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Research Article

Synthesis of Thiosemicarbazones Derivatives and their *in vitro* Antioxidant Activity

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ABSTRACT

Thiosemicarbazones were reported to have antineoplastic, antibacterial, antiviral, antifungal, antimalarial, nueroprotective, antitubercular activities. This study aimed to synthesis of Thiosemicarbazones and evaluation for its antioxidant activities. The two derivatives of thiosemicarbazones are synthesized by using a conventional one step processes in which the respective halo-substituted acetophenones are condensed with thiosemicarbazide to result in the formation of the product. The structures of thiosemicarbazones were confirmed by spectroscopic (IR, 1H NMR, 13C NMR and MS) method. The antioxidant activity of these thiosemicarbazones was evaluated, *in vitro* and it's shown that some of these compounds had significant antioxidant activity.

1. Introduction

Thiosemicarbazones belong to a class of compounds that occupy a wide range of biological activities and have been studied for their activity against tuberculosis [1-3], virus and most important against various cancerous cells [4-5]. SAR studies showed that a large number of Thiosemicarbazones of an N- heterocyclic compounds have low πelectron 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 [6] . Thiosemicarbazones in their neutral or deprotonated form, behave as an N N S thiodentate chelate towards metal ions essential for life. Important finding was that an N N S ligand system was a common feature of all compounds with carcinogenic potency [7].

The synthesis of transition metal complexes with thiosemicarbazone ligands has been receiving considerable attention due to the pharmacological properties of both ligands and complexes [12-13]. The deprotonated thiosemicarbazone ligands usually coordinate to platinum, palladium, copper, ruthenium, and osmium through oxygen, nitrogen, and sulphur donor atoms in their (N, S) bidentate form or (N, N, S or O, N, S) tridentate form, to form metallic complexes of different molecular geometry [14-16] and all these complexes are active against different cancer cells in their different geometries [17]. The square planar platinum(II) and palladium(II) complexes of M(HL)2Cl and M(L)Cl type with thiosemicarbazone ligands derived from phenylacetaldehyde and 2 formylpyridine showed high cytotoxicity in vitro against HL60 leukaemia and P388 mouse leukaemia cell lines [18], while platinum(II) and palladium(II) binuclear complexes with p-isopropylbenzaldehyde thiosemicarbazone ligands exhibit strong cytotoxic activities on mouse tumor cell growth inhibition [19-20]. The aim of this work is to synthesize thiosemicarbazones and their corresponding 1,3,4 thiadiazolines in order to compare their *in vitro* antioxidant activities.

2. Material and Methods

2.1 *Synthesis of the thiosemicarbazones*

Potassium hydrazine carbodithioate was prepared by the reaction of hydrazine hydrate, carbondisulfide and potassium hydroxide below 10 °C with constant stirring. This was then converted into methyl hydrazinecarbodithioate (1) by the action of methyl iodide, added drop wise with stirring and maintaining temperature below 10 °C.

2.2 *Synthesis of 1,3,4-thiadiazolines:*

Thiosemicarbazone (0.25 mmol) was dissolved in 0.5 mL of pyridine and 0.5 ml of acetic anhydride and the mixture was heated at 110°C during 3 h with magnetic stirring to give the 1,3,4- thiadiazoline derivative which is filtered and purified by flash chromatography (Figure 1).

2.3 2, 2-*Diphenyl-1-picrylhydrazyl assay:*

The method of Liyana-Pathiana and Shahidi [5,7] was used for the determination of scavenging activity of DPPH free radical. To 1 mL of 0.135 mM DPPH prepared in methanol was

Figure-1. Synthesis of 1,3,4-thiadiazolines (1-15)

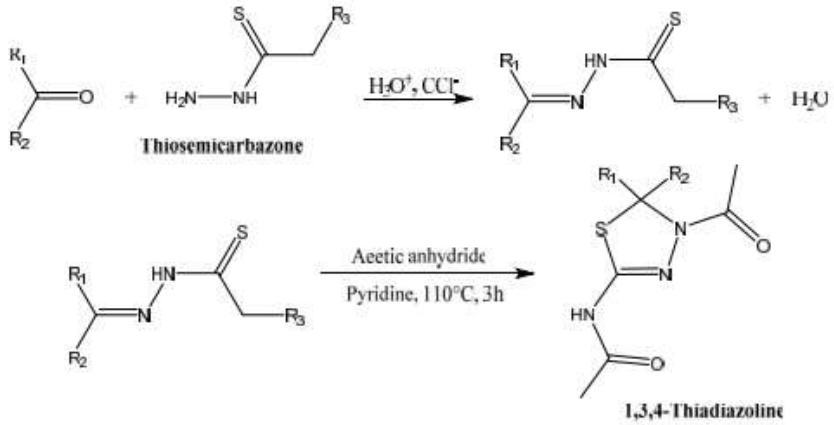


Table-1. Chemical structure, yield, and melting point of synthesized thiosemicarbazones (1-6)

Compounds		R_1	R_2	Yield (%)		*Rf*		M. P (°C)	
1	1C	H		65	87	0.80	0.40	162-163	221-222
2	2C	H		90	94	0.78	0.37	254-255	245-246
3	3C	H		78	77	0.82	0.77	212-213	228-230
4	4C	$-CH_3$		89	32	0.82	0.60	180-181	188-189
5	5C	$-CH_3$		82	49	0.75	0.33	224-225	156-157
6	6C	$-CH_2-CH_3$		78	66	0.80	0.60	126-127	209-210

mixed with 1.0 mL of aqueous extract ranging from 20-100 µg/mL. The reaction mixture was vortexed thoroughly and left in dark at room temperature for 30 min. The absorbance was measured spectrophotometrically at 517 nm. The scavenging ability of the extract was calculated using the standard equation.

The amount of DPPH radical was calculated following this equation: % inhibition of DPPH = [A0- As]/A0 × 100

Where A0 is the absorbance of control and As is the absorbance of sample. Absorbance and % inhibition of Compounds 4a-4l by DPPH Method was depicted in table. And the calculated IC50 and pIC50 values.

3. Results and Discussion

3.1 Chemistry

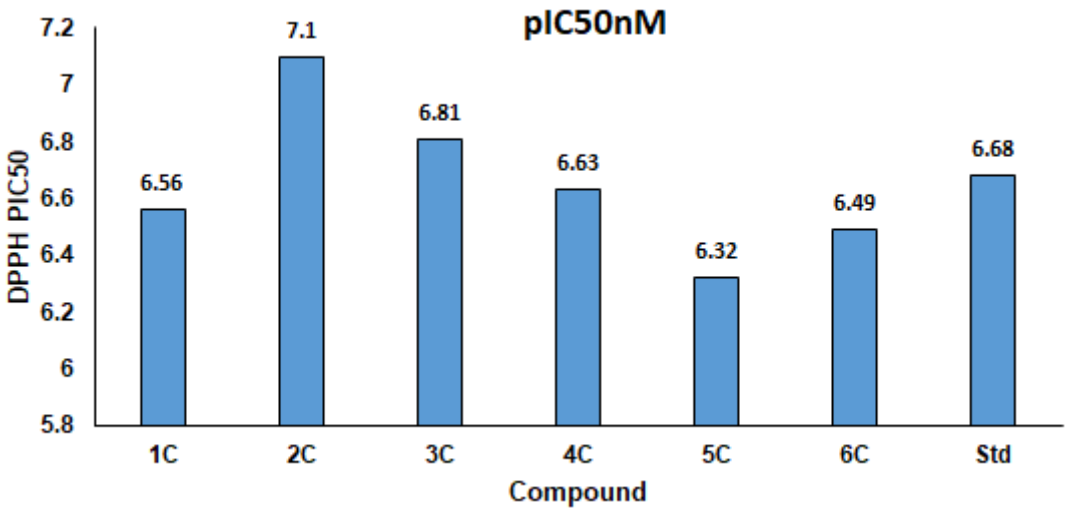
Six thiosemicarbazones and their corresponding 1,3,4-thiadiazolines were synthesized with yields going from 65to 90% for the thiosemicarbazone and 32 to 94% for 1′3′4-thiadiazolines. The physical and spectrometric data of the 12 compounds are reported in Table 1. Thin layer chromatography (TLC) shows that thiosemicarbazones with Rf ranging from 0.75 to 0.82 in hydrophobic mobile phases are generally more lipophilic than their corresponding 1,3,4-thiadiazolines, which have Rf up 0.33 to 0.60. The spectrometric data of this table are in conformity with the structures suggested for the products.

Thus the IR spectra of the thiosemicarbazones and 1,3,4-thiadiazolines show bands in the range of 3437- 3145 cm-1due to the stretching vibration of NH in both types of compounds. The thiosemicarbazones C=N stretching band which corresponds between the thiosemicarbazide part and carbonyl part of the molecule, appears at 1596 or 1525 cm-1. In the 1H NMR spectra the most deshielded proton, which is linked to the central nitrogen atom appears as a broadened singlet between 7.85 and 11.86 ppm for both types of molecules. In the 13C NMR spectra, the thiosemicarbazones C=N bond is indicated by chemical shifts between 140 and 152 ppm while the chemical shift of the, the C=S bond corresponding to the chemical shift between 177 and 179 ppm. Ring closure in 1,3,4-thiadiazolines may be observed by (1) the disappearance of the signal between 177 and 179corresponding to the thiocarbonyl group, (2) the appearance of a signal between 63 and 85 ppm assigned to C-2 and (3) the signals of the carbonyl and methyl moieties of the acetyl groups incorporated to the molecule. In mass spectrometry, the [MH]+ peaks obtained in APCI mode correspond to molecular weights expected for all products. In

Table-2. IC50 p IC50 values (nM) of the compounds by DPPH method

SAMPLE	IC_{50}µg/ml	IC_{50}µM	IC_{50}nM	pIC_{50}nM
1C	86.30	0.274	274.84	6.56
2C	25.74	0.078	78.950	7.10
3C	51.01	0.154	154.57	6.81
4C	85.40	0.232	232.21	6.63
5C	164.44	0.472	472.52	6.32
6C	115.41	0.321	321.47	6.49
Std	86.00	0.208	208.00	6.68

Figure-2. Antioxidant activity of Six thiosemicarbazones



LC mode, all 1,3,4-thiadiazoles have a single peak confirming their purity. The synthesized compounds were tested for their antioxidant activity. The test results are reported in table-2 and figure-2.

3.2 Anti-oxidant activity:

The anti-oxidant activity of synthesized thiosemicarbazones was studied *in-vitro* using DPPH method. The percent inhibition and IC50 values of all synthesized compounds were calculated against control on the basis of experimental data obtained. All the newly synthesized thiosemicarbazone derivatives exhibited moderate to potent activity when compared with standard. Among all the derivatives the aldehyde derivatives has the more potent when comparing with ketone derivatives.

4. Conclusions

A series of thiosemicarbazones derivatives synthesized by standard procedure. Antioxidant activity of these compounds were studied and compared. The derivatives showed activity as such as other antioxidant agents. Among the twelve derivatives of these compounds 1C, 2C, 3C and 4C showed potent antioxidant activity, compounds 4C and 5C, showed moderate activity. Further exploration of molecules is going on to find out the lead molecule to develop as an ideal antimicrobial agent. All the derivatives (1C-6C) were submitted to PASS software to evaluate the RR inhibitory activity. By the comparison of Pa and Pi it was concluded that all the derivatives have shown antineoplastic RR inhibitory action. In all the compounds 4a has the high pa value 4c has the low pi value.

Competing Interests

The authors have declared that no competing interests exist.

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