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Thiadiazole derivatives as protein kinase inhibitor: An insight to synthesis and structure activity relationship

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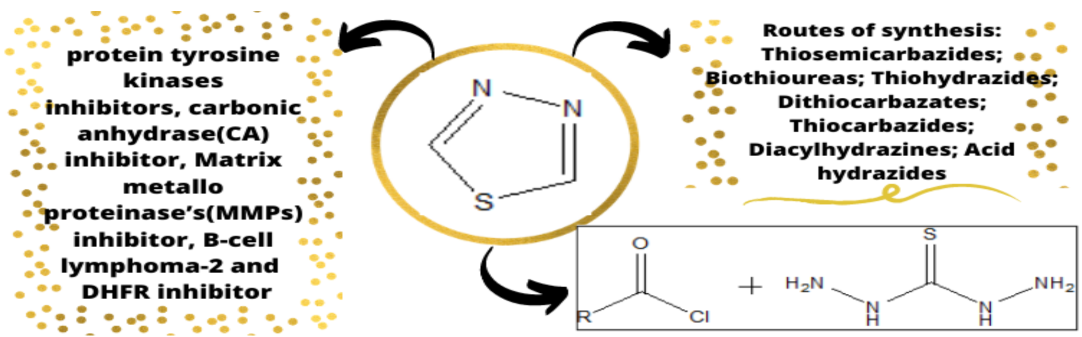
ABSTRACT



Cancer is the uncontrolled multiplication of cells and has become leading cause of deaths worldwide. A number of chemotherapeutic drugs have been developed to treat cancer which usually contains heterocyclic compounds like 1, 3, 4-Thiadiazole derivatives. Thiadiazole nucleus possesses various biological activities. 1,3,4-Thiadiazole act through various mechanisms like protein kinase inhibitor, EGFR inhibitor, Carbonic anhydrase inhibitor, etc. Thiadiazole derivatives indulge into the nucleic acid synthesis of cell leads to the cell death and cancer inhibition. Protein kinases have become most frequently explored targets for cancer treatment as these kinases phosphorylate the proteins and modulates their action. The main aim of review article is to enlighten the various synthesis routes, mechanism of thiadiazole and SAR of protein kinase activity.

Keywords: Protein kinase; Anti-tumor; Synthesis of thiadiazole; Mechanism of thiadiazole; TGF-β inhibitor

INTRODUCTION

Cancer is the fastest growing disease worldwide. Each year, about 12 million people are diagnosed with cancer across the globe. Seven million patients die of cancer annually, and 25 million people are currently living with a diagnosis of cancer. In developed countries, cancer has become the leading cause of death, and in developing countries, it is second only to heart disease.[1] It is predicted that the number of new cases could further rise to 19.3 million by 2025.[2,3] Cancer is a general name for more than 100 of diseases in which cells inhibited apoptosis or show uncontrolled cell division.[4] A correct cancer diagnosis includes surgery, radiotherapy,[5,6] and chemotherapy. However, drugs administered for chemotherapy have a narrow therapeutic index; cause drug resistance[7,8] and therefore, there is a high incidence of unwanted side effects.[9,10] Therefore, the search for novel and selective anticancer agents is urgently required due to problems associated with currently available anticancer drugs.[11–14]

Thiadiazole is a five membered heterocyclic nucleus having two carbons two nitrogens and one sulphur atom. They occur in nature in four isomeric forms- 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. Thiadiazole has received considerable attention as a privileged scaffold due to its significant therapeutic potential.[15] Due to presence of –N=C-S moiety in its structure[16] thiadiazole nucleus possess various biological activities[17] (Figure 1) including antitumor,[18,19,20] antimicrobial,[21,22,23,24] anticholinesterase,[25] antidiabetic,[26,27] antidepressant,[28,29] antibacterial,[30,31] Analgesic,[32] anticonvulsant,[33] anti-inflammatory,[34,35] antimalarial,[36,37] antiviral,[38] antitubercular,[39,40] antileishmanial,[41,42] antiglaucoma,[43] acetylcholinesterase inhibitory properties,[44,45,46] antifungal,[47] antioxidant.[48]

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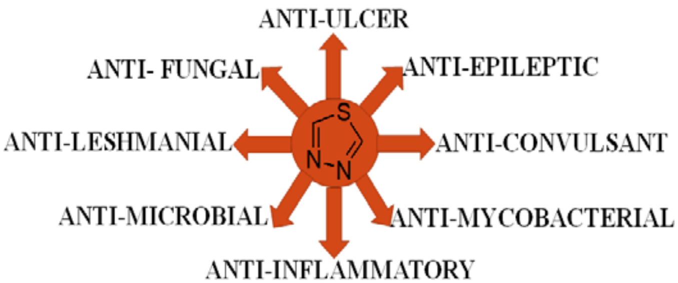


Figure 1: Various biological activities of Thiadiazole nucleus.

Thiadiazole derivatives are usually yellow in color with a pyridine like odor. It is soluble in alcohol, ether and slightly soluble in water. It is parent material for numerous chemical compounds including sulfur drugs, biocides, fungicides, dyes, chemical reaction accelerators, lubricants, optical active crystals, photographic materials, epoxy resins. Thiadiazoles are named according to Hantzsch-widman system of systematic name of heterocyclic compounds. The ending *-azole* designates a five membered ring system with two or more heteroatoms, one of which is Nitrogen. The ending *–ole* is used for other five membered heterocyclic ring without Nitrogen. The numbering of monocyclic azole system begins with the heteroatom that is in the highest group in the periodic table and with the element of lowest atomic weight in that group. Hence the numbering of 1, 3, 4- Thiadiazole is done in Figure 2.[49]

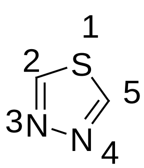


Figure 2. Numbering of Thiadiazole ring

The ring system is less aromatic than benzene, thiophene, and pyridine. The aromatic character is measured by π electron delocalization. 1, 3, 4 – thiadiazoles are weak base due to the inductive effects of extra hetero atoms and are readily alkylated and acylated at N_3 . The electron withdrawing nature of the nitrogen atoms ensures that electrophilic attack at carbon is very rare and nucleophilic substitution reactions are common. Electrophilic attack at the sulphur atom has been observed. The reactivity of ring nitrogen atom arises from electrophilic reactions depending on tautomeric equilibrium of thione-thiol or amine-imine. In thione or imine form deprotonation of ring N-H can take place and ring nitrogen atom becomes vulnerable to alkylation or acylation or transformation to 1,3,4 –thiadiazolium salt. The reactions are conducted with electrophiles such as alkyl halides, trimethylsilylmethyl trifluoro methanesulfonate, formaldehyde etc. The ring is relatively stable in aqueous acid solutions but the ring gets cleaved in aqueous basic solutions. 1, 3, 4-thiadiazole core skeletons are subjected to various substitution reactions with alkylhalides, acidchlorides, and sulfonyl chlorides to afford various drug like 2-amino-substituted 1, 3, 4- thiadiazole derivatives.[50] When substituents are introduced into 2' or 5' position of this ring, the ring is highly reactive and forms different derivatives of thiadiazole easily.[51]

A number of thiadiazole-containing drugs[52] are currently on the market: acetazolamide and methazolamide are diuretics, acting through inhibition of carbonic anhydrase[53]; their derivatives display additional activities, including anticonvulsant and selective cerebral vasodilation, as well as the anticipated inhibition of carbonic anhydrase. Acetazolamide show to inhibit the growth of several tumor cells in vivo and in vitro when targeting along cytotoxic agents.[54] Other thiadiazole containing drugs include, cefazolin sodium (CFZL)and cefazedone (CFZD) - first-generation cephalosporins; timolol - a nonselective β-adrenergic receptor blocker used for the treatment of hypertension, angina, tachycardia and glaucoma; xanomeline- a selective agonist of muscarinic acetylcholine receptor subtypes M1 and M4; and megazol- an antiparasitic drug.[55,56]

1,3,4-Thiadiazoles are mesoionic - a poly-heteroatomic system containing a five-membered heterocyclic ring associated with conjugated p electrons and distinct regions of positive and negative charges[57] (Figure 3).

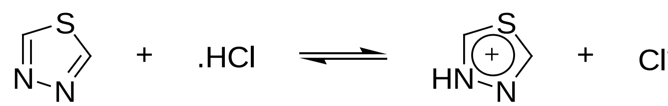


Figure 3: Mesoionic nature of 1,3,4-Thiadiazole

Mesoionic systems are dense and highly polarizable, with a net neutral electron charge; these characteristics allow mesoionic compounds to cross cellular membranes and interact with biological targets with distinct affinities.[58,59]

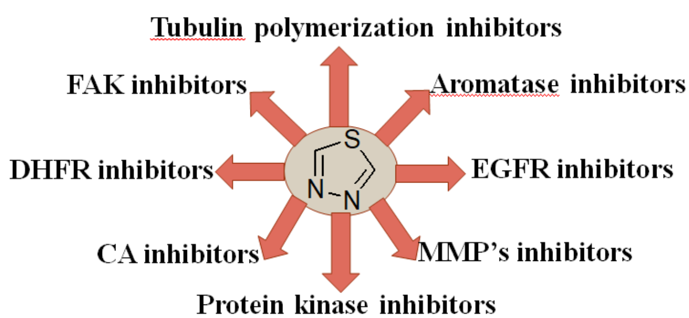


Figure 4. Various mechanisms through Thiadiazole derivatives act

Compounds containing the thiadiazole ring are known to possess excellent anticancer activities *in vitro*. Thiadiazoles shows broad-spectrum anticancer activities against human cancers and targeted molecular involved in proliferation, survival, and metastasis including the following mechanisms: protein tyrosine kinases,[60–63] carbonic anhydrase (CA), matrix metalloproteinase's (MMPs), B-cell lymphoma 2(Bcl-2), etc (Figure 4),[64] DHFR inhibitor.[65]

Mechanism:

Protein kinase becomes most frequent target in anti-cancer drug discovery. These are the enzymes that regulate the biological activity of proteins by phosphorylation of specific amino acids with

ATP as the source of phosphate thereby inducing a conformational change from an inactive to an active form of protein. Phosphorylation is the process in which phosphate group is adding chemically to other amino acid. Kinases are turned on or off by phosphorylation. The phosphate group is attached to the amino acid tyrosine on the protein that attach phosphate group to other amino acids(serine and threonine). Phosphorylation of protein by kinase helps in signal transduction, regulating cellular activity like cell division. When protein kinase stuck in 'on' position and cause unregulated growth of the cell and leads to cancer.[66,67]

Transforming growth factor-β (TGF-β) is a cytokine found in various normal cells and transformed cells, and has various biological functions, such as cell proliferation, differentiation, migration, apoptosis, and adhesion.[68] TGF-βs (TGF-β1, TGF-β2, TGF-β3) play an important role in cancer biology, including all aspects of tumor inhibition and tumor promotion. TGF-β has a dual action in cancer as a tumor suppressor and a tumor promoter.[69]

As a tumor suppressor, it inhibits tumorigenesis by inducing growth arrest and apoptosis. As a tumor promoter, it induces tumor cell migration and stimulates epithelial to mesenchymal transition. TGF-β also promotes tumorigenesis indirectly by acting on the tumor microenvironment. Epithelial-to-mesenchymal transition induced by TGF-β contributes to a chemoresistant phenotype.

The transforming growth factor (TGF)-β signaling pathway is deregulated in many diseases, including cancer. In healthy cells and early-stage cancer cells, this pathway has tumor-suppressor functions, including cell-cycle arrest and apoptosis. However, its activation in late-stage cancer can promote tumorigenesis, including metastasis and chemoresistance. The dual function and pleiotropic nature of TGF-β signaling make it a challenging target and imply the need for careful therapeutic dosing of TGF-β drugs.[70] TGF-β can effectively inhibit the proliferation of epithelium, endothelium, and hematopoietic cell lines, which is core to tumor inhibition mechanisms. TGF-β-mediated growth inhibition and TGF-β overexpress are conductive to tumor growth and metastasis. In particular, TGF-β overexpress occurs at various stages of illness, including cancer, inflammation, and fibrosis. TGF-β adjusts signaling through a transmembrane receptor, which is a serine–threonine complex composed of type-I (activin receptor-like kinase 5, ALK5) and type-II receptor kinases.[71] Initially ALK5 is phosphorylated by the combination of TGF-βs and a type-II receptor in the juxtamembrane glycine-serine (GS) domain and Smad proteins are produced simultaneously[72]. The activated ALK5 phosphorylates receptor associated Smads, such as Smad2 and Smad3, bind with Smad4 to form complexes. These Smad complexes are delivered into the nucleus, where they regulate the expression of several hundred genes, including cell differentiation, proliferation, apoptosis, migration, and extracellular matrix production. Through this mechanism, TGF-β signals can be transmitted into the nucleus and regulate various biological activities. As ALK5 is the key node of TGF-β signal transduction, inhibiting ALK5 phosphorylation with substrate Smad2/Smad3 can block transmission of the TGF-β signal to the nucleus.[73,74]

Imatinib is the first approved tyrosine kinase inhibitor that binds to the kinase domain of Bcr-Ablobserved in 95% of chronic myelogenous leukemia (CML) patients.[75]

Synthesis of 1,3,4-Thiadiazole

1. From Thiosemicarbazides: 1,3,4-Thiadiazole can be synthesized using thiosemicarazides as in Figure 5 in the presence of appropriate reagent like phosphorus oxychloride[76,77] and 1,3,4-oxadiazole-2-thione derivatives with amines give thiosemicarbazides derivatives, which on treatment with base or acid undergo cyclisation to form 1,3,4-thiadiazoles derivatives.[78]

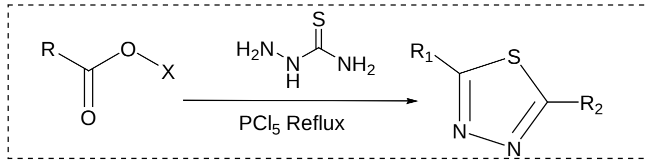


Figure 5: Synthesis of 1,3,4-Thiadiazole using thiosemicarbazide

2. From Biothioureas: 1,3,4- Thiadiazole derivatives can synthesize using symmetrical Dithiobiureas derivatives (Fig. 5a). A solution of Biothiourea derivatives in anhydrous tetrahydrofuran is added dropwise in solution of chloranil or bromanil in the same solvent i.e. THF.[79]

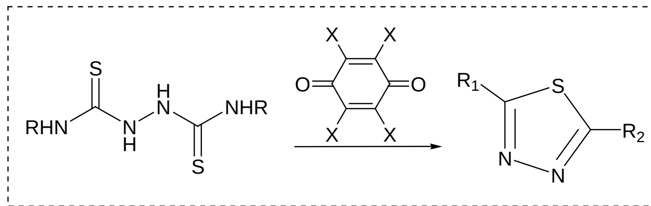


Figure 5a: Synthesis of 1,3,4-Thiadiazole using biothioureas

3. From Thiohydrazides: Thiadiazoles can also synthesized by treating thiobenzhydrazide with benzaldehyde to produce the thiohydrazide derivative (Fig. 5b) and with benzonitrile producing N-thiobenzoylbenzamidrazone.[80]

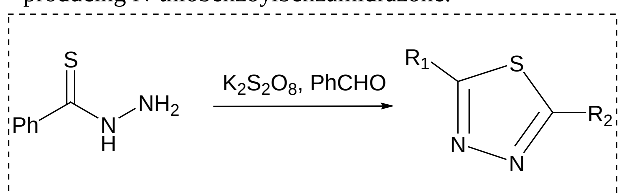


Figure 5b: Synthesis of 1,3,4-Thiadiazole from thiohydrazides

4. From Dithiocarbazates: 1,3,4-thiadiazole sythesis can done with acylhydrazide and Dithiocarbazates possessing substituted butenolide moiety.[81]

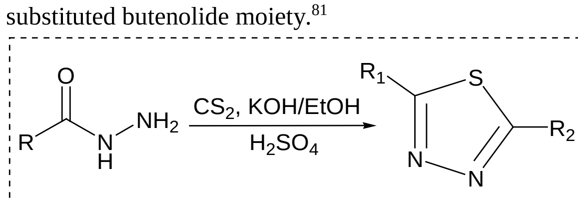


Figure 5c: Synthesis of 1,3,4-Thiadiazole by dithiocarbazates

5. From Thiocarbazides: Thiocarbazide is a new, an expeditious, and an ecofriendly route (Figure 5d) for preparation of substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl) hydrazones using thiocarbo-hydrazide as the starting material, using silica supported dichlorophosphate as the dehydrant, and

a microwave as the heat source. It is a high-yield method of reference.[82,83]

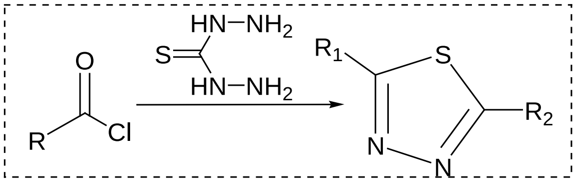


Figure 5d: Synthesis of 1,3,4-Thiadiazole using thiocarbazide

6. From Diacylhydrazines:1,3,4- thiadiazole can formed via cyclization of N,N-Diacylhydrazines (Fig. 5e) which is very common and convenient way to synthesize them using P_2S_5 and lawesson's reagent in the presence of various solvents like DMF, CH_2Cl_2, THF, dioxane, and PhMe. Solventless synthesis by microwave radiation has also been reported.[84]

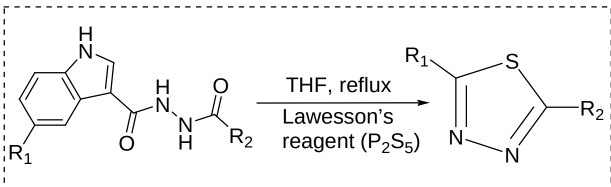


Figure 5e: Synthesis of 1,3,4-Thiadiazole from diacylhydrazines

7. From Acid Hydrazides: Synthesis of 1,3,4-thiadiazoles can done directly from carboxylic acids (Fig. 5f) using propylphosphonic anhydride (T_3P) wherein it acts as both a coupling and a cyclodehydration reagent. In most cases, the reaction proceeded with high efficiency; however, the products were contaminated with a small percentage of byproduct 1,3,4-oxadiazole (3−5%) but could be easily purified by recrystallization or column chromatography.[85]

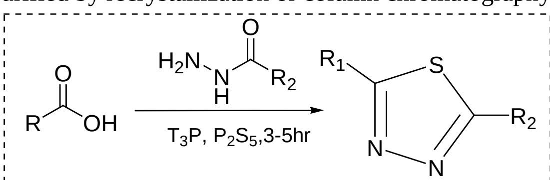


Figure 5f: Synthesis of 1,3,4-Thiadiazole from acid hydrazides

I. Others: A new series of 2,5-disubstituted-1,3,4-thiadiazoles can synthesized by different reagents, namely, ethoxymethylene malononitrile, ethoxymethylene ethyl cyanoacetate, triethyl orthoformate, phenylisothiocyanate, carbon disulfide, isatin, acetophenone, cyclohexanone, different aldehydes, and different anhydrides. The chemical structure of these products was characterized by the spectral data IR, ^{1}H-NMR, 13C-NMR, MS, and elemental analysis. All the synthesized compounds were screened for their antibacterial activity.[86]

II. 2-[[5-(2,4-Difluoro/dichlorophenylamino)-1,3,4-thiadiazol-2-yl]thio] acetophenone derivatives can also synthesize using hydrazine hydrate, thiosemicarbazides and carbon disulphide. The synthesized derivatives were evaluated for their human carbonic anhydrase inhibitor activity.[87]

III. *N*-(5-Mercapto-1,3,4-thiadiazol-2-yl)-2-(4-methoxyphenyl) acetamide reacts with benzyl chloride to give thiadiazole derivatives which were evaluated for in vitro cytotoxicity assessment using MTT assay method.[10]

IV. Styryl 1,3,4-thiadiazoles compounds formed via two-step methodology *via* benzohydrazide followed by treatment with Lawesson's reagent in the presence of Propylphosphonic anhydride and triethylamine produced styryl 1,3,4-thiadiazoles in excellent yields.[88,89]

V. 2-(1H-pyrazol-1-yl)-1,3,4-thiadiazole analogues can formed using carbonitrile derivatives which were prepared by Micheal addition then react further with 2,4-pentanedione derivatives in ethanol under reflux to give various thiadiazole derivatives [90] (Figure 5).

VI. 2,5-disubstituted-1,3,4-thiadiazoles can also prepaed by ultrasonic irradiation of a mixture of 1- naphthylacetyl chloride, ammonium cyanide, dichloromethane and polyethylene glycol-400 for 1.5 h at 10–20°C and subsequent irradiation for 1.5 h in the presence of N-arylglycine hydrazides. This method requires short time and gives thiadiazoles in high yields.[91]

1,3,4-Thiadiazole derivatives as protein kinase inhibitors with comparative SAR of different derivatives

- A series of benzo[*c*][1,2,5]thiadiazol-5-yl imidazoles(1) and thieno[3,2-*c*]-pyridin-2-yl imidazoles(2) derivatives were synthesized and evaluated for their activin receptor-like kinase 5 (ALK5) activities. The compounds having –R group 3-F or –CH_3in Figure 6 showed highest activity and results showed that introducing electron-withdrawing (F) and electron-donating group (CH_3) on the benzene ring can improve the ALK5 inhibitory activity as shown in Figure 7.[92,93]

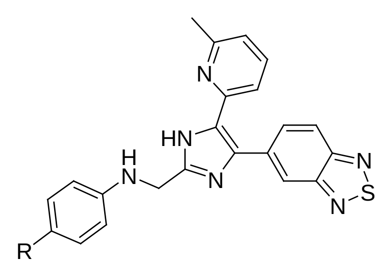


Figure 6: Compound shows maximum activity

- New 1,3,4-thiadiazole derivatives were synthesized and evaluated for their cytotoxic effects on multiple human cancer cell lines like K562 chronic myelogenous leukemia cell line expressed Bcr-Abl tyrosine kinase. Compound in Figure 8 [N-(5-Nitrothiazol-2-yl)-2-((5-((4-(trifluoromethyl)phenyl)amino) -1,3,4-thiadiazol-2-yl)thio)acetamide] showed selective activity against the Bcr-Abl positive K562 cell line. Molecular modeling in Figure 9 showed that the nitrothiazole moiety helps in bonding and hydrophobic interaction with the key amino acid residues which results in further development of novel kinase inhibitors.[94]

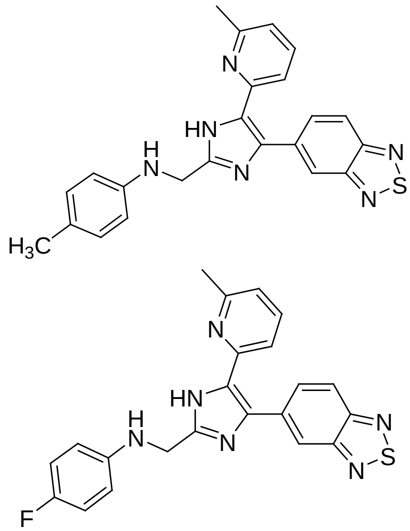


Figure 7: Substitutions which increase the protein kinase activity

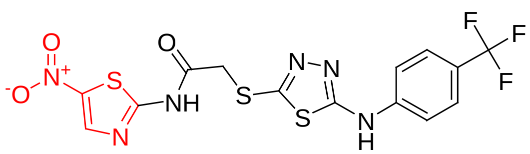


Figure 8: Compound shows selective activity against Protein kinase enzyme.

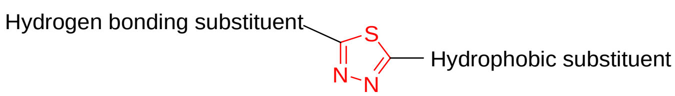


Figure 9: Substitutions shows maximum activity

- A new series of 5-(3,5-dinitrophenyl)-1,3,4-thiadiazole derivatives were synthesized which were evaluated for their anti-tumor activity against four human cancer cell lines, CCRF-CEM leukemia, HCT-15 colon, PC-3 prostate, and UACC-257 melanoma cell lines using Doxorubicin as a reference drug. Structure–activity relationships demonstrated that compounds with substitutions showed more potent inhibitory activity against the DHFR enzyme than those having no substituent's and following derivatives in Figure 10 exhibit anti-tumor activity.[95]

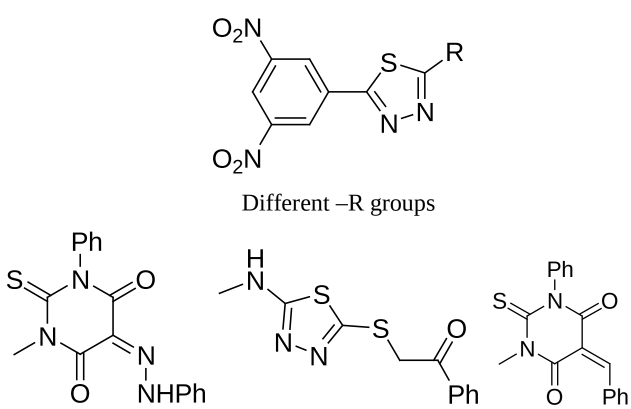


Figure 10: Substitutions having anti-tumor activity

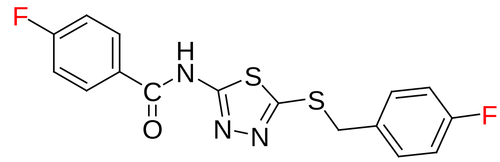


Figure 11: Addition of electronegative atoms at para positions enhanced tyrosine kinase inhibitors activity

- A series of substituted benzoylamino-2-[(4-benzyl)thio]-1,3,4 thiadiazoles was discovered as potent Abl tyrosine kinase inhibitors.Molecular docking studies on the Abl tyrosine kinase were conducted in order to rationalize the SAR of the synthesized inhibitors. SAR showed that the amide moiety was oriented outwards to bring together with thiadiazole nitrogen and two phenyl rings act as hydrophobic regions located at opposite sites of thiadiazole ring and the activity was enhanced by addition of electronegative atoms at para positions as in Figure 11 on both phenyl rings.[96]
- Various thiadiazoles and thiazoles derivatives were synthesized which target the Bcr-Abl T315I mutant and the such compounds having R is 3-Ethylpyridine or 1-(4-Fluorophenyl)ethanone show highest activity as in Figure 12.[97]

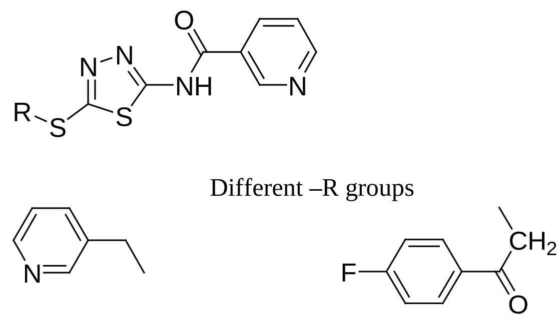
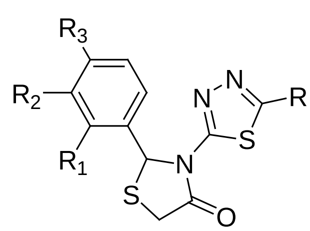


Figure 12: Thiadiazole derivatives having highest activity

- A new series of novel 5-alkyl/aryl thiadiazole substituted thiazolidin-4-ones were prepared and screened for *in vitro* anti-proliferative activity on human breast adenocarcinoma cells (MCF-7) by MTT assay. Most of the derivatives showed good anti tumor activity. Figure 13 derivatives shows potent activity

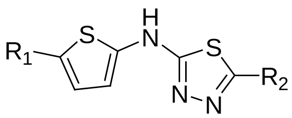


R= CH3, C2H5; R1= H, Br, NO2
R2= H, Br, F; R3= H, Cl, NO2

Figure 13: Potent compounds having anti-proliferative activity on human breast adenocarcinoma cells.

which shows that presence of 3-fluoro, 4-chloro, and 2-nitro groups at phenyl ring confer maximum activity, while bromo substitutions on phenyl ring resulted into the decreased activity.[98,99]

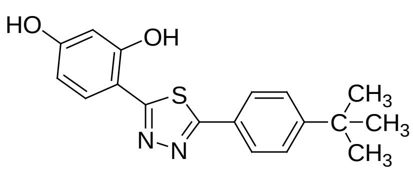
- A series of 5-aryl-2-(3-thienylamino)-1,3,4-thiadiazoles synthesized starting from thiophen-3-isothiocyanates. Those compounds as well as the thiosemicarbazide intermediates were screened for their antiproliferative activity against a panel of six cancer cell lines. Among them, two 5-aryl-2-(3-thienylamino)-1,3,4-thiadiazoles (A and B) have shown very interesting results with IC50 < 10μM on three cell lines.[100]



A, R_1=C_6H_5; R_2=4-OMeC_6H_4
B, R1=C_6H_5; R_2=4-OHC_6H_4

Figure 14: Potent 1,3,4-Thiadiazole derivatives

- Synthesis of series of new 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles was done and evaluated for their antiproliferative activity against the cells of human cancer lines. He found that derivatives 35 and 36 of different structures prove to be the most active. They exhibited higher inhibitory activity against T47D cells (human breast cancer cells) than cisplatin[101].



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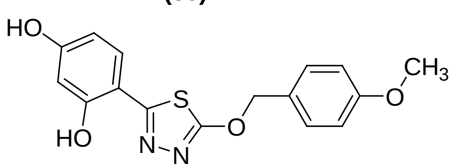

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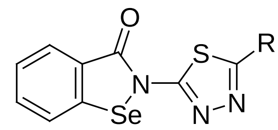
Figure 15: 1,3,4-Thiadiazole derivatives having higher inhibitory activity against T47D cells.

- A series of novel 1,3,4-thiadiazole-containing benzisoselenazolone derivatives was prepared by the condensation of 2-chloroselenobenzoyl chloride and 2-amino-5-substituted-1,3,4-thiadiazole and evaluated them for their in vitro antiproliferative activities in SSMC-7721, MCF-7 and A-549 cells. Among the synthesized compounds, the compound (A) showed significant antiproliferative activities in SSMC-7721, MCF-7 and A-549 cells, with IC_{50} values of 7.15, 3.44 and 3.24 μM, respectively. The compound (B)was found to be the most potent compound in A-549 cells, with IC_{50} values 2.48 μM. Similarly, the compound (C) also showed highly effective antiproliferative activities in MCF-7 and A-549 cells, with IC_{50} values of 3.92 and 3.12 μM, respectively.[102]



(A): R=Ph; (B): R= 2-OCH_3-Ph
(C): R= 3,4,5-$(OCH_3)_3$-Ph

Figure 16: Compounds having significant antiproliferative activity

- A series of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan have been synthesized to screen for FAK inhibitory activity. Compound (G) has shown the most potent biological activity against HEPG2 cancer cell line (EC50 = 10.28 μg/ml for HEPG2 and EC50 = 10.79 μM for FAK), which was comparable to the positive control. Docking simulation was performed to position compound (G) into the FAK structure active site to determine the probable binding model. The results of antiproliferative and Western-blot assay demonstrated that compound (G) possessed good antiproliferative activity against HEPG2 cancer cell line. Therefore, compound (G) with potent FAK inhibitory activity may be a potential anticancer agent against HEPG2 cancer cell.[103]

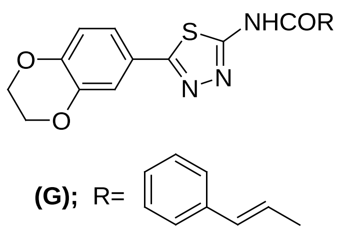


Figure 17: Active compound against HEPG2 cancer cell line.

The diverse therapeutic applications of thiadiazole derivatives have encouraged medicinal chemist to synthesize a large number of thiadiazole based therapeutic agent. Thiadiazole derivatives show potent antitumor activity against different cancer cell lines through the inhibition of kinases, pro-matrix metalloproteinase activation, etc. "Hydrogen bonding-Thiadiazole-Hydrophobic interaction" concept discussed in Figure 9 is suitable for potent 1,3,4-thiadiazole derivatives. Thiadiazole derivative without substitution of electron withdrawing group doesn't have proper interaction with receptor and leads to inactive compound. On the other hand if there is intervening groups like benzene between electron withdrawing group and thiadiazole ring leads to less activity of compound comparable to directly attached electron withdrawing group to thiadiazole ring. So, this concept suggest the anchoring role of electron withdrawing group directly attached to thiadiazole ring either at position 2^{nd} or 5^{th}.

Both electron-withdrawing and electron-donating groups at ortho- or meta-positions on the benzene ring attached to thiadiazole ring could improve the kinase activity, while para-substituents at benzene ring showed low improvements.

According to the above study, the introduction of a electron withdrawing substituent into the thiadiazole scaffold represents an important lead for the discovery of new protein kinase inhibitors, especially because of the emerging resistance to existing drugs.

Conclusion

In conclusion, Thiadiazole is beneficial ring for anti-tumor activity as protein kinase inhibitor which is shown in this article by its wide spectrum of biological profiles and their structure activity relationship. Also various methods for synthesis of thiadiazole derivatives are enlisted which show its versatility. So, thiadiazole is fruitful matrix for showing better efficacy and least restrictions for further development of better medicinal agents.

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Conflict of interest

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

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