Review Article

Recent Advances Made on Anticancer Drugs – The Therapeutic Potential of the Aromatic Heterocyclic Compounds

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ABSTRACT

The attractive biological activity profiles of many heterocyclic moieties put them in the category of compounds having a variety of pharmacological therapeutic activities. Although lots of heterocyclic moieties have been studied for their anti-cancer activity, the present review emphasizes on heterocyclic compounds having moieties like oxadiazole, quinoline, isoxazoles and nicotinonitrile containing Nitrogen, Oxygen, and Sulphur in the heterocyclic ring structures, together with the substituent groups of the core scaffold. Their practical application ranging from extensive clinical use to fields as diverse as medicine has perched them as the true cornerstone of medicinal chemistry and their prominence lies in their study about their strong impact on the physicochemical properties. But their most important role in cell physiology and as probable intermediates for numerous biological reactions leading to anticancer research and thus capitalizing on the intrinsic versatility and dynamic core scaffold of these compounds has put them in the most significant category. In this current review, the recent advances made on the anticancer therapeutic potential of the above mentioned aromatic heterocyclic compounds effective against human tumor/ cancer cell lines has been discussed. Their structure-activity relationships, mechanism of action and suppression activity along with the importance of the substitution pattern has also been dealt with.

Keywords: Anticancer drugs, heterocyclic compounds, clinical use.

INTRODUCTION

Cancer is a leading cause of death worldwide, accounting for 8.7 million deaths (around 14% of all deaths) in 2012 [1]. Many chemotherapeutic agents, such as cisplatin, 5 -fluorouracil and taxol, have been developed to treat different kinds of cancer effectively although with some side effects simultaneously. Therefore, it is vital and imperative to develop novel compounds as anticancer agents with higher bioactivities and lower side effects[2-3]. As medicine advances, cancer is still among one of the major health problems, posing significant threats to human health. New anticancer agent's features with novel scaffolds and/or unique mechanisms of action are highly desirable for the treatment of cancers, especially those highly aggressive.

One of the important objectives of organic and medicinal chemistry is to design, synthesize and produce molecules that have potential as human therapeutic agents. There are many which are being investigated against several malignancies for a variety of pharmacological activities like anti-inflammatory, antioxidants, antifungal, anti-viral, anti-microbial, antipyretic and antimicrobial[4-6], anti-inflammatory, analgesic, antipyretic, anticonvulsant, and cardiovascular[7-12] properties are shown by many organic compounds.

Among these organic compounds, the solitary ones, which are extensively encompassed and have vast and diverse applications, are heterocyclic compounds. The practical applications in which heterocyclics are being used range from extensive clinical use to fields as diverse as medicine, agriculture, photochemistry, biocidal formulations, and polymer science.

A large number of heterocyclic compounds occur naturally example Thiamine (Vitamin B_1), Riboflavin (Vitamin B_2), Nicotinamide (Vitamin B_3), Pyridoxal (Vitamin B_6) and Ascorbic acid (Vitamin C), essential amino acids, tryptophan, and histidine are heterocyclic compounds. Nucleic acids, hemoglobin, chlorophyll, and many enzymes are also containing an important heterocyclic nucleus.

Although heterocyclic compounds are quite promising for their biochemical modes and hence are being used against several ailments, infections, and maladies because of potential applications in medicine but they also do not come without shortcomings.

By the end of the second millennium, out of all of the 20 million chemical compounds documented in the literature, approximately half were heterocyclic[13]. The majority of heterocyclic compounds specially those containing Nitrogen, Oxygen and Sulphur having moieties like oxadiazole, quinoline, isoxazoles and nicotinonitrile have

been reckoned as true cornerstone of medicinal chemistry and as fundamental division of organic chemistry. These heterocyclic ring structures, together with the substituent groups of the core scaffold, impact strongly on the physicochemical properties[14, 15] of these compounds and thus reviewed in the present paper.

Oncology is one of the areas, which is still facing intrinsic limitations regarding the main therapeutic routes of chemotherapy, associated side effects, and toxicity to healthy tissues. Nevertheless, as for any other promising anticancer drugs, heterocyclic compounds are also finding their suitability as anticancer drugs. Because of the success of "molecularly targeted agents", such as imatinib, merely fortunate exceptions and that the number of success in this area is considerably low [16] but still with the advent of nanotechnology for effective selective targeting of drugs and possibility of deeper study of structure-activity relationships heterocyclic compounds are gaining a lot of importance as possible anticancer drugs [17].

At present, there are 30 main heterocyclic drug delivery products in the market with a total annual income of US$33 billion and an annual growth of 15%. But the recent trend in drug development which involves nanotechnology so that drug delivery with the global market trend for nanoparticles (NPs) in biotechnology was valued at US$17.5 billion in 2011 and is expected to reach US$53.3 billion in 2017 [17,18].

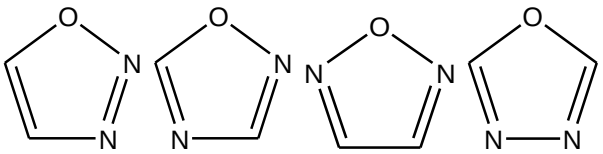
Doxorubicin is one of the most used compounds in Nano formulations for cancer therapy, using liposomes (Lipid-based carriers) as nanocarriers of doxorubicin for the treatment of Kaposi's sarcoma and breast and ovarian cancer [19-21]. The ability to bind and/or encapsulate heterocyclic compounds into nanocarriers allows the exploit of the enhanced permeability and retention effect suitable for tumor targeting, or passive targeting.

By the end of the second millennium, out of all of the 20 million chemical compounds documented in the literature, approximately half were heterocyclic[13]. The majority of heterocyclic compounds especially those containing Nitrogen, Oxygen and Sulphur having moieties like oxadiazole, quinoline, isoxazoles, and nicotinonitrile have been reckoned as the true cornerstone of medicinal chemistry and as the fundamental division of organic chemistry. These heterocyclic ring structures, together with the substituent groups of the core scaffold impact strongly on the physicochemical properties [14, 15] ofthese compounds and thus reviewed in the present paper.

OXADIAZOLE DERIVATIVES

Oxadiazoles constitute a privileged scaffold among heterocyclic compounds in modern medicinal chemistry which are known to have a broad spectrum of biological activities including antiviral, antimicrobial, antineoplastic, fungicidal, anticancer [22-29], inhibition of tyrosinase[30] and cathepsin K [31], monoamine oxidase [32-35]. Apart from these they also act as useful intermediates in the synthesis of certain organic compounds of interest and as electron transporters and hole-blocking materials [36-37]. In particular 2, 4- disubstituted 1, 3, 4- oxadiazoles are of significant interest due to their applications in organic light-emitting diodes, photoluminescence, polymers and material science [38, 39].

Based on the positions of heteroatoms in the chemical structure, there are four isomers of oxadiazoles. 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,5-oxadiazole being stable ones but 1,2,3-oxadiazole is unbalanced and reverse to the diazo ketone tautomers.



1, 2, 3- oxadiazole 1, 2, 4- oxadiazole 1, 2, 5- oxadiazole 1, 3, 4- oxadiazole

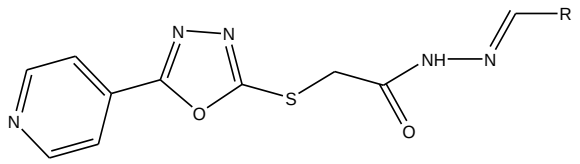
Oxadiazole is a five-membered heterocyclic moiety containing two nitrogen atoms and one oxygen atom having general formula $C_2H_2ON_2$. Among these 1,3,4-oxadiazole shows increased pharmacological activity which can be attributed to their participation in hydrogen bonding interactions with receptors as they are very good bioisosteres of amides and esters. The unique chemical structure of 1, 3, 4- oxadiazoles have encouraged the researchers to explore this moiety as a lead compound for the synthesis of novel anti-tumor/anti-proliferative/anti-cancer compounds.

The basis of mechanism of action which contributes for the tumor suppression activity of oxadiazoles can be, their monoamine oxidase and tyrosine kinase inhibitory effects, inhibition of glycogen synthase kinase 3 (GSK-3) which regulates both differentiation and cellular proliferation, inhibition of different growth factors and enzymes like telomerase, inhibition of processes involved in tumor growth e.g. angiogenesis. Certain oxadiazole derivatives which can inhibit angiogenesis are antagonists of integrin αvβ3 receptor which is found on the surface of many tumor cells and accounts for the recognition of arginine-glycine-aspartic acid sequence.

Previous studies, conducted on 1, 3, 4 –oxadiazoles have reported that the synthesized series of novel 1, 3, 4-oxadiazole containing pyridine and acyl hydrazones moieties. Among them, compound (E)-N´-(3,4-Dihydroxybenzylidene)-2-((5-(pyridine-4-yl)-1,3,4-oxadiazol-2-yl)thio) acetohydrazide (compound I) to be potential inhibitors of telomerase enzyme[40,41,42] while 2-(4-chlorophenyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole with methoxyphenyl (Compound II) at the fifth position of the oxadiazole ring (II) has been reported to show more anti-cancer activity (leukemia, prostate) than compound 2-(4-chlorophenyl)-5-(-(4-methoxyphenyl)-1,3,4-oxadiazole (compound III) with fluorophenyl group at fifth positon of oxadiazolenucleus (III) [42].

In few studies, the Evaluation of the synthesized compounds for their anti-proliferative activity against the HEPG2 (Human liver cancer cell), MCF (human breast

cancer cell), SW1116 (human colorectal carcinoma cell) and BGC823 (human gastric cancer cell) was done by MTT assay. Compounds exhibited significant broad-spectrum anticancer activity IC_{50} of 0.76 ± 1.54 µM against the above mentioned four cancer cell lines. The assay of the above-referred compound (I) for telomerase inhibition revealed that the compound (I) showed the highest anticancer activity against the tested cancer cell lines and also exhibited the most potent telomerase inhibitory activity.

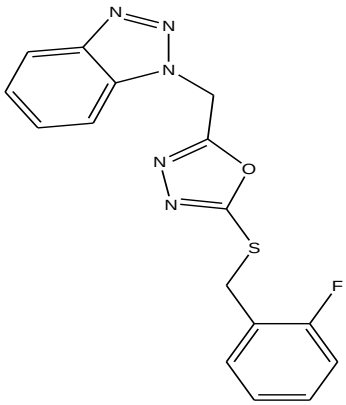


Compound (I), (II) and (III)

Compound	R group is substituted aryl	Reported by	Against cancer cell lines
(I)	N´-(3,4-Dihydroxybenzylidene)-	Zang F et .al	HEPG2, MCF, SW1116, BGC823
(II)	2-(4-chlorophenyl)-5-(4-methoxyphenyl)-	Ashan et .al	Leukemia and prostate cancer
(III)	2-(4-chlorophenyl)-5-(4-fluorophenyl)-	Ashan et .al	Leukemia and prostate cancer

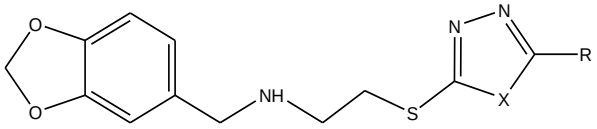
Zhang, S. et al [43] reported the synthesis of a series of 1, 3, 4-oxadiazole derivatives incorporating benzotriazole moiety as potential focal adhesion kinase inhibitors. Some of the synthesized compounds showed the most potent inhibitory activity against MCF-7 and HT-29 cell lines.

All the synthesized compounds were also assayed for FAK inhibitory activity. The results showed that the compound (IV) showed the most potent FAK inhibitory activity. The flow cytometry method was used to analyze apoptosis. Compound (IV) induced apoptosis against MCF-7 cells.



Compound (IV)

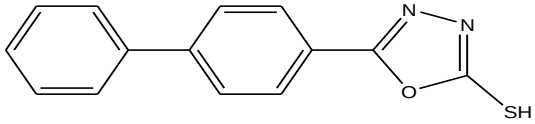
Ozdemir Ahmet et al, synthesized and evaluated new oxadiazole derivatives targeting MMP-9 as potential anticancer agents. Of all the synthesized compounds, N-(1,3-Benzodioxol-5-ylmethyl)-2-{[5-(((5,6,7,8–tetrahydronaphthalen-2-yl)oxy)methyl)-1,3,4-oxadiazol-2-yl]thio}acetamide (V) and N-(1,3-benzodioxol-5-ylmethyl)-2-[(5-phenyl-1,3,4-oxadiazol – 2-yl)thio]acetamide(VI) showed promising cytotoxic effects against C6 (rat glioma) cell lines whereas compound (V) showed maximum anticancer activity against A549 cell line. Moreover, docking studies pointed out that compounds (V) and (VI) had good affinity to the active site of the MMP-9 enzyme. The molecular docking and in vitro studies suggest that these two compounds can play an important role in Lung Adenocarcinoma and Gliomatreatment[44].



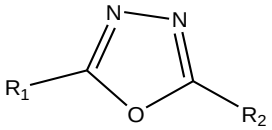
Compound (V) and (VI)

Compound	R	X
(V)	((5,6,7,8-tetrahydronapthalen-2-yl)oxy) methyl	O
(VI)	Phenyl	O

SuryanarayanaRaju D, synthesized novel derivatives of 1,3,4-oxadiazoles and screened them for their anticancer activity. Compounds (VII, VIII, IX, X) showed maximum activity against Hep G2 cells and compounds (X) and (XI) was found to be most active against Hep 2 cells[45].



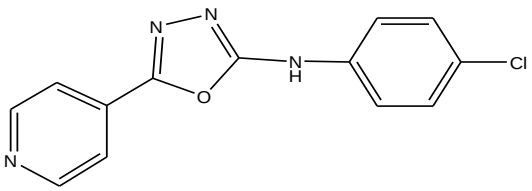
Compound (VII):5-Biphenyl-4-yl-[1, 3, 4] oxadiazole-2-thiol



Compound (VIII to XII)

Compound	R_1	R_2	IUPAC name
(VIII)	$C_{13}H_{12}$	$C_6H_4F_2$	2-Biphenyl-4-yl-5-(3,4-difluoro-phenyl)-[1,3,4]oxadiazole
(IX)	$C_{13}H_{12}$	C_7H_8O	2-Biphenyl-4-yl-5-(4-methoxy-phenyl)-[1,3,4] oxadiazole
(X)	$C_{13}H_{12}$	$C_8H_8O_2$	Acetic acid 4-(5-biphenyl-4-yl-1,3,4]oxadiazol -2-yl)-phenyl ester
(XI)	C_6H_6ClN	C_6H_5F	5-Chloro-2-[5-(4-fluoro-phenyl) [1,3,4] oxadiazol -2-yl]-phenylamine
(XII)	C_6H_6ClN	C_6H_5Cl	5-Chloro-2-[5-(4-chloro-phenyl)-[1,3,4]oxadiazol -2-yl]-phenylamine

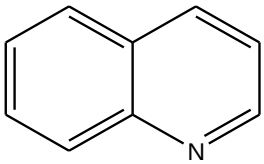
Nadia Youssef et al synthesized a series of new 1,3,4-oxadiazole derivatives incorporating a pyridine moiety and investigated their structure-activity relationship. In vitro cytotoxicity of the synthesized compounds was evaluated against six human cancer cell lines and normal fibroblast cells. Out of all the synthesized compounds, compound (XIII) N-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine showed selective moderate activity against gastric and colon cancer cell lines[46].



Compound (XIII)
N-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine

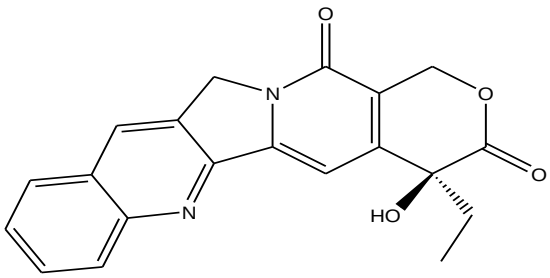
QUINOLINE DERIVATIVES

Among heterocyclic compounds, quinoline scaffold is also an important construction motif helping in the development of anticancer drugs. It is a heterocyclic aromatic organic compound with the chemical formula C_9H_7N.



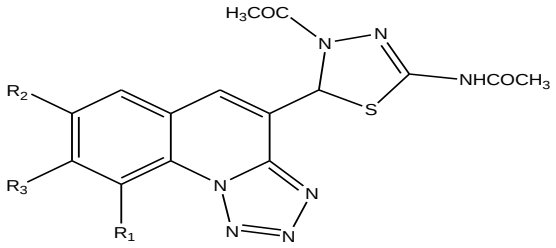
They have shown excellent results as anticancer agents through a different mechanism of action such as growth inhibitors by cell cycle arrest, apoptosis, inhibition of angiogenesis, disruption of cell migration and modulation. Several quinoline derivatives have been reported to date for their modes of function in the inhibition of tyrosine kinases, proteasome, tubulin polymerization, and DNA repair.

The present review summarizes heterocyclic substituent quinoline derivatives with potential in vitro and in vivo anticancer activities, mechanisms of action, structure-activity relationship (SAR), and selective and specific activity against various cancer drug targets. The most important quinoline moieties[47] which are being used as chemotherapeutic drugs are Camptothecin (a cytotoxic quinoline alkaloid which inhibits the DNA enzyme topoisomerase I, Irinotecan (used to treat colon cancer and small cell lung cancer), Topotecan ("topoisomerase 1 inhibitor) and Bosutinib (tyrosine kinase inhibitor).



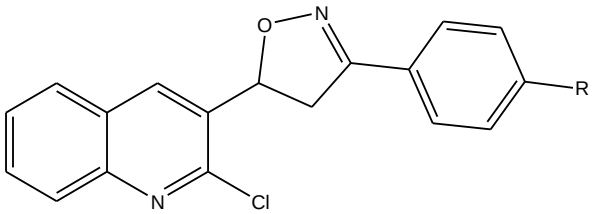
Camptothecin

Recent studies have reported that *N*-(4-acetyl-4,5-dihydro-5-(7,8,9-substituted-tetrazolo[1,5-*a*]-quinolin-4-yl)-1,3,4-thiadiazol-2-yl)acetamides (XIV) and (XV) and in vitro anticancer activity against two cell lines viz., human breast cancer cell line MCF7 and human cervix cancer cell line HeLa. GI50, LC50, TGI values were evaluated. Two of the compounds (XIV) and (XV) *with* halogen substituent at the 7th position of the target molecules have shown potent activity against human cervix cancer cell line HeLa. DNA cleavage studies revealed that most of these compounds show partial cleavage and few of them show complete cleavage of DNA[48].



Compound (XIV) R_1= R_3=H , R_2= Br
Compound (XV) R_1= R_3=H , R_2= Cl

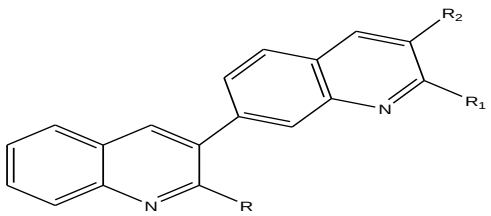
2, 3-disubstituted quinolones synthesized by Binduetal having 2-chloro-3-(5-aryl-4, 5-dihydroisoxazol-3- yl) derivatives (XVI) and (XVII). These compounds have been shown to possess photo-induced DNA cleavage properties studied through y neutral agarose gel electrophoresis as a possible target for anticancer therapy [49].



Compound (XVI) and (XVII)

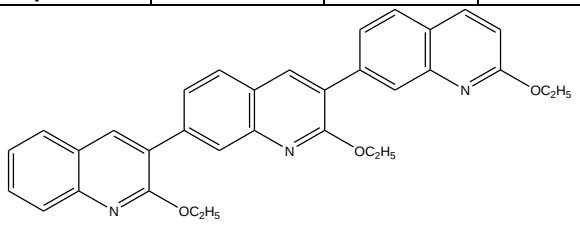
Compound	R
(XVI)	CH_3
(XVII)	NO_2

Broch et al, designed and synthesized Dimeric and trimeric analogues of 2,3 substituted quinoline derivatives and evaluated them for their in vitro antiproliferative activities toward a human fibroblast primary culture and two human solid cancer cell lines (MCF-7 breast and PA 1, ovarian carcinoma). Results showed that the dimeric analogous (2,2′ Dimethoxy-3,7′-biquinoline (**XVIII)** and 2,2′-Diethoxy-3,7′-biquinoline (XIX) are slightly active toward PA1 and MCF-7 cell lines with IC_{50} values in the range of 36–54 µM, and showed better cytotoxicities toward two human solid cancer cell lines. The Trimeric compound 2, 2′, 2″-triethoxy-3, 7′–3′,7″-terquinoline (XX) was mildly active against the PA1 cell line with an IC value of 50 $_{50}$µM. Further studies showed that the introduction of various substituents on the heteroaromatic nucleus improved the solubility of compounds and better biological profile results are obtained[50].



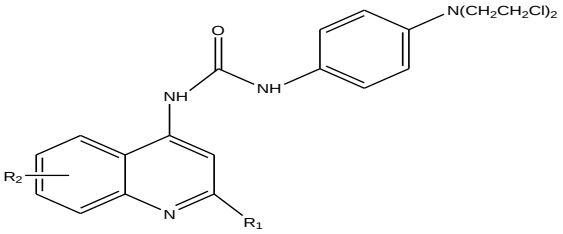
Compound (XVIII) and (XIX)

Compound	R	R_1	R_2
(XVIII)	OCH_3	OCH_3	H
(XIX)	OC_2H_5	OC_2H_5	H



Compound (XX)

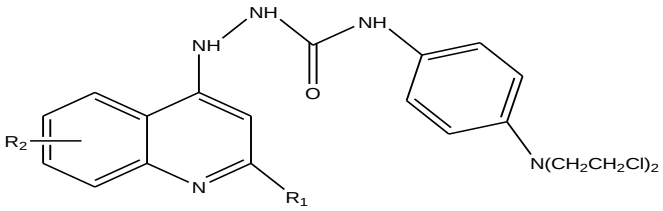
Kakadiyaetal have synthesized a series of 2, 4, 6-trisubstituted quinolines related to phenyl N-mustard quinoline-conjugates using urea or hydrazine carboxamide as stabilizing spacers. N-{4-[Bis(2-chloroethyl) amino]phenyl}-N0-(2-methyl-4-quinolinyl) urea (XXI) and N-{4-[Bis(2-chloroethyl)amino]phenyl}-N0-[6-methoxy- 2-(3-methoxy-phenyl) -4-quinolinyl]urea (XXII) have been found to possess potentiality for DNA-directed alkylating agents. These compounds showed good anticancer activity against breast carcinoma MX-1 xenograft.



Compound (XXI) and (XXII)

Compound	**R_1**	**R_2**
(XXI)	Me	H
(XXII)	3-CH_3O-C_6H_4	6-OCH_3

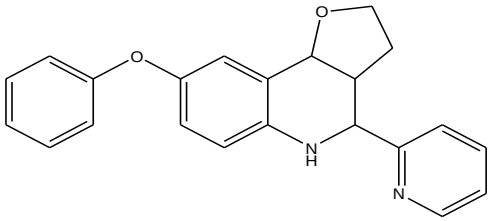
Compounds N-{4-[Bis(2-chloroethyl)amino]phenyl}-2-[6-(dimethylamino)- 2-methyl- 4-quinolinyl]-hydrazinecarboxamide (XXIII), N-{4-[Bis(2-chloroethyl)amino]phenyl}-2-(6-methyl[1,3]- dioxolo [4,5-g] quinolin-8-yl)-hydrazine carboxamide (XXIV) having hydrazine carboxamide as a linker showed increased cytotoxic activity in comparison with the corresponding compounds bearing a urea spacer. However, the study concluded that both linkers were able to lower the chemically reactive N-mustard pharmacophore and thus the newly synthesized conjugates possessed a long half-life in rat Plasma[51].



Compound (XXIII) and (XXIV)

Compound	**R_1**	**R_2**
(XXIII)	CH_3	6-$N(CH_3)_2$
(XXIV)	CH_3	6,7-(OCH_2O)

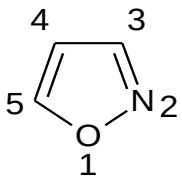
P.Y. Chung has synthesized hexahydrofuro [3, 2-c] quinoline, a martinelline type analogue2,3,3a,4,5,9b-hexahydro-8-phenoxy-4-(pyridin-2-yl)furo[3,2-c]quinoline (XXV), and investigation of its biological activity showed its potential anticancer activity against MDAMB-231 breast cancer cells[52].



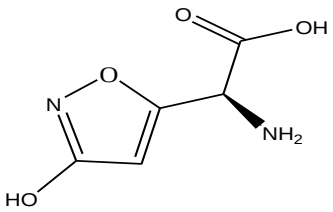
Compound (XXV)

ISOXAZOLE DERIVATIVES

Isoxazoles are unsaturated aromatic heterocyclic compounds containing a ring with three carbon atoms, one oxygen atom, and one nitrogen atom. The trivial name for the title five-membered fully unsaturated heterocycles as "isoxazole" was originally proposed by Hantszch as it was the first isomer of "oxazole" discovered. Isoxazole derivatives show hypoglycemic, analgesic, anti-inflammatory, antifungal, anti-bacterial and HIV-inhibitory activities [53] Isoxazole is an azole with an oxygen atom next to a nitrogen atom.



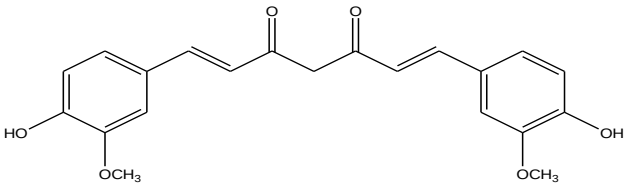
Isoxazole ring is found in some natural products, such as ibotenic acid.



Ibotenic acid

Paola P. et al, have demonstrated the use of information from nature and compounds that though formally considered as 'synthetic' compounds, can be considered to mimic natural product topography leading to novel structure with good therapeutic potential. They have examined the effects of curcumin (XXVI) [(1E, 6E)-1, 7-bis (4-hydroxy- 3-methoxyphenyl) -1,6- heptadiene-3,5-dione]and of its isoxazole analogue (XXVII) MR39 in MCF-7 breast cancer cell line and in its multidrug-resistant (MDR) variant MCF-7R. Curcumin is known to exhibit the remarkable property of modifying its molecular effects according to diverse gene expression patterns existing in MDR cell lines compared to parental lines, maintaining antitumor activity but its Isoxazole analogue compound (XXVII) (MR 39) has shown more potent antitumor and molecular activities both in parental and in MDR tumor

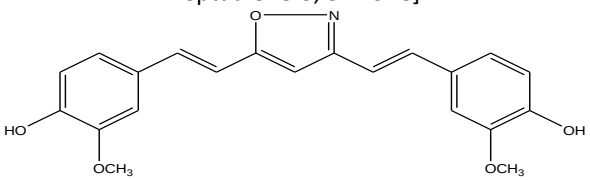
cells. Isoxazole derivatives produce significantly higher direct inhibition of the COX-2 catalytic activity than curcumin and proved better because of minimum metal chelation when compared to curcumin[54].



Chemical structure of Curcumin (diferuloylmethane)

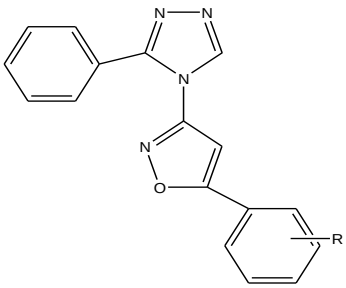
(XXVI)

[(1E, 6E)-1, 7-bis (4-hydroxy- 3-methoxyphenyl) -1, 6-heptadiene-3, 5-Dione]



Chemical structure of isoxazole derivative of curcumin **(XXVII)** (MR39)

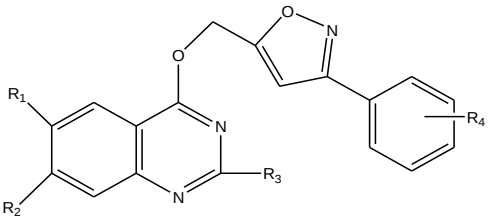
Bhaskar et al[55] synthesized a series of isoxazole derivatives and evaluated for their anticancer activity. Results showed that compounds (XXVIII), (XXIX), (XXX), (XXXI) and (XXXII) are highly effective against human tumor cell lines especially on renal cancer, CNS cancer cell and ovarian cancer cell lines [Bhaskar et al 2010]. The most efficient compound (XXVIII) showed appreciable activity with selective influence on ovarian cancer cell lines, especially on SK-OV-3 with a growth % of 34.94.



Compounds (XXVIII) - (XXXII)

Compound	R	IUPAC name
(XXVIII)	2-Cl	1-[5-(2-chloro phenyl) isoxazol-3-yl]-5-phenyl-1H –tetrazole
(XXIX)	4-Cl	1-[5-(4-chloro phenyl) isoxazol-3-yl]-5-phenyl-1H-tetrazole
(XXX)	4-Br	1-[5-(4-bromo phenyl) isoxazol-3-yl]-5-phenyl-1H-tetrazole
(XXXI)	4-OCH_3	1-[5-(4-methoxy phenyl) isoxazol-3-yl]-5-phenyl-1 H –tetrazole
(XXXII)	3-NO_2	1-[5-(3-nitro phenyl) isoxazol-3-yl]-5-phenyl-1 H –tetrazole

Yong et .al synthesized fourteen novel isoxazole-moiety-containing quinazoline derivatives with the potential of having a better activity and selectivity towards the cancer cells. Most compounds revealed good to excellent anticancer activity especially XXXIII, XXXIV, XXXV, XXXVI exhibited more potent anticancer activity against A549, HCT-116, and MCF-7 cell lines and can be regarded as promising candidates for the development of anticancer drugs[56].

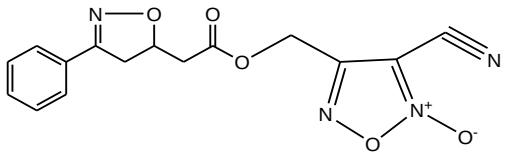


Compounds **XXXIII-XXXVI**

Compound	IUPAC name
XXXIII	2-phenyl-4-{[3-(2-chloro-phenyl)-isoxazol-5-yl-]-methoxy-}- quinazoline
XXXIV	2-chloro-6,7-dimethoxy-4-[(3-p-tolyl-isoxazol-5-yl-)-methoxy-]- quinazoline
XXXV	2-chloro-6,7-dimethoxy-4-{[3-(2-chloro-phenyl)-isoxazol-5-yl-]-methoxy}-quinazoline
XXXVI	2-chloro-6,7- dimethoxy-4-{[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl-]-methoxy}- quinazoline

Compd	R_1	R_2	R_3	R_4	Inhibition		
					A549	HCT116	MCF-7
XXXIII	R_1=H	R_2=H	R_3=Ph	R_4= 2-Cl	IC_{50} =13.29µM	IC_{50}=77.05µM	IC_{50}= 42.82 µM
XXXIV	R_1= OCH_3	R_2= OCH_3	R_3=Cl	R_4= 4-CH_3	IC_{50}= 24.07 µM	IC_{50} =31.08µM	IC_{50} =0.11µM
XXXV	R_1=OCH_3	R_2= OCH_3	R_3=Cl	R_4= 2-Cl	IC_{50}= 1.04µM	IC_{50} =58.90µM	IC_{50}= 1.99µM
XXXVI	R_1=OCH_3	R_2= OCH_3	R_3=Cl	R_4= 2, 4-diCl	IC_{50}=42.58µM	IC_{50}=74.80µM	IC_{50}= 5.74 µM

Recently NO-NSAID has been established as potent anti-cancer agents rather than their anti-inflammatory property[56].

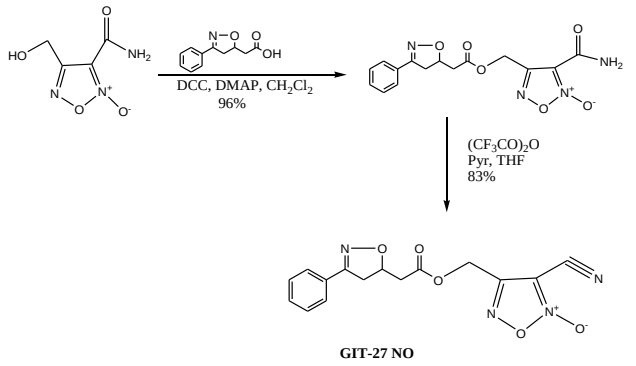


Compound (XXXV) known as **(GIT-27NO)**

(S, R)-3-phenyl-4, 5-dihydro-5- isoxazole acetic acid–nitric oxide

Mijatovic S. etal[57] in the studies have evaluated the effects of the new NO donating compound (S, R)-3-phenyl-4,5-dihydro-5-isoxazole acetic acid-nitric oxide (GIT-27NO) on the A375 human melanoma cell line. And it has been shown to possess strong immunomodulatory properties both in vitro and in vivo. Treatment with the drug led to a concentration-dependent reduction of mitochondrial respiration and the number of viable cells in cultures. Decreased cell viability correlated with the release and internalization of NO and was neutralized by the extracellular scavenger hemoglobin. GIT-27NO neither

influenced cell division nor induced accidental or autophagic cell death. Early signs of apoptosis were observed upon co-culture with the drug and resulting in marked accumulation of hypodiploid cells, suggesting that the induction of apoptosis is one primary mode of action of the compound in A375 cells. GIT-27NO significantly inhibited the expression of the transcription repressor and apoptotic resistant factor YY1 and, in parallel, augmented the presence of total p53.



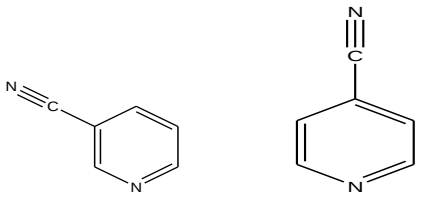
Scheme for the synthesis of GIT-27 NO

NICOTINONITRILE DERIVATIVES

Pyridine scaffold is one of the most popular N-heteroaromatics which forms an integral part of the structure of a wide variety of pharmaceuticals. Over the years, there has been considerable interest in the pyridine nucleus and their fused heterocyclic systems.

Special emphasis has been laid on cyanopyridines (Nicotinonitriles) with different alkyl and aryl groups because of their promising biological potential such as anti-inflammatory, antimicrobial, analgesic, antipyretic, cardiotonic and anticancer activity.

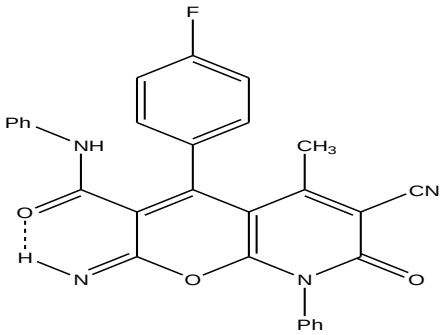
These compounds show prominent anticancer activity owing to their interference with different types of biological targets like PDE3, PIM1 kinase and survivin protein.



3-cyano pyridine 4-cyano pyridine

The basic scaffold of nicotinonitrile moiety

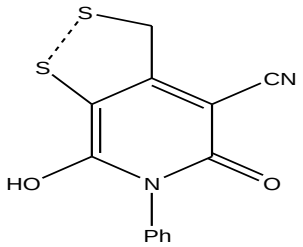
El-Sayed Hassan. and coworkers[58] synthesized a series of fused 2-oxonicotinonitrile derivatives using 4-methyl-2,6-dioxo-1-phenyl 1,2,5,6-tetrahydropyridine-3-carbonitrile as a starting material and screened the synthesized compounds for their in vitro antitumor activity against three human tumor cell lines MCF-7 (breast adenocarcinoma), NCI-H460(non-small cell lung cancer) and SF-268(CNS cancer) and ascertained compound (XXXVI) 6-Cyano-4-(4-fluorophenyl)-2-imino-5-methyl-7-oxo- N,8-diphenyl-7,8-dihydro-2H-pyrano[2,3-b]pyridine-3-carboxamide and (XXXVII)7-hydroxy-5-oxo-6-phenyl-5,6-dihydro-3H-[1,2] dithiolo[3,4-c]pyridine-4-carbonitrile with highest inhibitory effects in comparison to other synthesized compounds but none showed activity higher than doxorubicin.



Compound (XXXVI)

Compound	X	R	R_2
(XXXVIII)	Br	3,4-$(OCH_2O)C_6H_3$	CH_3
(XXXIX)	Br	3,4-$(OCH_2O)C_6H_3$	C_2H_5
(XL)	OCH_3	2-thienyl	C_2H_5

6-Cyano-4-(4-fluorophenyl)-2-imino-5-methyl-7-oxo-N,8-diphenyl-7,8-dihydro-2H-pyrano[2,3-b]pyridine-3-carboxamide



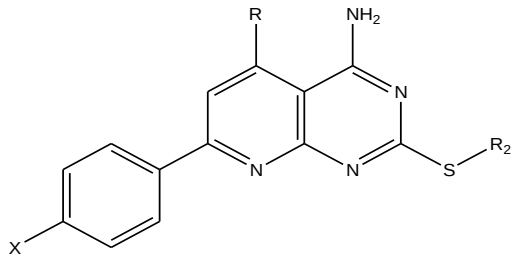
Compound (XXXVII)

7-hydroxy-5-oxo-6-phenyl-5,6-dihydro-3H-[1,2] dithiolo [3,4-c] pyridine-4-carbonitrile

An extensive study of the structure-activity relationship led to the conclusion that in compound (XXXVI), the amide group present as a side chain accounts for its higher activity while in compound (XXXVII) Dithiol ring at position 4 and 5 leads to an increase in its activity.

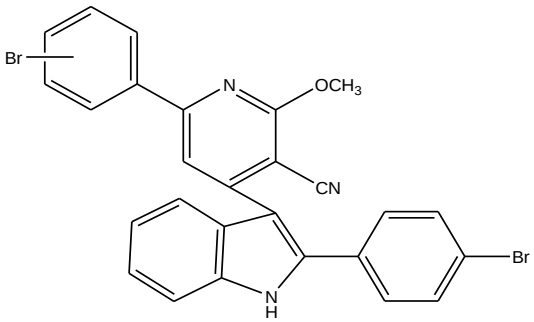
HassanM.Faidallah et al [59] described the synthesis of a novel series of structurally related polysubstituted pyridines and pyrido[2,3] pyrimidine ring systems. All the newly synthesized compounds were evaluated for their in-vitro cytotoxic effects against HT-29(human colon carcinoma), Hep G2 (hepatocellular carcinoma), MCF-7(Caucasian breast adenocarcinoma) and Hs 27 (normal nontransformed human foreskin fibroblast) cell lines. Compounds (XXXVIII), (XXXIX), and (XL) showed particular effectiveness against both colon carcinoma HT29 (almost twice the activity of doxorubicin with LC_{50} 25.2, 28.8, 26.9 versus 40 µM respectively) and human breast cancer MCF-7 cell lines (40-60% of activity of doxorubicin with LC_{50} 6.4, 7.9, 8.91 versus 4.0 µM respectively). Also, they exerted a

marginal inhibitory effect on the growth of Hs 27 cell line (LC_{50} > 200µM. Compounds (XXXVIII) and (XXXIX) emerged as promising scaffolds for future anticancer studies.



Compound XXXVIII-XL

Patel M. et al synthesized and evaluated the anticancer activity of a series of novel nicotinonitrile derivatives incorporatingindole moiety. Results showed that 4-(2-(4-Bromo phenyl)-1H indol-3-yl)-2-methoxy-6-(4-bromophenyl)nicotinonitrile (compound XLI) was found to be the most potent derivative compared to other compounds but less potent as compared to standard drug Methotrexate[60].

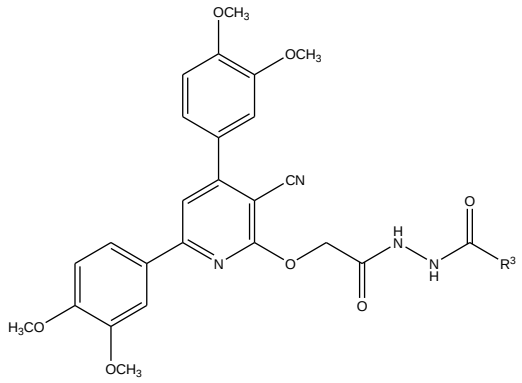


(Compound XLI)

For compound XLI, it was concluded that the halogenated phenyl ring on 6th position of pyridine ring contributes for more activity and Substitution at phenyl ring on 6th position of pyridine ring gives good anticancer activity in the following order: Br > NH_2 > CH_3 > OH > H

Malki A. et al described the synthesis of 3-cyano-2 substituted pyridine derivatives and tested them for their in vitro anticancer activity against five cancer cell lines. The results demonstrated that benzohydrazide derivative [N'-[2-(3-cyano-4,6-bis(3,4-dimethoxy phenyl) pyridin-2-yloxy)acetyl] benzohydrazide] (XLII) was found to be of principle interest which could be considered as a potential scaffold for the development of more potent anticancer agents. The results demonstrated that the compound (XLII) reduced viability and induced apoptosis in MCF 7 breast cancer cells at an IC50 value of 2 µM and was less cytotoxic to normal breast epithelial cells (MCF-12a) than MCF 7 cells. The proposed mechanism of its action is that it inhibits the proliferation of MCF-7 cancer cells by inducing apoptosis and arresting the cell cycle at the G1 phase via inhibition of CDK2 and CDK4. Besides, it further modifies apoptotic response and increased the expression levels of p53, p21, p27, Bax, and caspase-3, while it reduced expression levels of Bcl-2, Mdm-2, and Akt. In addition to the above-mentioned modifications, it induced the release of cytochrome c from mitochondria to the cytoplasm.

Moreover, the expression of β -catenin and phospho AKT was down-regulated by it along with inhibition of the expression of MMP-9 and VEGF[61]



Compound (XLII)

N'-[2-(3-cyano-4,6-bis(3,4-dimethoxyphenyl)pyridin-2-yloxy)acetyl]benzohydrazide

CONCLUSION

This review gives an overview of the importance of heterocyclic engineering and rational design which is intricately connected to the wide range of heterocyclic structures present in the biological systems.

Most of these moieties show in vivo and in vitro anticancer anti-proliferative effects associated with different mechanisms, like enzyme inhibitory effects like inhibition of growth factors, kinase inhibitory effects, inhibition of enzymes, etc. The best part is these moieties are non-selective broad-spectrum moieties having promising activity against many cancer cell lines.

In recent years, a large number of heterocyclic moieties have been identified possessing remarkable anticancer activity. Although, only five types of moieties have been discussed in the present review due to their structure diversity, to date a large number of heterocyclic compounds with diversified ring structures have been synthesized for their cytotoxic activity.

This paper proves to be significant for further research work on other bioactive rings that can be used as potential anticancer drugs.

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