Review Article

Thiadiazole: An amazing anticancer moiety


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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, 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 cells, 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 de...

2. Anticancer Derivatives of Thiadiazole:
3, 6- disubstituted triazolo [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.

A series of N-substituted 2-amino-5-(2, 4-dihydroxyphenyl)-1,3,4-thiadiazoles were 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.

A series of N-(5-Mercapto-1,3,4-thiadiazol-2-yl)-2-(4-methoxyphenyl) acetamide4(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), 4i (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.

Some novel 2, 6-dimethyl-N'-substituted phenylmethylen-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 5e 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 5e showed the most favorable cytotoxicity.

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-cyclopropyl-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).

Synthesis and biological evaluation of N1-acetylaminio-(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.

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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.

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-benzothen-2-yl)-1,3,4-thiadiazole-2-amine 9 possessed high cytotoxicity in vitro against thymocytes. The corresponding IC50 being $5.2 \times 10^{-6}$ mM. The derivatives containing ethyl-amino group at the second position of 1,3,4-thiadiazole cycle resulted in good activity.

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.

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 naphthyloxymethyl12a and fluorophenyl12b groups as substituents showed excellent antiproliferative effect.
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 (MOGGCM) and glioma (C6) was studied by means of MTT assay.13

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 (SF268).16

A series of novel 5-alkyl/aryl thiadiazole substituted thiazolidin-4-ones were synthesized and screened for in vitro anti-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 IC50 below 70 μmol L-1.17

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References


