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Research Article

RECENT ADVANCES IN THIOSEMICARBAZONES AS ANTICANCER AGENTS

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ABSTRACT

Cancer is the leading cause of death in both developed and developing countries. Researchers are still developing new and more effective drugs to combat this disease. Thiosemicarbazones and their analogs have shown various potential medical applications but presently the areas in which thiosemicarbazones receiving more attention is its use against cancer. Thiosemicarbazone inhibit Topoisomerase IIa and Ribonucleotide reductase enzymes. Structural variations of these compounds were found to be highly selective in their action. The present review gives a brief outline of the recent advances in various thiosemicarbazones as anticancer agents.

Keywords: Thiosemicarbazone, Topoisomerase IIa and Ribonucleotide reductase inhibitors.

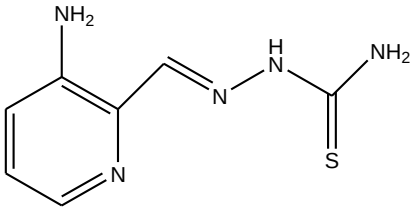
INTRODUCTION

Cancer is the second leading cause of death globally and is a multi-step disease. Deaths from cancer worldwide are projected to continue to rise to over 13.1 million in 2030[1]. Cancer is a group of diseases, there is no specific treatment for some kinds of tumours. Emergence of resistance to anticancer drugs possesses a major clinical challenge in successful treatment of cancer since some tumour cells develop a particular phenotype, called multi drug resistance [MDR][2]. On the basis of molecular hybridisation strategies, researchers synthesised various derivatives of thiosemicarbzones[3].

Thiosemicarbazone is formed from aldehyde/ketone when reacts with a thiosemicarbazide through a condensation reaction and it is derivative of imine. Chemically thiosemicarbazones have the general structure $R^1R^2CNNHCSNH_2$ while $R^1$and R^2 may be aromatic or heterocyclic systems[4]. In general, the IR spectrum of thiosemicarbazones displayed stretching of C=N and C=S bonds around 1537-1547 cm^{-1} and 1203-1243 cm^{-1}, respectively[5]. The electronic and stearic features of the attached ring system or the fragments are often found to have an effect on the biological activity of the thiosemicarbazone derivatives[4].

Thiosemicarbazones were found to inhibit Topoisomerase IIa and Ribonucleotide reductase (catalyses the synthesis of deoxy ribonucleotide required for DNA synthesis). Thiosemicarbazones could stabilize cleavable complexes forms by Topo II and DNA leading to apoptosis. The stabilization occurs as a result of alkylation of thiol residues on the topoIIa-DNA complex[6]. Besides, thiosemicarbazones were found to inhibit ribonucleotide reductase (RR). RR enzyme catalyses the synthesis of deoxyribonucleotides required for DNA synthesis. Since deoxyribonucleotides are present in extremely low levels in mammalian cells, it is a crucial and rate-controlling step in the pathway leading to the biosynthesis of DNA. Mammalian ribonucleotide reductase (RR) is composed of two dissimilar proteins, (R1), which contains polythiols and (R2), which contains non-heme iron and a free tyrosyl radical. Both the R_1 and R_2 subunits contribute to the active site of the enzyme[7]. Since thiosemicarbazones are known iron chelators and the chelates of iron are redox active thus they can destabilize or damage the non-heme iron-stabilized tyrosyl free radical and thus inhibit the catalytic function of RR[4].

The 3-aminopyridine-2-carboxaldehyde thiosemicarbazone commonly known as Triapine (**1**) is the most promising thiosemicarbazone molecule undergoing clinical phase II studies for Cervical Cancer. It has been reported to inhibit ribonuclease diphosphate reductase, responsible for replication of tumor cells[8-9].

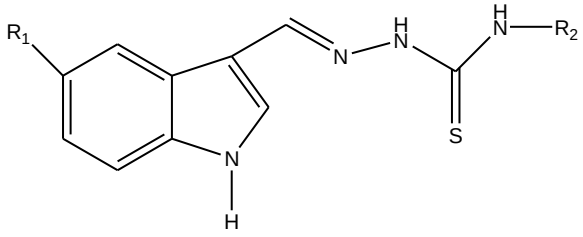


(**1**)

Though the parent aldehyde or ketone group had been considered crucial for the anticancer activity of thiosemicarbazones. Heterocyclic thiosemicarbazone exhibited higher activity compared with aromatic thiosemicarbazones[2]. Thiosemicarbazones have been reported to exhibit anti-tumour, anti-bacterial, anti-convulsant, anti-fungal, anti HIV, anti-leishmaniac, anti-malaria, anti-viral, anti-trypansomal, analgesic and anti-inflammatory[4].

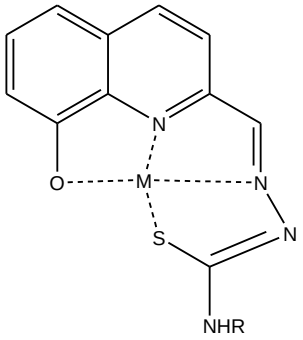
Thiosemicarbazones as an anticancer agent:

J.F. de Oliveria *et al* **(2017)**; reported the synthesis and structural characterization of a series of thiosemicarbazone and 4-thiazolidinones derivatives, as well as their *in vitro* antiproliferative activity against eight human tumor cell lines. For the most potent compound further studies were performed which includes evaluation of cell death induction, cell cycle profile, ctDNA interaction and topoisomerase IIα inhibition. Compound **2a** was the most promising especially against colorectal adenocarcinoma (HT-29) and leukemia (K562) cells (GI50 = 0.01 μM for both cell lines). Mechanism studies demonstrated that 24hr treatment with compound **2a** (5 μM) induced phosphatidylserine residues exposition and G_2/M arrest on HT-29 cells. Moreover, **2a** (50 μM) was able to interact with ctDNA and inhibited topoisomerase Iiαactivity[5].



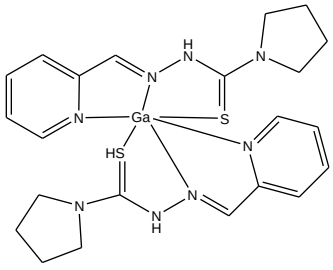
2a: R_1 = 1-naphtyl; R_2 = H

D. Rogolino *et al* **(2017)**; designed eight hydroxyquninoline thiosemicarbazone ligands containing an ONN'S donor set , their Zn (II) and Cu (II) complexes and evaluated for their anti-tumour activity. The Cu^{2+} Complexes were more stable and active than corresponding ligands towards NSCLC and breast cancer cell proliferation, with IC_{50} values ranging from 0.3 to 0.7 μM, in A549 cell line and zinc (II) complexes showed reduced activity. The most active copper (II) complex **3** reduced the cell proliferation with IC_{50} lower than 1μM, with an increase of cells in G2/M phase[10].



3: M= Cu (II); R=CH_2CH_3

Q. Jinxu *et al* **(2017)**; synthesized and determined X- ray single crystal diffraction of two types of 2-pyridine carboxaldehyde thiosemicarbazones Ga (III) complexes which are 2:1 and 1:1 ligand/Ga (III) complexes and evaluated their anti-proliferative activity. Ga (III) complexes (**5**) where the metal/ligand ratio is 1:1 had higher anti proliferative activity than 1:2 (**4**). After incubation, Ga (III) complexes caused a marked increase of caspase 3 and 9 activity in NCI-H460 compared to metal free ligand. Caspase activation was mediated by the release of Cyt C from the mitochondria. Both types of Ga (III) complexes showed more effective in inhibition of the G_1/S transition than the ligand alone[11].



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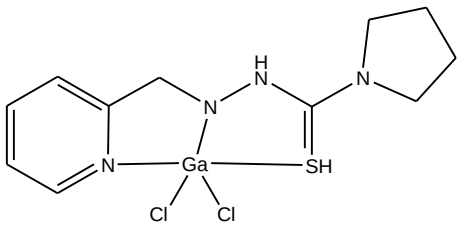

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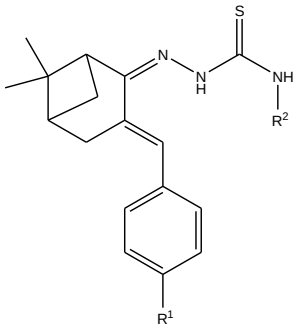
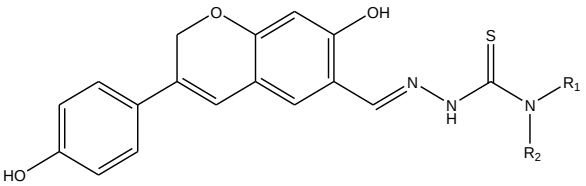
Y. Wang *et al* **(2017)**; synthesized a series of eighteen nopinone-based thiosemicarbazone derivatives and evaluated *in vitro* study against three human cancer cell lines (MDA-MB-231, SMMC-7721 and Hela). Among them, compound **6a** exhibited most potent antitumor activity

against three cancer cell lines with the IC_{50} values of 2.79 ± 0.38, 2.64 ± 0.17 and 3.64 ± 0.13 µM, respectively. Furthermore, the cell cycle analysis indicated that compound **6i** caused cell cycle arrest of MDA-MB-231 cells at G_2/M phase. The Annexin V-FITC/7-AAD dual staining assay also revealed that compound **6a** induced the early apoptosis of MDA-MB-231 cells[12].



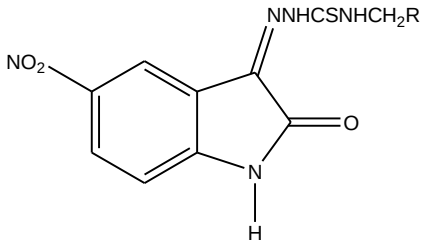
6a: R^1=OCH_3; R^2=Ph

M.H. Eugene *et al* **(2017)**;synthesized a series of novel eight monosubstituted and five disubstituted phenoxodiol-thiosemicarbazone hybrids and *in vitro* anti-proliferative activities of the hybrids were evaluated against the neuroblastoma SKN-BE(2)C, the triple negative breast cancer MDA-MB-231, and the glioblastoma U87 cancer cell lines. The mono-substituted hybrids exhibited potent anti-proliferative activity against all three cancer cell lines than di-substituted hybrids. The mono-substituted hybrids were active in the U87 brain cancer cell line, whereas phenoxodiol had no activity even at the highest dosage of 100 µM. Although hybrids were generally more toxic against normal cells compared to phenoxodiol, analogues **7a** and 7**b** actually displayed an overall improvement in specificity against breast and brain cancer cells as compared to phenoxodiol[13].



7a: R_1= H; R_2=allyl
7e: R_1= H; R_2=phenyl

H. Pervez *et al* **(2017)**; synthesized a series of fifteen N^4-benzyl substituted 5-nitroisatin-3-thiosemicarbazones and evaluated for urease inhibitory, phytotoxic and cytotoxic influences. All the compounds proved to be highly potent inhibitors of the enzyme, showing inhibitory activity (IC50 = 0.87 ± 0.25 – 8.09 ±0.23 µM) much better than the reference inhibitor, thiourea (IC50 = 22.3 ± 1.12 µM). Only one compound *i.e.* **9a** was active in the brine shrimp *(Artemia salina)* lethality bioassay, demonstrating cytotoxic activity with LD_{50} value 2.55 X 10^{-5} M[14].

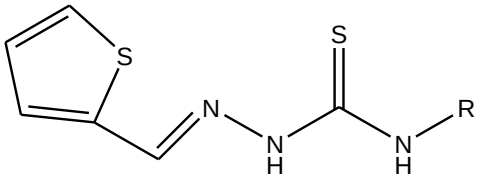


9a: R= 3-FC_6H_4

Yi Gou *et al* **(2016)**; synthesized a α-N_heterocyclic thiosemicarbazone ligand **L** ($C_{17}H_{14}N_4OS$) and its Fe complex **C10** ($C_{34}H_{26}FeN_9O_3S_2$) and assessed their chemical and biological properties in order to understand their anti-tumour activity. Electrochemical studies and ascorbate oxidation studies demonstrated that **C10** shows considerable redox activity, and Fe III/II redox potentials was within the range accessible to cellular oxidants and reductants. Absorption spectral, emission spectral and viscosity analysis reveal that **L** and **C10** interacted with DNA through intercalation and **C10** exhibited a higher DNA binding ability. Agarose gel electrophoresis experiments indicated that **C10** exhibited the highest pBR322 DNA cleaving ability. *In vitro* analysis the **C10** showed significantly more anticancer activity than the ligand alone. Moreover, **C10** induces production of reactive oxygen species (ROS) and DNA damage, resulting in activation of the p53 pathway, cell cycle arrest at the S phase, and mitochondria-mediated apoptosis by regulating the expression of Bcl_2 family proteins[15].

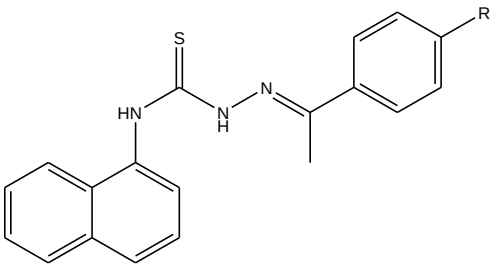
J.F. de Oliveira *et al* **(2015)**; designed a series of thiophene-thiosemicarbazone derivatives **(11a-j)** and evaluated their anti-tumour activity against human tumour cell lines through the colorimetric method. Compounds **11a** and **11b** were the most effective in inhibiting 50% of the cell growth after 48 hours of treatment. As compound **11a** showed a potent anti-proliferative profile, it has been chosen for further studies in 786-0 cell line by flow cytometry. Treatments with compound **11a** (50 µM) induced early phosphatidylserine exposure after 18 hours of exposure and this process progressed phosphatidylserine exposure with loss of cell membrane integrity after 24 hours of treatment, suggesting a time-dependent cell death process. Regarding the cell cycle profile, no changes were observed after treatment with compound **11a** (25 µM), suggesting a mechanism of cell death independent on the cell cycle. The *in vivo* studies

show that compound **11a** possess low acute toxicity, being the doses of 30-300 mgKg-1 chosen for studies in Ehrlich solid tumor model in mice. All doses were able to inhibit tumour development being the lowest one the most effective[3].



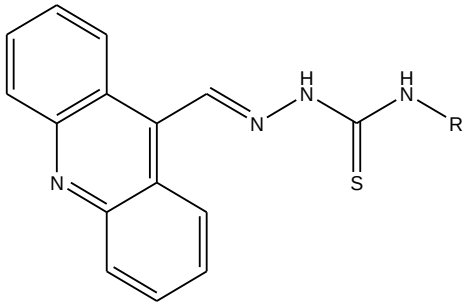
11a: R= p-bromophenyl
11b: R= p-tolyl

M.D. Altintop *et al* **(2015);** synthesized fourteen new naphthalene-based thiosemicarbazone derivatives and evaluated as new anticancer agents against LNCaP prostate cancer cells. MTT assay indicated that compounds **12a**, **12b** and **12c** exhibited inhibitory effect on LNCaP cells. Among these compounds, 4-(naphthalen-1-yl)-1-[1-(4-hydroxyphenyl)ethylidene) thiosemicarbazide **12a,** which caused more than 50% death on LNCaP cells, was chosen for flow cytometric analysis of apoptosis. Flow cytometric analysis pointed out that compound **12a** also showed apoptotic effect on LNCaP cells[16].



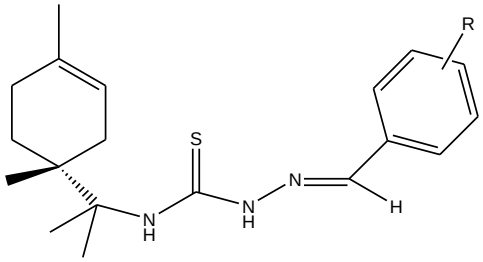
12a: R=OH
12b: R= CH_3
12c: R= CN

S.M.V. de Almeida *et al* **(2015)**; synthesised eight new (*Z*)-2-(acridin-9-ylmethylene)-*N*-phenylhydrazinecarbothioamide derivatives and their anti-proliferative activities were evaluated, and DNA binding properties were performed with calf thymus DNA (ctDNA) by electronic absorption and fluorescence spectroscopies. Both hyperchromic and hypochromic effects, as well as red or blue shifts were demonstrated by addition of ctDNA to the derivatives. The calculated binding constants ranged from 1.74 × 10^4 to 1.0 × 10^6 M^{-1} and quenching constants from −0.2 × 10^4 to 2.18 × 10^1 M^{-1} indicating high affinity to ctDNA base pairs. The most efficient compound in binding to ctDNA *in vitro* was (*Z*)-2-(acridin-9-ylmethylene)-*N*-(4-chlorophenyl) hydrazinecarbothioamide (**13b**), which was demonstrated by hypochromism, red shift and fluorescence quenching. On the other hand the non-substituted phenyl ring derivative (*Z*)-2-(Acridin-9-ylmethylene)-*N*-phenylhydrazinecarbothioamide **13a** showed the highest antiproliferative activity. In comparison with biochemical and biological properties, compounds produced in this study the following conclusions can be drawn: both binding constants with ctDNA and anti-proliferative activities were influenced by substitution on the phenyl ring of thiosemicarbazone moieties since the most active compounds did not possess substitution (**13a**). There was no correlation between electron-withdrawing or electron-donating substituents on the phenyl ring and anti-proliferative activity, since both dramatically decreased this property[17].



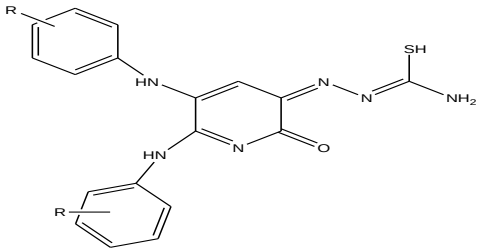
13a: R= phenyl
13b: R= chloro-phenyl

F. Vandresen *et al* **(2014)**; synthesized a series of nineteen thiosemicarbazones derived from a natural monoterpene R-(+)-limonene and evaluated their antitumor activity. Overall, the majority of tested compounds exhibited considerable inhibitory effects on the growth of a wide range of cancer cell lines. Almost all of tested thiosemicarbazones were especially sensitive to prostate cells (PC-3). The 4-fluorobenzaldehyde derivative **14b** was the most selective compound for prostate cells, while 2-hydroxybenzaldehyde derivative **14a** was the most active compound, with potent antitumor activity against all tested cell lines[18].



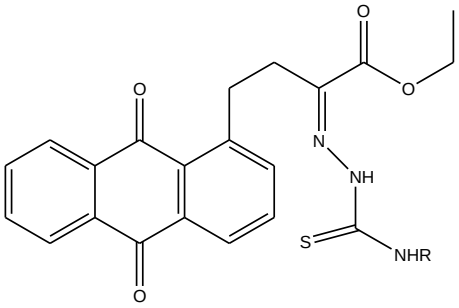
14a: R=2-OH
14b: R=4-F

W. Xie *et al* (2014); a series of fourteen 5,6-disubstituted pyridine-2,3-dione-3-thiosemicarbazone derivatives and seven 5,6-disubstituted pyridine-2,3-dione S-benzyl-3-thiosemicarbazones were synthesized starting from 2,3-dihydroxypyridine via oxidation-Michael additions, condensations and nucleophilic substitutions and evaluated their anticancer activity against Breast cancer (MCF-7), Colon cancer (HCT-116) and hepatocellular cancer (BEL7402) cell lines. It was observed that most of the synthesized compounds exhibited more potent cytotoxic activities(IC50 < 7.0 mM) against the three human cancer cell lines in comparison with 5-FU. Special compounds **15a, 15b, 15c, 15d, 15e, 15f, 15g** and **15h** displayed higher cytotoxicity activity than 5-FU against all three human cancer cell lines, the compound **15f** showed promising antiproliferative activity with IC_{50} values in the range of 0.19e-1.37 μM. Although most compounds showed potent antitumor activity (IC_{50} < 7.0 mM), some compounds exhibited selectivity between the three human cancer cell lines. For MCF-7 cell line, the compounds **15a, 15b, 15e, 15f** and **15h**, showed the more potent inhibitory activity with IC_{50} 0.58 ± 0.06 μM, 0.15 ± 0.02 μM, 0.634 ± 0.06 μM, 1.37 ± 0.04 μM and 1.12 ± 0.22 μM, respectively. For HCT-116 cell line, the compounds **15a** and **15f** displayed the best inhibitory activity with IC50 1.52 ± 0.18 μM and 0.19 ±0.02 μM respectively. For BEL-7402 cell line, the compounds **15a** and **15f** exhibited more potent inhibitory activity with corresponding IC_{50} 1.71 ± 0.26 μM and 0.82 ± 0.03 μM respectively[19].



15a: R=o-CH_3
15b: R=m-CH_3
15c: R=p-CH_3
15d: R=o-Cl
15e: R=m-Cl
15f: R=p-Cl
15g: R=p-F
15h: R=p-Br

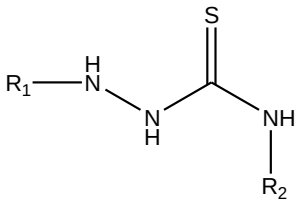
V. Markovic *et al* **(2013);** Synthesized a series of novel anthraquinoneethiosemicarbazone derivatives in a tautomerizable keto-imine form and evaluated for their in vitro cytotoxic activity against human cancer cells (HeLa, MDAMB-361, MDA-MB-453, K562, A549) and human normal MRC-5 cells. The compounds demonstrated good cytotoxic activity, IC_{50} values range from 2.17 to 50.54 μM against all the tested cell lines. The K562 cell line is much more sensitive to the compounds than the other cell lines; in this case, the activity of compounds can even be compared with the activity of cisplatin (IC50 values range from 2.17 to 7.99 μM). Compounds **17a, 17b, 17c** and **17e** exhibit the strongest activity against all five cancer cell lines. Compound **17e** exhibits the highest activity against A549 cancer cell lines and **17a** against HeLa cancer cell line. Selectivity was observed for **17a** against resistant MDA-MB-361 cell lines (IC_{50} value of 4.45 μM) while **17d** exhibited an excellent selectivity against K562 cell line (IC_{50} value of 2.17 μM). In the non-cancerous lung fibroblasts (MRC-5), most of the compounds were slightly less cytotoxic than cisplatin. The cytotoxicities of **17a** and **17c** in the lung fibroblasts were marked by IC_{50} values of 42.13 and 24.35 μM, respectively[20].



17a: R=$CH_2(CH_2)_4CH_3$
17b: R=Cyclohexane
17c: R=2-ethylthiophene
17d: R=3-ethylpyridine
17e: R=Benzene

STRUCTURE ACTIVTY RELATIONSHIP

SAR studies showed that a large number of thiosemicarbazones of N-heterocyclic compounds have low π-electron density at the side chain part and the ring N- atom should be reasonably a good electron pair donor to transition metals to form co-ordination compounds[2].



General Structure of Thiosemicarbazone

S.No	R_1	R_2	Active Against
1.	5-(naphalen-1-yl)-1-H-indole	H	Colorectal adrenocarcinoma and leukemia
2.	3-(4-methoxybenzylidiene-6,6-dimethylbicyclo[3.3.1]heptane	Ph	Human Breast Cancer cell line (MDA-MB-231) Cellosaurus Cell line (SMMC-7721) HeLa (Immortal Cell Lines)
3.	3-(4-hydroxyphenyl)-6-methyl-2H-chromene-7-ol	Phenyl, Allyl	Brain and Breast Cancer Cell line
4.	5-niroindolin-2-one	3-flurophenyl	Cytotoxic activity
5.	2-methylthiophene	p-tolyl	Human tumour cell line (786-0)
6.	1-ethyl-4-methylbenzene 4-ethylbenzonirtile 4-ethylphenol	Naphthlene	Prostate Cancer Cell line (LnCap)
7.	4-flurophenyl 4-phenol	R-4-isopropyl-1,4-dimethylcyclohex-1-ene	Prostate cell lines (PC-3)
8.	5,6-bis(2-methoxyphenylamino) pyridine -2(3H)-one 5,6 bis(4-chlorophenylamino) pyridine -2(3H)-one	H	Breast Cancer Cell line (MCF-7) Cellosaurus Cell line (BEL-7402) Human Colon Carcinoma Cell line(HCT-116)
9.	Ethyl 4-(9,10 doxo-9,10 dihydroanthracen-1-yl)butanoate9	Hexane Benzene Hexane, 2-ethylthiophene	Cervix adenocarcinoma cell line (HeLa) Non-small cell lung carcinoma (A549) Lung fibroblast

CONCLUSION

Thiosemicarbazones have been shown to be active antiproliferative agents in both *in vitro* as well as *in vivo.* In recent studies Thiosemicarbazone derivatives have also been found to possess low acute toxicity with no to minimal mutagenic as well as teratogenic potential. Due to structural variations these derivatives have also shown selectivity towards particular cell lines.

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