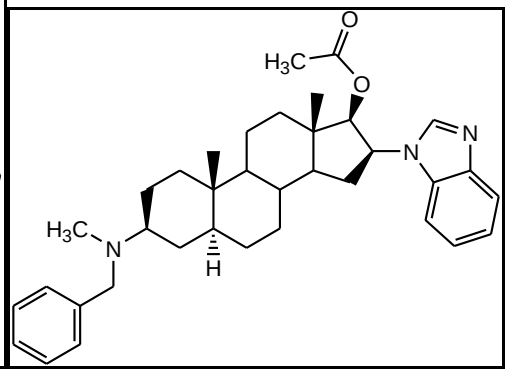


6

Guo and coworker [76] reported a series of new 16b-azolyl-3b-amino-5a-androstane derivatives, The newly synthesized compounds 16aeg, 17aeg, 18aeg, 19aeg were evaluated for their anticancer activities against human cancer cell lines derived from various human cancer types, including HeLa (human cervical cancer cells), SW480 (human colon adenocarcinoma cells), A549 (human lung carcinoma cells), HepG2 (human hepatic carcinoma cells) and SiHa (human cervical cancer cells). 293 (human embryonic cells) is non-cancer cell line. In vitro evaluation of the anticancer activities of the synthesized compounds was carried out using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Doxorubicin was employed as the positive control. The anticancer potency of these compounds was indicated by IC_{50} values that were calculated by linear regression analysis of the concentration response curves obtained for each compound. anticancer activities against all the tested cells. Six of the twenty-eight new compounds showed strong anticancer activities against more than three cell lines (IC_{50}< 20 mM). Compounds 18f and 19g were the most promising compounds amongst the tested derivatives, with IC_{50} values of 5.12-18.63 mM and 4.22-15.76 mM, respectively.



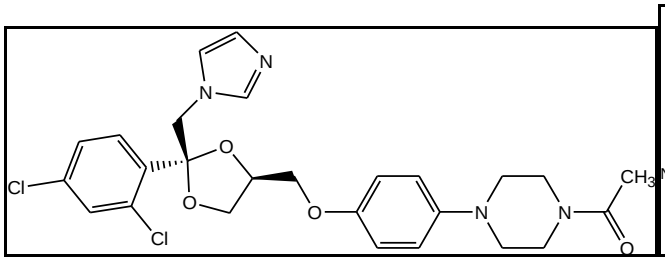
18f



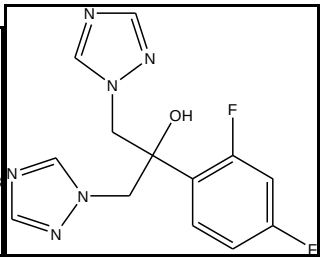
19g

Gupta and coworker [77]reported the interactions of azole antifungal agents, ketoconazole, itraconazole, fluconazole, and voriconazole, with BCRP. First, the effect of the azoles on BCRP efflux activity in BCRP-overexpressing HEK cells was determined by measuring intracellular pheophorbide A (PhA) fluorescence using flow cytometry. We found that keotoconazole and itraconazole significantly inhibited BCRP-mediated efflux of PhA at low mM concentrations. However, fluconazole only mildly inhibited and voriconazole did not inhibit BCRP efflux activity at concentrations up to 100 mM. The IC50 value of ketoconazole for inhibition of BCRP-mediated PhA efflux was 15.36.5 mM. Ketoconazole and itraconazole also effectively reversed BCRP-mediated resistance of HEK cells to topotecan. When direct efflux of [3H]ketoconazole was measured in BCRP-overexpressing HEK cells, we found that [3H]ketoconazole was not transported by BCRP. Consistent with this finding, BCRP did not confer resistance to ketoconazole and itraconazole in HEK cells. Taken together, ketoconazole and itraconazole are BCRP inhibitors, but fluconazole and voriconazole are not. These results

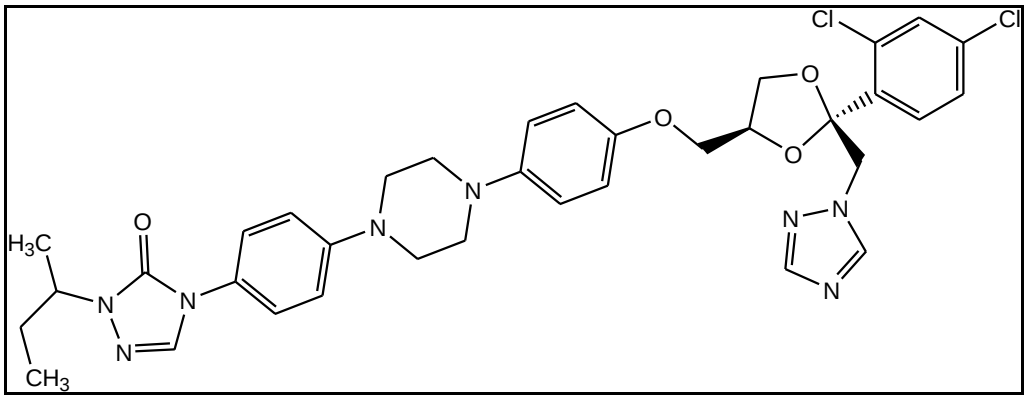
suggest that BCRP could play a significant role in the pharmacokinetic interactions of ketoconazole or itraconazole with BCRP substrate drugs.



Ketoconazole

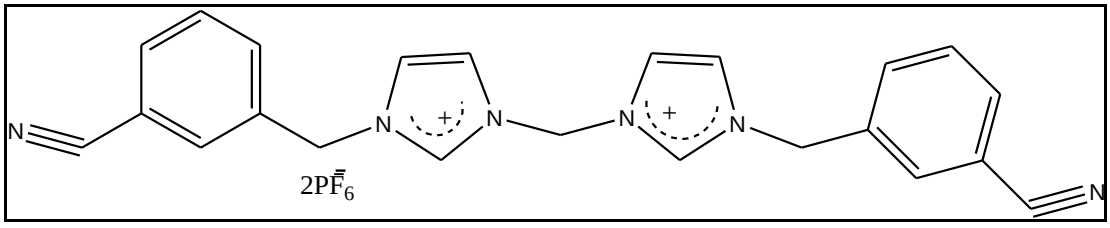


Fluconazole



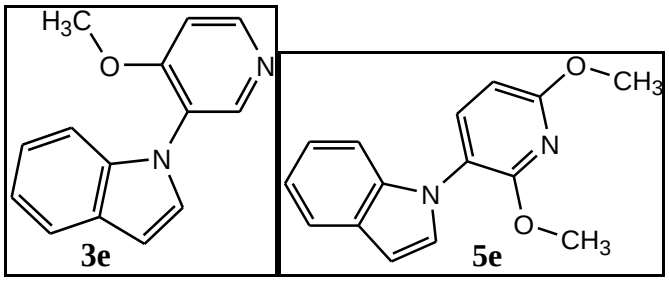
Itraconazole

Haque and coworker [78] reportedthe promising anticancer potentials of silver(I)–NHC complexes against HCT 116 and MCF-7 cancer cell lines, the reported imidazolium salts and corresponding silver complexes have been studied for their anticancer abilities using MTT assay [22,23]. The surviving cells were determined by measuring their ability to reduce the yellow dye 3-(4,5-dimethyl-2-thiozolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to a purple formazan product. Though the unsymmetrically substituted salt 1 exhibited least activity (IC50 value of N200 μM) towards HCT 116 cells, its symmetric version, salt 2, displayed moderate activity with the IC50 value of 20.3 ±0.2 μM. However, treatment of salt 1 with HCT 116 cells showed an insignificant inhibitory effect on proliferation as the growth and morphology of the cells were unaltered with respect to that of the negative control. In the case of salt 2, the viability of the HCT 116 cells was severely affected, showing a moderate anti-proliferative effect. The silver(I) complexes 4 and 5 exhibited significant anticancer potential against HCT 116 cells with the IC50 values of 6.0 ± 0.2 and 14.0 ± 0.6 μM, respectively. Specifically, complex 4 displayed a strong anti-proliferative activity in culture, which is nearly equal to the potential of the standard used (5-fluorouracil IC50=5.2±1.0 μM). The treatment of complex 4 reduced the doubling time of HCT 116 cells drastically so that the population of cells decreased significantly when compared to the negative control. While the photomicrograph of the cells treated with complex 5 illustrated a significant anti-proliferative effect of the complex. The cells showed marked signs of cytotoxicity caused by affecting the cellular morphology and viability.

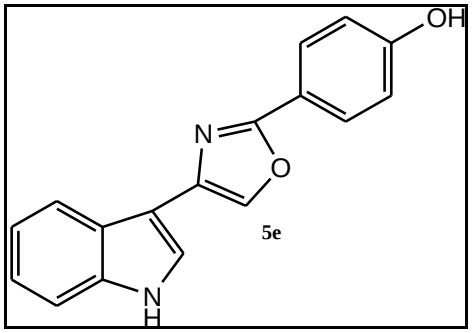


Hedidi and coworker [79] reported the N-Arylation of pyrrole with 3-iodo-4-methoxypyridine, The antiproliferative activity of N-pyridyl azoles was studied in the A2058 (ATCC-CRL-11147) cell line. A2058 are highly invasive human epithelial adherent melanoma cells, derived from lymph nodes metastatic cells

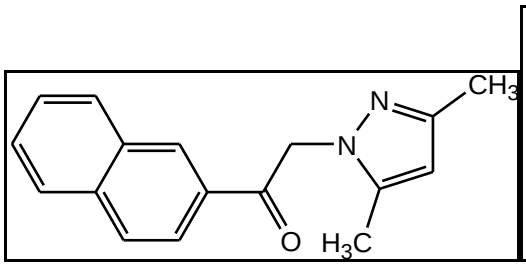
obtained from a 43 years male patient. They are tumorigenic at 100% frequency in nude mice, andconsidered as very resistant to anticancer drugs blue formazan salt for 4 h.



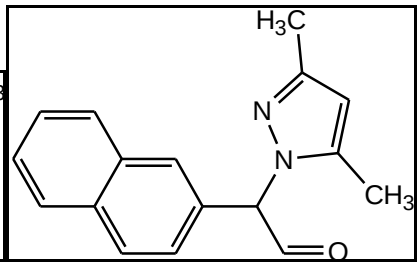
Kumar and coworker [80] reported the series of 4-(30-indolyl)oxazole congeners have been synthesized and studied for their cytotoxicity against six cancer cell lines. A series of indolyl oxazoles 5a–m, 8–12 were screened against prostate (PC3, DU145 and LnCaP), breast (MCF7 and MDA231) and pancreatic (PaCa2) cancer cell lines. The human cancer cell lines. screened were cultured in RPMI 1640 medium containing 5% fetal bovine serum. The compound 5d is active against all the cancer cell lines, suggesting that p-fluorophenyl at C-2 position is beneficial for the activity. Alkylation of indole nitrogen improved the activity, however, p-chlorobenzyl as an alkylating group is preferred over methyl (10 and 11). The compound 11 with N-(p-chlorobenzyl) and C-2 p-chlorophenyl moiety is potent and showed selective cytotoxicity against MCF7 (14.1 mM) and PaCa2 (26 mM) cell lines. Substitution at C-2 position of oxazole ring is important for the activity as compound 5k without any substituent exhibited very poor activity. In general, an aromatic/heteroaromatic ring with an electronegative atom at C-2 position is beneficial for the activity. The compound 5l with C-2 ethenyl moietywas found to be active against DU145 (59.8 mM) and PaCa2 (37.6 mM) cell lines. Introduction of a p-methoxyphenyl group at C-2 position (compound 5j) showed selective cytotoxicity against MCF7 (43.8 mM) and PaCa2 (35 mM) cell lines. However, an additional electron-donating group at the meta position in C-2 aryl ring (compounds 5c, 5m and 12) is detrimental for the activity. Compounds 8 and 9 with a piperidinyl ring at C-2 also exhibited poor activity.



Kumar and coworker [81] reported the synthesis and biological evaluation of some 2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-arylethanones, The novel agents were first screened against colon cancer cell line HCT116 and HT29, prostate (DU145), and ovarian (SKOV3) cancer cell lines. Cells were treated with various concentrations (0, 0.5, 1, 2.5, 5, 10, 25 and 50 μM) of the compounds for 48h , compound 4j was found to be cytotoxic to colon and prostate cancer cells, with relatively more pronounced efficacy towards colon cancer cells (Fig. 6) in 72h cell viability assay. The % cell viability of different cancer cell lines in presence of increasing dose of 4j clearly shows it to be more effective in colon cancer cells, as compared to prostate and ovarian cancer cells. Since, pyrazole derivatives have been particularly shown to be effective against lung cancer [13-15, 18], we also evaluated the anticancer activity of 4a, 4c, 4j and 4k against human lung adenocarcinoma epithelial cell line A549 and compared their cytotoxicity with clinically used carboplatin. Compounds 4j and 4k were equally effective as carboplatin in inhibiting A549 cell viability

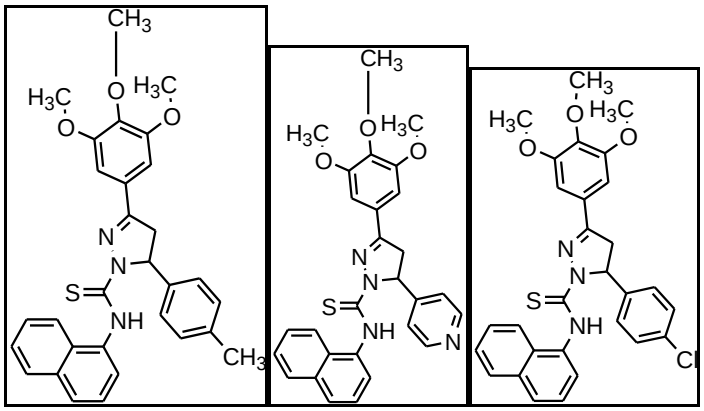


4j



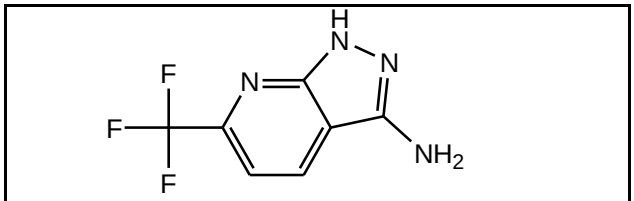
4k

Labib and coworker [82] reported the synthesis of three series of azole-hydrazone derivatives namely, benzimidazole, benzoxazole and benzothiazole. The target compounds 3a-m were evaluated for their in vitro cytotoxic activity against two human cell lines, a breast cancer cell line (MCF-7) and a liver cancer cell line (Hep G2). Both erlotinib and 5-fluorouracil (5-FU) were used as reference drugs for MCF-7 and HepG2, respectively. Most of the tested compounds showed potent activity when compared to the reference drugs. Concerning MCF-7 cell line, the most potent compounds were benzoxazole derivative containing 4-chlorophenyl moiety 3h and benzimidazole hybrid with 4-hydroxyphenyl part 3a with IC50 =0.067 and 0.074 lM, respectively if compared to erlotinib, the reference drug (IC_{50} = 0.74 lM). The activity of the compounds was extended to benzoxazole 3g and 3i and benzimidazole 3d derivatives bearing electron donating groups on phenyl ring such as 4-methoxy group 3g and 4-dimethylamino group (3i and 3d) with IC_{50} = 0.38, 0.46 and 0.47 lM, sequentially. Moreover, high lipophilic character of electron withdrawing group such as (Cl) with benzimidazole ring 3c and less lipophilic electron withdrawing group (NO2) with benzothiazole scaffold 3m afforded potent compounds with IC_{50} = 0.5 and 0.73 lM, respectively. Moderate activity was observed in both benzimidazole derivative 3b (IC_{50} = 0.81 lM) and benzothiazole derivatives 3k (IC_{50} = 0.89 lM) and 3l (IC_{50} = 0.92 lM). Benzimidazole 3e, afforded less active compounds IC_{50} = 1.76 and 3.27 lM, in the same order. On the other hand, benzoxazole bearing 4-hydroxyphenyl moiety 3f showed weak cytotoxic activity against MCF-7 cell line (IC_{50}= 4.13 lM), The most potent compounds 3h and 3l against MCF-7 and HepG2 cell lines, respectively were further evaluated for EGFR inhibitory activity. EGFR was treated with 10 lM of the compounds and reference erlotinib. The most active 3h on EGFR was then screened for HER2 and VEGFR enzymes inhibitory activity. The % inhibition was 92.46% and 76.54%, respectively. Cell Cycle analysis, apoptosis, caspase-3, caspase-9 and gene expression of Bax and Bcl-2 were performed on the most active compounds 3h and 3l. Molecular docking study was used to explore the mode of action of the synthesized compounds inside the active site of EGFR kinase enzyme.Lu and coworker [83] reported a new series of pyrazoline analogs was furnished and evaluated for their in vitro anticancer efficacies against human non-small-cell lung cancer cell line A549. Claisen–Schmidt condensation between intended acetophenone compound and different substituted aldehydes resulted in the formation of corresponding chalcones which were cyclized using hydrazine hydrate to yield the final pyrazoline intermediates. a-Naphthyl isothiocyanate was prepared from benzoyl chloride anda-naphthyl amine through a-naphthyl thiourea to react with pyrazoline intermediates to furnish title compounds 10a–h, disubstituted pyrazolines in good yields and purity. All final analogs were screened for their anticancer potential using MTT and SRB assay in addition to the determination of their cytotoxic nature. Final compounds revealed a good deal of potential against A549 cell lines with reasonable level of cytotoxic nature, particularly analogs with fluorine and thiomethyl and methoxy functional group demonstrated good potencies. SAR showed that the activity level varied with the variation in the nature of substituent present on the phenyl ring attached to the C-4 position of the pyrazoline ring. This study revealed the efficacies of presented molecules for further development as anticancer congeners.



10b **10f** **10g**

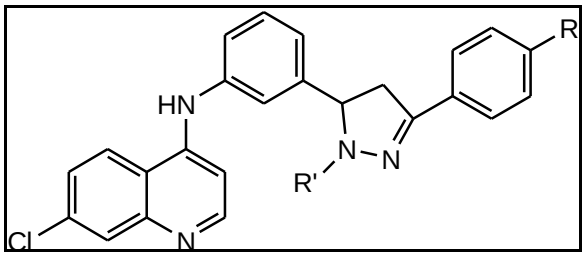
Nagender and coworker reported [84] Synthesis of novel hydrazone and azole functionalized pyrazolo[3,4-b]pyridine derivatives, The azole and hydrazone functionalized pyrazolo[3,4-b]pyridine derivatives 7a-d, 8a-c, 10a-d and 11a-d were evaluated for their anticancer activity against a panel of four different human cancer cell lines namely A549 - human lung (CCL-185), MCF7 – breast (HTB-22), DU145 - prostate (HTB-81) and HeLa- cervical (CCL-2) using the MTT assay method. Structure-activity relationship (SAR) studies revealed that the 1,2,4 triazole derivatives 10a-d showed very good activity when compared to oxadiazoles 8a-c and thiadiazoles 11a-d. Among the1,2,4 triazole derivatives 10a-d, the compound 10d which has trifluoromethylthio group in the para position of the phenyl ring exhibited promising cytotoxicity against all the tested cell lines, while compounds 10a/10c with no substituent/fluorine on the phenyl ring showed good cytotoxicity and the compound 10b which has a CH3 group present on the phenyl ring showed moderate cytotoxicity, (i.e) the fluorine or trifluoromethylthio group on phenyl ring increasing the activity. Similarly, hydrazone derivative 7d with trifluoromethylthio group present on phenyl ring in the para position also showed good cytotoxicity as compared to other substituted hydazone derivatives, 7a, 7b, and 7c. The fluorine substituent in compound 7c could not show activity whereas other fluorine substituted compounds were showed very good activity. In the case of oxadiazole derivatives, furyl substituent 8b showed promising cytotoxicity as compared to thiophenyl substituent 8c against A549 and MCF7 human cancer cell lines with IC_{50} values of 8 μM and 7.6 μM, respectively. While, thiophenyl substituent 8c showed good cytotoxicity as compared to furyl substituent 8b against DU145 and HeLa human cancer cell lines with IC_{50} values of 8.8 μM and 8.2 μM, respectively. In thiadiazole derivatives, compound 11c with fluorine substituent on phenyl ring in para position showed significant cytotoxicity against all the tested cell lines with IC50 values ranging between 7.6-9.1 μM and compound 11d, trifluoromethylthio substituent on phenyl ring showed promising activity. In all the cases, the fluorine or trifluoromethylthio substituent present on the phenyl ring increased the activity except 7c. Among all the compounds screened, the 1,2,4 triazole derivative 10d was considered as a lead compound which has trifluoromethylthio group on phenyl ring in the para position. Further studies are underway to optimize the structure in order to find a potent lead molecule.



3-amino-6-(trifluoromethyl)-1H-pyrazolo[3,4-b] pyridine

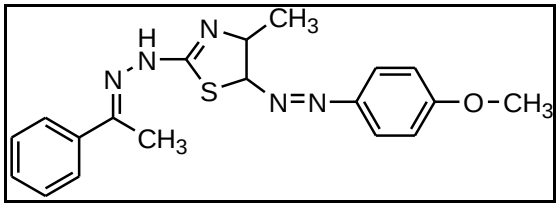
Prada and coworker reported [85] a new series of N–substituted 2–pyrazolines 9a–f, 10a–f, 11a–f, 12a–f and 13a–f, All compounds were tested first for toxicity on U–937 human cells at four serial dilution concentrations (200, 50, 12.5 and 3.125 μg/mL) to determine their 50% Lethal Concentration (LC_{50}) (Table 4). All compounds of series A and B1 (6, 8a–f, 9a–f and 10a–f) and few compounds of series B2 (11b, 11c, 11e and 12b) exhibiting LC_{50}< 100 μg/mL were considered as potentially cytotoxic whereas almost all compounds of the series B2 (11a, 11d, 11f, 12a, 12c–f and 13a–f) showed a LC_{50} > 200 μg/mL and therefore classified as potentially non cytotoxic. Amphotericin B showed a LC50 = 36.0 μg/mL (potentially cytotoxic) and

benznidazole had a LC_{50} = 180.0 µg/mL (mildly cytotoxic). Substitution with a phenyl group on N–1 of the 2–pyrazoline ring decreases the cytotoxic activity of the compounds and the decrease is greater when this ring is attached to one or two chlorine atoms. The results obtained with the aldehyde 6 show that the 7–chloro–4–aminoquinoline nucleus confer cytotoxic activity, but this activity is diminished when the nucleus is functionalized with rings A and B and specially with ring C. However, these results cannot be misinterpreted, since amphotericin B hashigh cytotoxicity and is still a commercial drug.



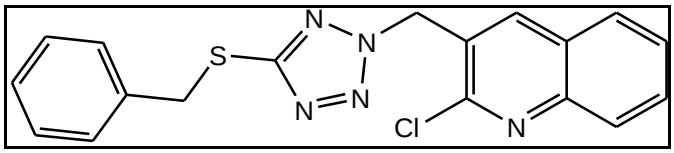
9-13a-f

Riyadh and coworker [86] reported the synthesis of Novel Thiazoles and [1,3,4]Thiadiazoles Incorporating Sulfonamide Group and evaluated for cytotoxicity. The newly synthesized compounds 6a-j and 10a-d were evaluated for their in vitro anticancer activity against one breast cancer cell line MCF-7 and another colon carcinoma cell line HCT-116 according to MTT assay method by using Erlotinib as positive TK drug. Moreover, four representative active cytotoxic compounds 6b, 6d, 6i, and 10d were tested for measuring their normal toxicity against normal HFL-1 cell line, thiazole analogs 6b, 6d, 6f, 6h, 6i, and 6j showed good anticancer activity with IC_{50} 0.26 to 3.6 µM against the cell lines. In contrast, 6a, 6c, and 6e derivatives displayed weak anticancer activity compared to the rest by high micromolar values. Moreover, the compounds 10a-d of thiadiazole scaffold exhibited less antiproliferative effect compared to the thiazole ones by (9-207 µM) and control drug.



6a

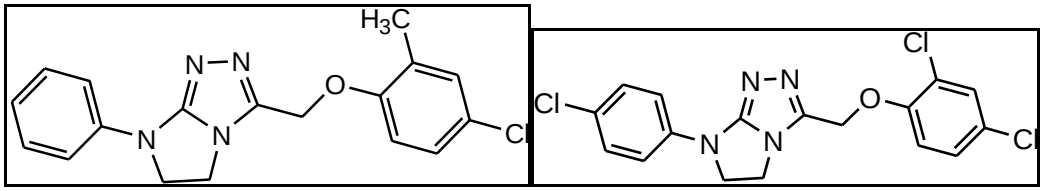
Shaikh and coworker [87] reported the new series of 2,5 and 1,5-regioisomers of the tetrazolyl group viz., 3-[(5-benzyl/benzylthio-2H-tetrazol-2-yl) methyl]-2-chloro-6-substituted quinoline 6h-q and 3-[(5-benzyl/benzylthio-1H-tetrazol-1-yl)methyl]-2-chloro-6-substituted quinolines 7h-q, The newly synthesized compounds were also subjected to in vitro anticancer screening in a single high dose (105 M) concentration against full 60 human cancer cell lines. Compounds 6h and 6i have shown 40e99% growth inhibition of the tumor cells against various cell lines at 105 M concentration. Compounds 6h and 6i were also cytotoxic against Renal Cancer UO-31 and Melanoma SK-MEL-5 cell lines respectively. Docking into the active pocket of NMT and DHFR revealed that compounds (with bromo and fluoro substituents) 6k, 6l, 6p and 7q exhibited good binding mode into the amino acids, which are compatible with their in vitro screening results, compounds (6k-m, 6o, 6q and 7h-7q) showed moderate GI% against all the cell lines.



6m

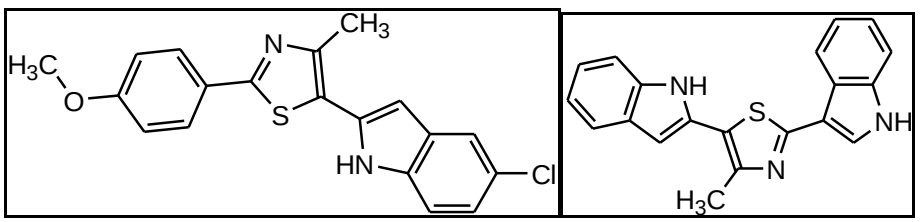
Sztanke and coworker [88] reported the synthesis of 3-Unsubstituted and 3-substituted-7-aryl-5H-6,7-dihydroimidazo[2,1-c][1,2,4]triazoles, Compounds 7 and 12 were evaluated for their cytotoxic activity against three cancer cell lines: human Caucasian colon adenocarcinoma cell line e LS180 (ECACC 87021202), human

uterus carcinoma cell line SiHa (ECACC 85060701) and human breast carcinoma cell line T47D (ECACC 85102201). Compounds 7 and 12 were found to be active. These compounds were proved to exhibit different levels of anticancer properties. compound 12 was found to be the most active against the human Caucasian colon adenocarcinoma cell line (LS180), Both examined heterobicycles (7, 12) are the 3-phenoxymethyl-7-aryl-5H-6, 7-dihydroimidazo[2,1-c][1,2,4]triazole derivatives and these molecules differ from in the presence of a methyl (7) or a chloro (12) substituent in ortho position of the phenoxymethylene formation and in the location of a chloro substituent at para position of the phenyl ring (12) or its lack in the case of compound 7. Compounds 7 and 12 showed different log kW values of 1.17 and 4.15, respectively, in dioxanewater system. It was found that the introduction of a chloro substituent to the phenyl ring, and the replacement of a methyl substituent by a chloro substituent at the 2-position of the phenyl ring, that of the phenoxymethylene formation in the case of compound 12 led to significant increase in lipophilicity (log kW ¼ 4.15 in aqueous system with dioxane) and influenced in increase of anticancer activity. Moreover, the distinctly marked lower cytotoxicity of derivatives 7 and 12 against normal cell lines (human skin fibroblast cells e HSF and Vero African Green Monkey Kidney cells e GMK clone) and almost several fold higher against the majority of cancer cell lines.



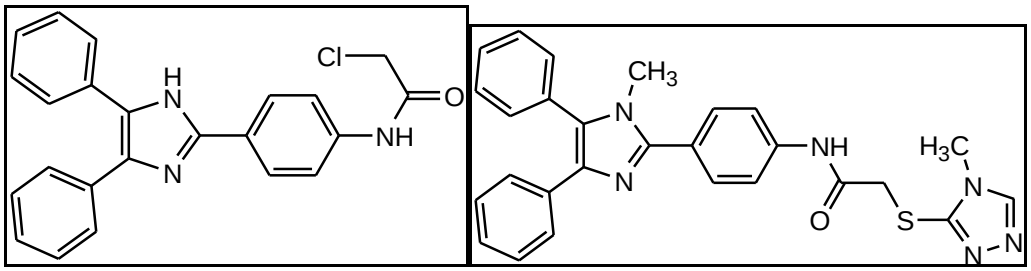
7 **12**

Vaddula and coworker [89] reported the synthesis of prominent 5-(2′ -indolyl)thiazoles, then screened for their in vitro cytotoxicity against five human cancer cell lines: breast (BT-474, MCF-7 and MDA-MB-231, MDA-MB-157) and colon (HTC-116). Anticancer activity of 5-(2′ -indolyl)thiazoles 2a–j against cancer cell lines are expressed in terms of IC_{50} values. Some of the compounds have shown moderate activity. Structure–activity relationship (SAR) study revealed that substitution at C-2 position of the thiazole ring is crucial for inducing cytotoxicity and selectivity against particular cancer cell line. The presence of a 4-methoxyphenyl group at C-2 position and absence of any substituent on the C-5 indole ring led to compound 2a not having any significant activity against the tested cancer cell lines (IC_{50}> 100 μM). Upon placing a chloro substituent on the indole ring of 2a led to compound 2b also without any improvement in activity (IC_{50}> 100 μM). The anticancer activity was further studied by replacing the 4-methoxyphenyl in 2a with 4-chlorophenyl resulting in compound 2c without any improvement in activity (IC_{50} > 100 μM). The presence of a methyl substituent at the C-2 position of thiazole 2d exhibited selectivity towards breast cancer cell line, BT-474, with an improved activity (IC_{50} = 30 μM), but relatively moderate towards colon cancer cell line, HTC- 116 (IC_{50}> 30 μM). The presence of a heterocyclic indole ring at the C-2 position resulted in bis(indolyl)thiazole 2e, which closely resembles the naturally occurring bisindolyl alkaloids such as Nortopsentins. Compound 2e exhibited very good selectivity and potency (IC_{50} = 10 μM) when compared to other compounds of the series. It was earlier shown that one of the important structural units is a trimethoxyphenyl moiety in several known natural antimitotic agents (Combretastatin A-4, Colchicine, Podophyllotoxin and Steganacin) that binds at the Colchicine site of tubulin, Incorporation of such a crucial structural feature of lead anticancer compounds into 5-(2′-indolyl)thiazoles 2 may results in a potent anticancer compound. The compound 2f with no substituents on the indole ring at C-5 of thiazole exhibited very good selectivity towards BT-474 breast cancer cell line (IC50 = 20 μM) whereas, the presence of a fluoro substituent on the indole ring (compound 2h) could inhibit both BT-474 and MDA-MB-157 (IC50 = 30 μM). The other compounds exhibited moderate to insignificant activity. Further improvement in activity may be achieved to a great extent by investigating the compound 2e with further substitutions on both indole rings.



2b **2e**

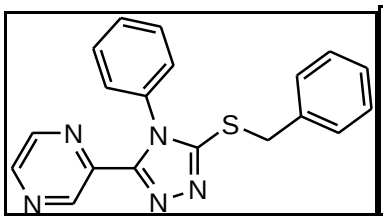
Ozkay and coworker reported [90] the synthesis of of2-substituted-N-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl]acetamide derivatives, Compounds subjected to cytotoxicity test were designed to contain two different pharmacophore groups which exist on the chemical structures of some anticancer agents and are estimated to be responsible for the anticancer activity. N-[4-(4,5-diphenyl-1Himidazole- 2-yl) phenyl] acetamide sub structure was fixed in all of the compounds. This sub structure was substituted from second position of the acetamide moiety in order to classify the compounds in two different groups. The first group was constituted by using different azole and benzazole heterocycles and named imidazole-(benz)azoles. The second group was imidazole piperazines and formed by substitution of corresponding piperazine derivatives. The starting compound(6) wasalsoimplicatedtocytotoxicitytestinordertodeterminethe contribution of variable groups to activity. Cytotoxic activity of the compounds against HT-29andMCF-7 cell lines. In the first group the 7, 10, 11, 12 and 13 displayed higher cytotoxic activity against both of the cell lines than the 6. Cytotoxicity of the 15 was lower than that of the 6. The other thiol-(benz)azole moiety bearing compounds 8, 9 and 14 showed approximate cytotoxic activity to the 6. These resultssuggestthatbenzoxazole-2-thiol,benzothiazole-2-thiol, 1,2,4-triazole-5-thiol,1,2,3,4-tetrazole-5-thioland1,2,4-thiadia- zole-3-thiol moieties supply a substantial contribution to increase of the cytotoxicity. On the other hand, determination of lower cytotoxicity with the 15 than the 6 indicates that substitution of the 6 with 1-methyl-imidazole-2-thiol causes an activity decrease. The observed findings also refer that 5-methyl-benzoxazole-2-thiol,5- chloro-benzoxazole-2-thiolandthiazoline-2-thiolsubstituted compounds have no effect on the cytotoxicity. In the second group, most of the compounds exhibited lower cytotoxicity against both of the celllines than the 6.



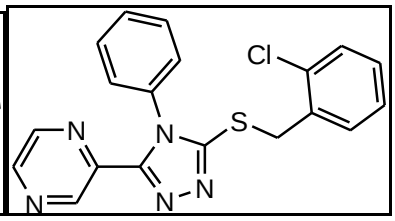
6 **11**

Zhang and coworker reported [91] thethree series of novel heterocyclic azoles derivatives containing pyrazine, the synthesized heterocyclic azoles derivatives were evaluated for their anti-proliferative activity against the HEPG2 (human liver cancer cell), SW1116 (human colorectal carcinoma cell), HELA (human cervical cancer cell) and BGC823 (human gastric cancer), the active analogs showed a distinctive potential pattern of selectivity as well as broad-spectrum antitumor activity. With regard to selectivity against individual cell lines, most of the compounds showed better activities against cell lines HEPG2 and SW1116 than HELA and BGC823 with lower IC_{50} values. Especially, these compounds showed effectiveness against cell line human hepatocellular liver carcinoma HEPG2 with IC_{50} values range of 0.78–22.57 lM comparative to staurosporine (1.30 lM). Among these compounds, compound 8h showed the most potent biological activity (IC_{50} = 0.78 lM). Overall, series 8a–8k mostly showed better activities against the cell lines than series 5a–5k and 11a–11k, but not absolutely. When regarding HEPG2 cell line, IC_{50} values of compounds 8e, 8g, 8h and 8j ranged of 0.78–6.90 lM, compared with 5c, 5d, 5e (4.22–7.50 lM) and 11e, 11f,11i (10.07–10.64 lM). Also, the same regular pattern was observed with compounds 8e, 8g, 8h and 8i with IC_{50} values range of 1.47–5.26 lM, comparable with 5c, 5d, 5e (2.46–7.88 lM) and 11d, 11f, compounds 5c, 5d, 5e (11.48–17.55 lM) and compounds 11e, 11h, and 11i (17.82–19.76 lM). It was concluded that compounds 5c, 5d, 8e, 8g, 8h, 11e, 11f, 11h and 11i showed broad-spectrum antitumor activity with IC50 concentration range of 0.78–27.15 lM against the mentioned four cancer cell lines. Tested compounds showed stronger activities against HEPG2 than other three cancer cell lines. Among the tested compounds, compound 8h showed the most potent biological activity against HEPG2 cancer cell line with IC50 value of 0.78 lM. Some rules were summarized, respectively, in different skeletons (oxadiazole, thiadiazole, and triazole) with different halogen atom substituent on benzene ring against the four cell lines, the rules were quite different, but not absolutely, which might lead to different antitumor activity. With regard to the 1,3,4-oxadiazole derivatives 5a–5k, comparisons of antitumor activities with different halogen atoms substituent on benzene ring were demonstrated as follows: when the compounds were ortho-position halogen substituted derivatives, the potency order was Br > Cl = F (e.g., 5a,5b, 5c) and among the meta-position halogen-substituted compounds the potent inhibitory action order could be summarized as Br > Cl (e.g., 5d, 5e); while when the substitute happened on the para-position of benzene ring, the potency order

was Cl > Br > F (e.g., 5f, 5g, 5h). The rules were quite similar to the 1,3,4-thiadiazole derivatives 8a–8k, possibly because their structures were very alike. The difference was just on the ortho-position which presented as F = Br > Cl (e.g., 8a, 8b, 8c). However, the potent inhibitory activity order of 1,2,4-triazole derivatives 11a–11k with halogen atom substituent was quite different from the compounds mentioned before. Among the meta-position halogen-substituted compounds, the potent inhibitory action order could be summarizedas Br > Cl (e.g., 11d, 11e); while when the substitute happened on the para-position, the potency order was F > Br > Cl (e.g., 11f, 11g, 11h), but the potency was not very obvious when happened on ortho-position. Overall, most Br-substituted compounds showed better activities than other halogen-substituted compounds, like compounds 5c, 5h, 8c, 8e, 8h, 11e and 11h with IC50 values ranged of 0.78–25.68 lM. The same halogen atom substituent on different positions of benzene ring also presented quite different orders in different skeletons. With regard to the Br-substituted compounds, no similarities were found as follows:ortho > meta > para (e.g., 5c, 5e, 5h) in 1,3,4-oxadiazole derivatives, para > meta > ortho (e.g., 8c, 8e, 8h) in 1,3,4-thiadiazole derivatives and meta > para = ortho (e.g., 11c, 11e, 11h) in 1,2,4-triazole derivatives. While the potent inhibitory activity orders of compounds with Cl-substituted on the benzene ring were meta > para = ortho (e.g., 5b, 5d, 5g) in 1,3,4-oxadiazole derivatives, para > meta > ortho (e.g., 8b, 8d, 8g) which was similar to the Br-substituted compounds in 1,3,4-thiadiazole derivatives, and para > ortho = meta (e.g., 11b, 11d, 11g) in triazole derivatives. However, the potent inhibitory activity orders were uncertain of F-substituted compounds, the potency order of fluorine substituted 1,2,4-triazole derivatives was summarized as ortho > 2,4-disubstituded > para = 2,6-disubstituded. The results showed that Br-substituted on benzene ring could enhance the activity of compounds, but the position of bromine atom was not absolutely. It could be a promising lead for the further development of novel telomerase inhibition agents.



11k



11b

4. Conclusion

In summary, the exploration of naturallyencouragingnovelcompound entities to counter cancer maintainsprodigiousmaintenance in medicationdiscovery. Although numerousmedicationbeing exploitedfor the management of cancer, still numerousencounters to emerging new drug contenders, subsequentlyfurthermostof the chemotherapy drugs succession have the restraint ofdetrimental side effects and it evidentlyaccentuates the prerequisite forthe enlargement of novel chemotherapeutic agents as extraoperative cancer dealings. The present-day paper emphasizedentirely an imperative class of heterocyclic compoundsthat can be used as proficient and active drugs for thedealing of cancers. The manmade and naturalinvestigationreveal that azoles have wide scope. This paper provide detailed study on SAR of the synthesized compounds. The instancesunfilled in this paper displayed anremarkableimpression of basic variations and the SARanalysis discovered that the bustleoutline of these upon the locus and nature of substituents arranged parent skeleton, transcriptionseveralcomplexesextradynamic as related to positive controls used for assessment.The accumulative power of computational methodologies alsostrengthened the action results and, in amalgamation withinvestigations, simplifies the identification ofnovel and effectual anticancer agents.

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