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New Dithiocarbamates as a Possible Human Serum Albumin Metal Carrier in Drug Delivery Systems and their Antioxidant and Antiproliferative Activities.

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Abstract. New *mono-* and *bis-*dithiocarbamates were prepared from the reaction of organic dihydrazides -NHNH-(C=O)(CH₂)_x-(C=O)NHNH- (where x = 0, 2, 4) and basic carbon disulfide with varying chain length 10-14 atom as a human serum metal carrier. The products were characterized by various spectrophotometric such as ¹H and ¹³C NMR and elemental analysis. Their antiproliferative activities were examined on two species of the standard strains of the Gram-positive *Staphylococcus aureus* ATCC 25923 and Gram-negative *Escherichia coli* ATCC 25922 by following the procedure of broth micro-dilution method (BMM), which was applied at the concentrations: 0.0, 100, 200, and 300 ppm for each compound. The antioxidant properties were investigated by following the DPPH method, which was applied for each of the above concentrations. All prepared compounds exhibited antiproliferative and antioxidant activity.

Keywords: Dithiocarbamates, metal carrier, drug delivery, antiproliferative activity, antioxidant, DPPH.

1. Introduction:

Dithiocarbamates are thiol that possesses the general structure R₁R₂-N-C(=S)-SNa [1-2], their first commercial application was as a fungicide during the forties of the past century. They are important therapeutic and industrial chemicals and one of the dithiocarbamates, thiuram disulphide (R₂NC(=S)S)₂ where R = Et used as a fungicide both in the field and as a seed protectant. A large number of articles dealing with the formation of complexes of dithiocarbamates with metal ions were reported in the works of literature covering wide fields, among them is their use as chemotherapeutic agent for Alzheimer's disease [3], as antifungal agents and antibacterial agents [4], in agriculture as pesticide [5], and in the industry as stabilizers for PVC [6]. They have been studied extensively over the last decades in a response to their growing applications in many new areas of chemistry, industry and medicine [7-8].

The ability of dithiocarbamates with coordinate to metal ions offer important biological value because a lot of proteins, molecules, and enzymes, which are current in their metal compositions centres, are imperative for these structures [9]. They behave as metal chelators at the same time change and destabilize their structure and consequently reduce their toxic behaviour [10], and hence their interaction with some metals can be related to oxidative processes that are vital mechanisms in the elimination of microorganisms [11-12]. There have been a large number of recent experimental studies, particularly related to the regulation of transcription factors and apoptosis, in which dithiocarbamates were used to modify the cellular redox environment [10-12].

Dithiocarbamate complexes have attracted great interest due to their anticancer properties [13-16], cocaine addiction [17], antimalarial [18], antifungal [19] and inflammation [20]. Evidence that Sodium 1-dithiocarboxylatopyrrolidne-2-carboxylate (Py-m-DTC) efficiently reduces CVB3 replication and CVB3 viral progeny release and such inhibitory effect are unbiased of its antioxidant recreation [16-17]. Their complexes with platinum, vanadium, ruthenium, gold, rhodium and many others have been determined to possess therapeutic homes [18-19]. In this situation, they behave like a vehicle for transporting the metal to their intended target site [20] and also has the tendency to reduce toxicity, improve solubility and biocompatibility [21]. Gold dithiocarbamates have been evaluated for their



potential to inhibit cisplatin-induced nephrotoxicity and for their *in vitro* cytotoxicity toward a variety of human tumour cell lines by 1-4-fold [22-23].

Human serum albumin (HSA) demonstrated its important role as a drug delivery vehicle for organic small molecules. It possesses a high concentration in the tumour area, superior binding efficacy with various ligands and the extension of circulatory half-life [24-25]. It has several binding pockets where various ligands such as fatty acids, ions can bind, providing drugs with the option for non-covalent binding sites [25-29]. Many published articles dealing with dithiocarbamate complexes [30-31]. The present work aim is to prepare new dithiocarbamates as a potential human serum albumin metal carrier in drug delivery systems and study their antioxidant and antiproliferative activity.

2. Materials and methods:

2.1 Instrument:

Melting points of synthesized compounds were recorded in open capillary tubes using model SMP1 from the UK melting point apparatus. The elemental analysis was measured by EuroEA model 3000/Italy elemental Analyzer for C, H, S, and N. ^1H NMR, ^{13}C NMR spectra were recorded by using Bruker spectrometer model Ultra-Shield at 300.15 MHz using deuterated dimethyl sulfoxide (DMSO-d_6) and chloroform (CDCl_3) as a solvent for samples with TMS as internal reference standard at 298 K, in Al-Bayt university.

2.2 Chemicals:

General-purpose grade of oxalyl dihydrazide (ODH), succinyl (SDH), adipyl dihydrazide (ADH) and proline (Pr), and 2,2-diphenyl-1-picryl-hydrazylhydrate (DPPH) were obtained from Sigma-Aldrich. The other dithiocarbamates used in this study were prepared by the following procedures:

2.2.1 Sodium 1-dithiocarboxylatopyrrolidne-2-carboxylate (Py-m-DTC): A solution of CS_2 (2.36 g, 1.81 ml, 40 mMole) in 50 mL methanol was gradually added to a solution of sodium hydroxide (2.24 g, 40 mMole) and pyrrolidene-2-carboxylic acid (20 mmol) in 75 mL of ethanol over a period of 30 minutes. The solution was stirred for 12 hours and the precipitates were filtered and washed with 3×10 mL ethanol and 3×10 mL ether. The product of the title compound was dried under vacuum for 5 hours to get white crystals, yield 95 % with M.p. 255-258°C. ^1H NMR (DMSO-d_6) δ ppm: 1.54-1.64 (m, 2H, $\text{C}_2\text{-H}$); 1.7-1.95 (m, 2H, $\text{C}_3\text{-H}$); 2.7-2.8 (m, 2H, $\text{C}_4\text{-H}$); 3.7(t, 1H, $\text{C}_1\text{-H}$). ^{13}C NMR (DMSO-d_6) δ ppm: 23.8 (C_3), 29.5 (C_2), 52.2 (C_4), 74.8 (C_1), 176.1 (C=O), 211.8 (C=S).

2.2.2 Sodium 2-(2-hydrazinyl-2-oxoacetyl) hydrazinecarbodithioate (ODH-m-DTC): A solution of CS_2 (1.18 g, 0.905 ml, 20 mMole) in 50 mL methanol was gradually added to a solution of sodium hydroxide (1.12 g, 20 mMole) and oxalyl dihydrazide (2.36 g, 20 mMole) in 75 mL of ethanol over a period of 30 minutes. The solution was stirred for 12 hours and the precipitates were filtered and washed with 3×10 mL ethanol and 3×10 mL ether. The product of the title compound was dried under vacuum for 5 hours to get white crystals, Yield 65 % and M.pt. 220 -225°C. ^1H NMR (DMSO-d_6) δ ppm: 2.0 (s, 2H, H-N_1 and 1H, H-N_3), 8.2 (s, 1H, H-N_2 and 1H, H-N_3); ^{13}C NMR (DMSO-d_6) δ ppm: 159.0 ($\text{C}_1=\text{O}$ and $\text{C}_2=\text{O}$), 203.5 ($\text{C}_3=\text{S}$).

2.2.3 Sodium 2,2'-oxalyl bis-(hydrazinecarbodithioate) (ODH-b-DTC): A solution of CS_2 (2.36 g, 1.81 ml, 40 mmole) in 50 mL methanol was added to a solution of sodium hydroxide (2.25 g, 40 mmole) and oxalyl dihydrazide (I) (2.36 g, 20 mmole) in 75 ml of ethanol over a period of 30 minutes. The solution was stirred for 12 hours and then was filtered and washed with 3×10 mL ethanol and 3×10 mL ether. The product of the title compound was dried under vacuum for 5 hours to get white crystals, 100 % Yield: 6.93 g, M.pt. 270 -275°C. ^1H NMR (DMSO-d_6) δ ppm: 2.0(s, 2H, H-N_1 and 1H, H-N_4), 2.5(s, 2H, H-C_2 and 1H, H-N_3), 8.02(s, 1H, H-N_2 , and 1H, H-N_3); ^{13}C NMR (DMSO-d_6) δ ppm: 159.6(C_2 and C_3), 203.5 ($\text{C}_1=\text{S}$, $\text{C}_4=\text{S}$).

2.2.4 Sodium 2-(4-hydrazinyl-4-oxobutanoyl) hydrazinecarbodithioate (SDH-m-DTC): By following the procedure used in section (b) for (ODH-MDTC) by using succinyl dihydrazide (2.93 g, 20 mmole) instead of oxalyl dihydrazide. The product of the title compound was dried under vacuum for 5 hours to get white crystals, yield 3.03 g (90.3 %) and M.pt 162-164°C. ¹H NMR (DMSO-d₆) δ ppm: 2.0 (s, 1H, H-N₁ and 2H, H-N₄), 2.5 (s, 2H, C₁H₂ and 2H, C₂H₂), 8.1 (s, 1H, H-N₂, 1H, H-N₃), ¹³C NMR (DMSO-d₆) δ ppm: 34.0 (C₂ and C₃), 177.1 (C₁=O and C₄=O), 203.5 (C₅=S).

2.2.5 Sodium 2,2'-succinyl bis-(hydrazinecarbodithioate) (SDH-b-DTC): By following procedure mentioned in (f) above using succinyl dihydrazide (I) (2.36 g, 20 mmole) and refluxed for a period of 30 minutes. The solution was stirred for 12 hours and then was treated similarly. The product of the title compound was dried under vacuum for 5 hours to get white crystals, 100 % Yield: 6.93 g, M.pt. 270 - 275°C. ¹H NMR (DMSO-d₆) δ ppm: 2.05(s, 2H, H-N₁, and 1H, H-N₄), 2.5(s, 2H, H-C₂ and 1H, H-C₃), 8.10(s, 1H, H-N₂ and 1H, H-N₃); ¹³C NMR (DMSO-d₆) δ ppm: 34.0 (C₃H₂, C₄H₂), 177.5(C₂=O and C₅=O), and 203.6((C₁=S and C₆=S).

2.3 Antiproliferative activity:

The antiproliferative activities (antibacterial activity) of seven newly prepared compounds Py-*m*-DTC, ODH-*m*-DTC, SDH-*m*-DTC, ADH-*m*-DTC, ODH-*b*-DTC, SDH-*b*-DTC, ADH-*b*-DTC as well as their precursors ODH, SDH, ADH were tested against two standard strains of the Gram-positive *Staphylococcus aureus* ATCC 25923 and the Gram-negative *Escherichia coli* ATCC 25922, by the broth micro-dilution method (BMM) [32]. The procedure includes the transfer of 100 μL volumes of 10⁶ CFU/mL logarithmic phase cultures of each bacterial suspension to inoculate in 25 mL sterile Mueller-Hinton broth, which was consisting of serial concentrations (0, 100, 200, and 300) ppm of each compound. All tubes were incubated at 37°C ± 0.2°C for 24 hr. The optical density (OD) was measured at 600 nm wavelength by using UV-VIS spectrophotometer after the specified incubation time.

2.4 Antioxidant and chromosomal assay:

The chromosomal analyses were carried out according to [34], while the percentage of antioxidant activity (AA %) often tested compounds were assessed by using 2, 2-diphenyl-1-picryl-hydrazylhydrate (DPPH) method. Free radical scavenger assay was conducted according to Brand-Williams *et al.* [34-35]. The experiment includes the transfer of 0.5 mL of serial concentrations (0, 100, 200, and 300) ppm of each compounds in a mixture of (0.5 mM of DPPH in 3.3 mL absolute ethanol). The change in the mixture color was recorded at 515 nm by UV-VIS Spectrophotometer within 100 minutes at room temperature. The blank tube consists of (3.3 ml of ethanol + 0.5 ml of sample blank is the absorbance of the control reaction.

Except for the test compound, while the control tube consists of (3.5 mL ethanol + 0.3 mL of DPPH). The scavenging activity percentage (AA %) was determined according to the following formula:

$$AA\% = 100 - \frac{(\text{Abs. sample} - \text{Abs. blank}) \times 100}{\text{Abs. control}}$$

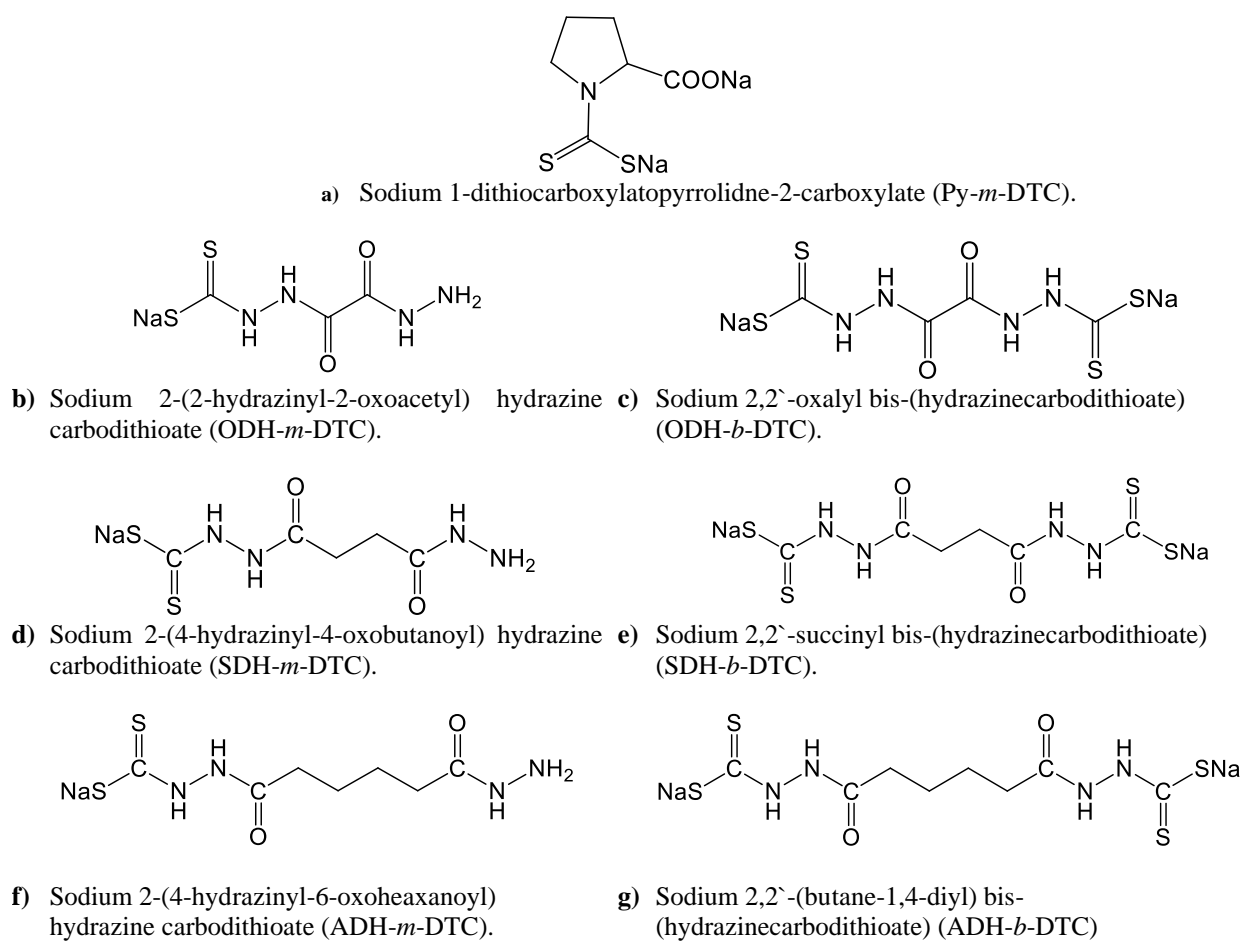


Figure 1: The Structures and nomenclatures of the prepared *mono*- and *bis*-dithiocarbamates.

2.5 Statistical analysis:

The results are reported as the mean \pm SD of three independent replicates. Statistical analysis of data was carried out by computer using SPSS version 16 software. The level of significance was measured by using the Analysis of Variance (ANOVA) test [35]. The level of significance was shown using the least significant difference (LSD) test.

Table 1: The physical properties and elemental analysis of the prepared dithiocarbamates.

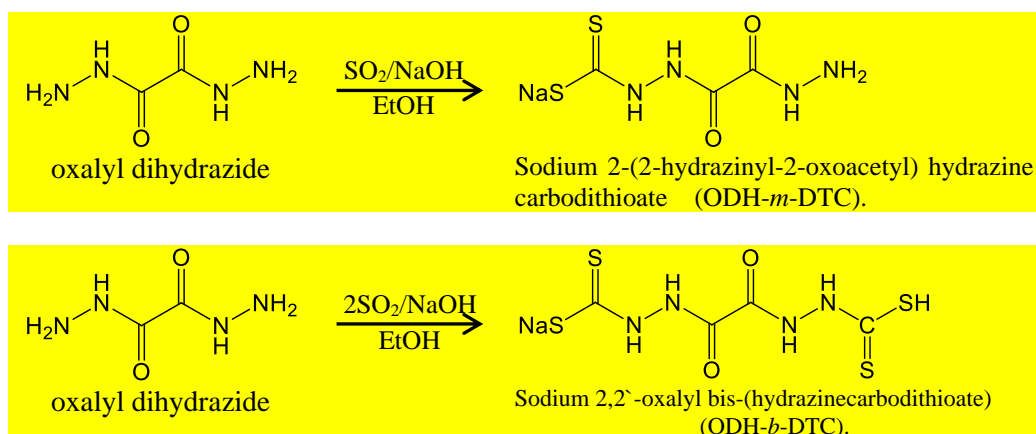
#	Compound	Formula	M. wt	M. pt (°C)	Color	Yield (%)	C %		H %		N %	
							Found	Theo.	Found	Theo.	Found	Theo.
a)	Py- <i>m</i> -DTC	C ₆ H ₇ NNa ₂ O ₂ S ₂	235.23	255-258°	White	95%	30.60	30.64	3.00	3.00	5.93	5.95
b)	ODH- <i>m</i> -DTC	C ₃ H ₅ N ₄ NaO ₂ S ₂	216.22	170-173°	White	65%	16.63	16.66	2.37	2.33	25.76	25.91
c)	ODH- <i>b</i> -DTC	C ₄ H ₄ N ₄ Na ₂ O ₂ S ₄	314.34	270 -275°	White	90.3 %	15.23	15.28	1.35	1.28	17.67	17.82
d)	SDH- <i>m</i> -DTC	C ₅ H ₉ N ₄ NaO ₂ S ₂	244.27	103-105°	White	90.3 %	24.49	24.58	3.76	3.71	22.65	22.94
e)	SDH- <i>b</i> -DTC	C ₆ H ₈ N ₄ Na ₂ O ₂ S ₄	342.39	126-128°	White	100%	21.00	21.05	2.54	2.36	16.33	16.43
f)	ADH- <i>m</i> -DTC	C ₇ H ₁₃ N ₄ NaO ₂ S ₂	272.32	107-109°	White	83%	30.85	30.87	4.83	4.81	20.43	20.57
g)	ADH- <i>b</i> -DTC	C ₈ H ₁₂ N ₄ Na ₂ O ₂ S ₄	370.45	155-157°	White	94%	25.83	25.94	3.31	3.27	15.09	15.12

Table 2: The antiproliferative activities were examined on two species of standard bacteria viz. *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922 using broth micro-dilution method (BMM) at different concentrations (0.0, 100, 200, and 300 ppm) of each compound. The antioxidant properties were investigated by 2, 2-diphenyl-1-picryl-hydrazylhydrate (DPPH) method at the same concentrations

#	Compound	Conc. (ppm)	OD ₆₀₀				AA % Activity	Increasing rate %	
			Mitotic index	<i>S. aureus</i> ATCC 25923 (+)	Inhibition rate%	<i>E. coli</i> ATCC 25922			Inhibition rate %
1	-	0	0.88±0.02	0.84±0.22	-	0.96±0.22	-	100	82
2	Py- <i>m</i> -DTC (a)	100	0.84±0.01	0.71*±0.12	15.47	0.88*±0.13	8.33	82	100
		200	0.83±0.04	0.62*±0.11	26.19	0.82*±0.05	14.5	85	103.65
		300	0.80±0.01	0.55*±0.09	34.53	0.76*±0.11	20.8	91	110.97
3	ODH	100	0.88±0.07	0.65*±0.11	22.61	0.78*±0.03	18.75	82	100
		200	0.86±0.03	0.58*±0.05	30.95	0.65*±0.02	32.29	85	103.65
		300	0.82±0.03	0.45*±0.07	53.57	0.61*±0.06	36.45	89	108.53
4	ODH- <i>m</i> -DTC (b)	100	0.86±0.02	0.55*±0.12	33.33	0.78*±0.11	22.45	82	100
		200	0.84±0.01	0.44*±0.11	40.30	0.70*±0.09	32.29	85	103.65
		300	0.83±0.01	0.38*±0.12	56.35	0.64*±0.06	34.34	89	108.53
5	ODH- <i>b</i> -DTC (c)	100	0.87±0.06	0.56*±0.12	33.33	0.78*±0.12	18.75	61	100
		200	0.85±0.03	0.42*±0.12	50.00	0.73*±0.09	23.95	65	106.55
		300	0.82±0.01	0.33*±0.09	60.71	0.64*±0.09	33.33	72	118.03
6	SDH	100	0.86±0.04	0.78*±0.18	7.14	0.78*±0.02	18.75	7.14	100
		200	0.83±0.05	0.67*±0.23	20.23	0.63*±0.06	34.37	20.23	104.41
		300	0.81±0.01	0.78*±0.18	48.8	0.61*±0.02	36.45	48.8	114.7
7	SDH- <i>m</i> -DTC (d)	100	0.87±0.01	0.69*±0.12	11.41	0.84*±0.04	20.42	43.7	100
		200	0.87±0.06	0.58*±0.06	32.45	0.80*±0.02	46.85	48	103.35
		300	0.85±0.05	0.47*±0.13	55.30	0.62*±0.07	47.31	56	119.16
8	SDH- <i>b</i> -DTC (e)	100	0.86±0.07	0.66*±0.06	21.42	0.84*±0.04	21.42	53	100
		200	0.85±0.09	0.48*±0.06	42.85	0.77*±0.03	42.85	57	107.54
		300	0.83±0.02	0.42*±0.08	50	0.65*±0.02	50	65	122.64
9	ADH	100	0.88±0.09	0.75*±0.07	10.71	0.92*±0.02	4.16	62	100
		200	0.87±0.04	0.63*±0.13	25.00	0.87*±0.07	9.37	67	108.06
		300	0.85±0.01	0.52*±0.18	38.10	0.71*±0.07	26.04	71	114.51
10	ADH- <i>m</i> -DTC (f)	100	0.86±0.01	0.69*±0.12	11.41	0.84*±0.04	20.42	43.7	100
		200	0.85±0.12	0.50*±0.08	32.45	0.80*±0.02	46.85	48	103.35
		300	0.85±0.4	0.41*±0.12	55.30	0.62*±0.07	47.31	56	119.16
11	ADH- <i>b</i> -DTC (g)	100	0.87±0.03	0.60*±0.06	21.42	0.84*±0.04	21.42	53	100
		200	0.87±0.20	0.51*±0.06	42.85	0.77*±0.03	42.85	57	107.54
		300	0.86±0.12	0.49*±0.08	50.00	0.65*±0.02	50.00	65	122.64
12	Ascorbic acid (as reference)	50		-	-	-	-	91	110.97
P-value			0.799666			0.441566		0.000264	-
*Significant at p ≤ 0.05, Data represented as M±SD									

3. Results and discussion:

Products of the reactions mentioned in Section 2-2(a-f) were separated and characterized by the available physical and spectrometric techniques. These compounds were prepared for the first time to accept sodium 1-dithiocarboxylatopyrrolidne-2-carboxylate (Py-m-DTC) by using the following general route:



However, all these compounds are water-soluble products with a relatively higher melting point and obtained in good yield and purity. They possess the general structure $\text{NaS}-(\text{S}=\text{C})-\text{NHNH}-(\text{C}=\text{O})(\text{CH}_2)_x-(\text{C}=\text{O})\text{NHNH}-\text{C}(\text{S})-\text{SNa}$ (where $x = 0, 2, 4$), having a chain length of 11-16 atom. This structure will enable these compounds to interact with human serum albumin, with a fat metal-binding site.

Organic compounds were synthesized owning sulphur and nitrogen are shown to possess broad biological activity [36-38]. Dithiocarbamates get great applications in a different pharmaceutical sector that displays considerably oxidation state metal cation stabilizing technique. The antiproliferative effect of these new dithiocarbamates was investigated on the growth rate of most dominant bacteria *S. aureus* through its two standard strains of the Gram-positive *Staphylococcus aureus* ATCC 25923 and Gram-negative *Escherichia coli* ATCC 25922. The results were presented in Table 3 and showed that the highest inhibition rate for *S. aureus* was (60.71 %) at 300 ppm of ODH-b-DTC (c), while the highest inhibition rate of *E. coli* was (36.45%) at 300 ppm of SDH and ODH with significant differences at ($p \leq 0.05$), but there are no differences in the antioxidant activity among the six synthesized compounds (P value, 0.000264). The results obtained for these dithiocarbamates exhibited a moderate to high inhibition rate for the tested bacteria viz. Gram-positive *Staphylococcus aureus* ATCC 25923 and Gram-negative *Escherichia coli* ATCC 25922 both Gram-positive and Gram-negative bacteria may be associated with bacterial strains. The bacterial isolates are more responsive to these new dithiocarbamates rather than to their precursors, viz the starting hydrazine starting materials; ODH, SDH, and ADH.

Oxidants and free radicals play a dual role as useful and toxic compounds, considering that they can be both hazardous or beneficial to the body. They are produced both from regular cell metabolisms in situ or from exterior sources such as cigarette smoke, radiation, medication ...etc. When an overload of free radicals cannot steadily be destroyed, their accumulation in the body generates a phenomenon known as oxidative stress [36-38]. Ascorbic acid is usually used as a reference compound to measure antioxidant activity, 50 pmm of ascorbic acid gives 91% antioxidant activity with significant differences at ($p \leq 0.05$).

All the prepared dithiocarbamates and their precursors showed suitable antioxidant activity. The values of DPPH antioxidant things to do of Na-DPDTDC and their precursors were presented in

Figure-3. They all show good antioxidant activity, beside the absence of geno-toxicity through the use of mitotic index on peripheral blood lymphocytes as a bioindicator and does not cause a damage to the DNA molecule, which in turn will present them as a hot candidate for use in drug synthesis as metal carriers.

4. Conclusion:

New mono- and bis-dithiocarbamates of acid were synthesized as a possible human serum albumin metal carrier in drug delivery systems. The products were characterized by available techniques. They possess the general structure $\text{NaS}-(\text{S}=\text{C})-\text{NHNH}-(\text{C}=\text{O})(\text{CH}_2)_x-(\text{C}=\text{O})\text{NHNH}-\text{C}(=\text{S})-\text{SNa}$ (where $x = 0, 2, 4$), having a chain length of 11-16 atom. These compounds were very stable and soluble in water, which enables them to interact with human serum albumin and excreted easily from the human body. Their antiproliferative effect was investigated on the Gram-positive *Staphylococcus aureus* ATCC 25923 and Gram-negative *Escherichia coli* ATCC 25922. The results showed that the highest inhibition rate for *S. aureus* was (60.71 %) at 300 ppm of ODH-*b*-DTC (c), while the highest inhibition rate of *E. coli* was (36.45%) at 300 ppm of SDH and ODH with significant differences at ($p \leq 0.05$), but there are no differences in the antioxidant activity among the six synthesized compounds (P value, 0.000264). These dithiocarbamates and their precursors showed good antioxidant activity, which in turn will present them as a hot candidate for use in drug synthesis as metal carriers.

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