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Review Article

Thiadiazole: An amazing anticancer moeity

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Abstract

Cancer is a general name for a group of more than 100 diseases in which cells belonging to a part of the body, begin uncontrolled proliferation. Nowadays, cancer is an important public health problem in all countries. For decades, conventional chemotherapy has been the most common type of anticancer pharmacotherapy. Cancer chemotherapy has been one of the major advances in the field of medicine in the last few decades. However, drugs administered for chemotherapy have a narrow therapeutic index and therefore, there is a high incidence of unwanted side effects. Thiadiazole is a five-membered ring system that has gained prominence by exhibiting a wide variety of biological activities. It has interesting pharmacophores that display a broad spectrum biological activity. The lower toxicity and *in vivo* stability of 1,3,4-thiadiazole nucleus are attributed to its aromaticity. Thiadiazole has exhibited potential antiglaucoma, antiinflammatory, antitumor, antiulcer, antibacterial, antiviral, analgesic, antiepileptic, antifungal and radioprotective activities. In this review article antitumor activity of various thiadiazole derivatives has been discussed.

Keywords: proliferation, Thiadiazole, pharmacophore

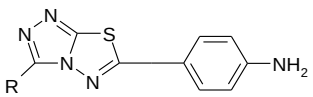
1. Introduction

Cancer is a class of diseases in which cell, or a group of cells display uncontrolled growth, invasion, and sometimes metastasis. It affects people at all ages with the risk of most types increasing with age. It caused about 13% (7.6 million) of all human deaths in 2007. Levamisole (I) an anthelmintic agent was found to be an immuno-stimulant by Rebnoux in 1972. It appears to be most effective in patients with small tumor burdens and it acts by stimulating the responsiveness of lymphocytes to tumor antigen.[1] Similarly the problem of multidrug resistant microorganisms has reached on alarming level around the world, and the synthesis of new anti-infective compounds has become an urgent need for the treatment of microbial infections. Therefore the search of novel antibacterial and anticancer agents devoid of side effects continues to be an active area of research in medicinal chemistry.[2]

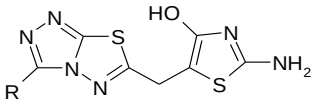
In recent years 1, 3, 4-thiadiazole derivatives have received significant attention and have been increasingly investigated due to their diverse range of biological properties. They exhibit, for example, antimicrobial, antimycobacterial, anticancer, antiinflammatory, carbonic anhydrase inhibiting effect, antianxiety, antidepressant, antioxidant properties. 1, 3, 4- Thiadiazoles exhibit diverse biological activities, possibly due to the presence of =N–C–S moiety.[3] In this review article we discussed about the anticancer activity of various thiadiazole derivatives.

2. Anticancer Derivatives of Thiadiazole:

3, 6- disubstitutedtriazolo [3,4-b] thiadiazole derivatives was evaluated that compounds **1a** and **1b** maintained the highest growth inhibition activity at micromolar concentrations in different human tumor cell lines. The compound **1a** displayed high activity against NCI-H226 (log GI50 - 5.14) cell line of non-small cell lung cancer subpanel and against CCRF-CEM (log GI50 -5.0) cell line of Leukaemia subpanel. Compound **1b** exhibited the highest sensitivity against Renal, Colon and Melanoma Cancer cell lines, the best results being against Renal Cancer A498 cell line with log GI50 -7.27.[4]

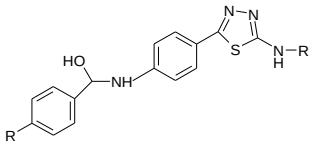


1a



1b

5-[-4-(4fluorobezoylolamino) phenyl]-2-subsitutedamino-1, 3, 4-thiadiazole derivativeswere synthesized and evaluated for the cytotoxic activity.[5]



2

A series of N-substituted 2-amino-5-(2, 4-dihydroxyphenyl)-1,3,4-thiadiazoleswere synthesized and evaluated for their antiproliferative activities against human cancer cell lines. The cytotoxicity in vitro against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549

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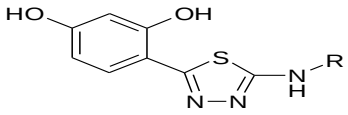
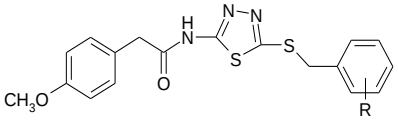
(lung), and T47D (breast) was determined. The highest antiproliferative activity was found for 2-(2,4-dichlorophenylamino) 5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole, with ID50 two times lower (SW707, T47D) than for cisplatin studied comparatively as the control compound.[6]



3

R = alkyl, aryl, morpholinoalkyl

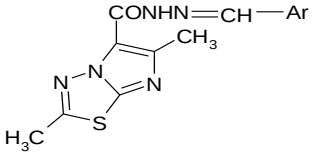
A series of N-(5-Mercapto-1,3,4-thiadiazol-2-yl)-2-(4-methoxyphenyl) acetamide**4(a-l)** was synthesized. All compounds **4(a-l)** demonstrated a higher cytotoxic activity against MDA-MB-231 breast cancer cell line in comparison with other cell lines. Compounds **4h** (IC50= 11 ± 0.18 μM), **4j** (IC50= 10 ± 0.39 μM), **4k** (IC50= 11 ± 0.77 μM) and **4l** (IC50= 8 ± 0.69 μM) exhibited higher cytotoxic activity against MDA-MB-231 cell line compared to imatinib (IC50= 20 ± 0.69 μM) as the reference drug.[7]



4(a-l)

4a	2-Cl	4g	3-OCH3
4b	3-Cl	4h	4-OCH3
4c	4-Cl	4i	2-F
4d	2-NO2	4j	3-F
4e	3-NO2	4k	4-F
4f	4-NO2	4l	H

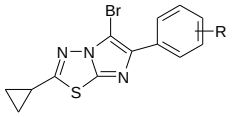
Some novel 2, 6-dimethyl-N'-substituted phenylmethylene-imidazo [2,1-b][1,3,4]thiadiazole-5 carbohydrazides were synthesized . The newly synthesized compounds **5(a-h)** were evaluated in the National Cancer Institute's 3-cell line, one dose in vitro primary cytotoxicity assay Compounds **5c** and **5h** which passed the criteria for activity in this assay (20-29% growth percentages) were scheduled automatically for evaluation against the full panel of 60 human tumor cell lines at a minimum of five concentrations at 10- fold dilutions. 2, 6-Dimethyl-N'-(2-hydroxyphenylmethylidene)imidazo[2,1-b][1,3,4]thiadiazole-5 carbohydrazide **5c** showed the most favorable cytotoxicity.[8]



5(a-h)

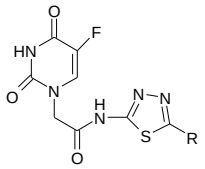
5a	C_6H_5	5e	4-BrC_6H_4
5b	4-$CH_3C_6H_4$	5f	4-ClC_6H_4
5c	2-HOC_6H_4	5g	4-FC_6H_4
5d	4-$CH_3OC_6H_4$	5h	4-NO_2C6H_4

Anti-tumor activity of series of 2-cyclopropylimidazo [2,1-b][1,3,4]thiadiazoles were found. These compounds were prepared by the cyclodehydration process between 2-amino-5-cyclpropyl-1,3,4-thiadiazole and an appropriate phenacyl bromide. In light of the NCI-60 results, five dose selected compound 5-bromo-6-(4-chlorophenyl)-2-cyclopropylimidazo[2, b][1,3,4]thiadiazole (NSC D-96022/1) was found to be the most active candidate of the series against Leukemia K-562, Colon Cancer HCT-15, Melanoma SK-MEL and Prostate Cancer PC-3 with GI50 1.79, 2.02, 2.17, and 2.22 mM respectively with degree of selectivity toward Leukemic cancer cell line based upon MG MID ratio (3.6).[9]



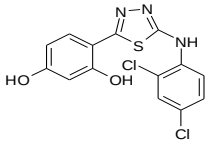
R= 4-Cl

Synthesis and biological evaluation of N1-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2- yl)-5-fluorouracil derivatives **7** were found as novel class of potential anti-tumor agents A-54 (human lung cancer cell), Bcap-37 (human breast cancer cell). While comparing activity with standard drug 5-fluorouracil; phenyl, 4-fluorophenyl, 4- methylphenyl, 3,5-dinitrophenyl substituted compounds showed higher activity against A- 549 and 4-fluorophenyl, 4 methylphenyl, 3,5-dinitrophenyl substituted compounds showed higher activity against Bcap-37.

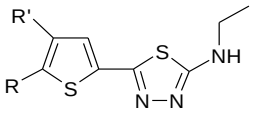


R= -CH_3, -C_2H_5, -C_3H_7, -$CH(CH_3)_2$, -C_6H_5, 4-ClC_6H_4, 4-FC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 3,5-$(NO_2)_2C_6H_3$

A number of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles were synthesized and evaluated for their antiproliferative activity. The panel substitution included alkyl, aryl and morphinoalkyl derivatives. The cytotoxicity in-vitro against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung) and T47D (breast) was determined. Alkyl and morphinoalkyl derivatives exhibited significantly lower effect than phenyl ones. The highest antiproliferative activity was found for 2-(2,4- dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole **8** with ID50 two times lower (SW707, T47D) than for cisplatin studied comparatively as the control compound.[10]

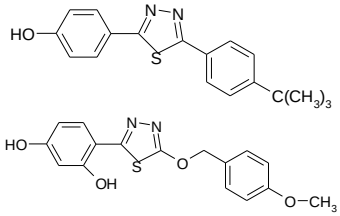


Novel derivatives of 2,5-substituted-1,3,4-thiadiazoles were synthesized and evaluated for their cytotoxicity. The biological study indicated that n-ethyl-5- (4,5,6,7-tetrahydro-1-benzothien-2-yl)-1,3,4-thiadiazole-2-amine **9** possessed high cytotoxicity in-vitro against thymocytes. The corresponding IC50 being 5.2 x 10-6 mM. The derivatives containing ethyl-amino group at the second position of 1,3,4-thiadiazole cycle resulted in good activity.[11]

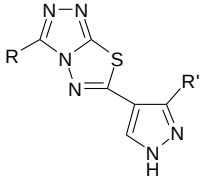


R = R' = - $(CH_2)_4$

A series of new 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4- thiadiazoles and evaluated for their antiproliferative activity against the cells of human cancer lines. Derivatives **10** and **11** of different structures prove to be the most active. They exhibited higher inhibitory activity against T47D cells (human breast cancer cells) than cisplatin.[12]



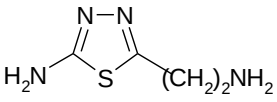
A series of 3,6-disubstituted 1,2,4–triazolo[3,4-b]-1,3,4-thiadiazoles were synthesized. Most of the newly synthesized compounds were screened for their anticancer activity in hepatic cell lines. Many of the compounds were found to be potent. The thiadiazole with naphthyloxymethyl**12a** and fluorophenyl**12b** groups as substituents showed excellent antiproliferative effect.[13]



12(a-b)

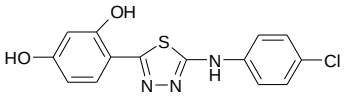
	R	R’
12a	o-Cresyloxymethyl	p-Methoxyphenyl
12b	2-Naphthyloxymethyl	p-Fluorophenyl

5-amino-l, 3, 4-thiadiazole derivatives was investigaed as antitumor and gastroprotective drug.[14]

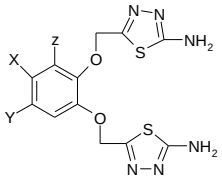


1

The 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole set are well known compounds with interesting in vitro and in vivo anti-cancer profiles. The antiproliferative activity of 4ClABT in tumor cells derived from peripheral cancers including breast carcinoma (T47D), colon carcinoma (HT-29), thyroid carcinoma (FTC-238), teratoma (P19), and T-cell leukemia (Jurkat E6.1), as well as cancers of the nervous system including rhabdomyosarcoma/medulloblastoma (TE671), brain astrocytoma (MOGGCCM) and glioma (C6) was studied by means of MTT assay.[15]



Substituted 2-amino-1,3,4-thiadiazoles compounds **15(a-c)**were synthesized and screened for their anticancer activity against three human cell lines , breast cancer (MCF7), non- small cell lung cancer (NCI-H460), CNS (SF-268).[16]



15(a-c)

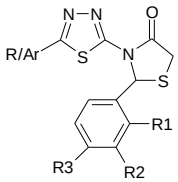
a: X= H, Y=H, Z=H

b: X=Br, Y=Br, Z=H

c: X= NO_2,Y=H, Z=H

A series of novel 5-alkyl/aryl thiadiazole substituted thiazolidin-4-ones were synthesized and screened for in vitroanti-proliferative activity on human breast adenocarcinoma cells (MCF-7) by MTT assay.The SAR study of tested compounds revealed that substitution of 3-fluorophenyl

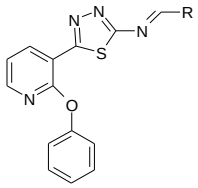
(**16a**), 4-chlorophenyl (**16b**), and 2-nitrophenyl (**16c**) at the 2nd position of thiazolidin-4-one moiety produced the most potent cytotoxic agents that exhibited *IC*50 below 70 μmol L–1.[17]



16(a-c)

	R	R1	R2	R3
16a	CH_3	H	F	H
16b	CH_3	H	H	Cl
16c	CH3	NO_2	H	H

5-(2-phenoxy pyridine-3-yl)- 1,3,4- Thiadiazole-2- amine derivatives were synthesized and evaluated for their anticancer activity.[18]



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