

Synthesis and study of antioxidant activity of some Schiff's bases containing 1,2,3-triazole rings

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Abstract: Synthesis and study of antioxidant activity of some Schiff's bases containing 1,2,3-triazole rings.

Keywords: antioxidant; Schiff's bases; 1,2,3-triazole.

Introduction

Triazoles, like many other five membered heterocyclic compounds are used very often in the pharmacological and medicinal applications. 1,2,3-Triazole and its derivatives enhanced considerable attention for the past few decades due to their chemotherapeutical value. Many 1,2,3-triazoles are found to be more potent anti-microbial [1], anti-inflammatory [2], analgesic [3], local anesthetic [4], anti-allergic, anti-convulsant [5], antineoplastic [6], anti-malarial [7], anti-HIV [8] and anti-cancer activities [9]. Some of the 1,2,3-triazoles are used as deoxyribose nucleic acid (DNA) cleaving agents [10] and potassium channel activators [11].

1,2,3-Triazoles are useful building blocks in chemistry and are stable to moisture, oxygen, light and also metabolism in the body. Moreover, these moieties can be turned to form powerful pharmacophores and also plays an important role in bio-conjugation. 1,2,3-Triazole moieties are attractive connecting units, since they are stable to metabolic degradation and capable of hydrogen bonding which can be favorable in binding of biomolecular targets [5].

Experimental and Methods:

The synthesis of the series shown in Scheme below characterized by (^1H -NMR, F.T.IR-8300 Fourier Transform Infrared Spectrophotometer *SHIMADZU* using potassium bromide disc and Double-beam UV-VISIBLE spectrophotometer (UV1700C), *SHIMADZU* and Melting points ($^{\circ}\text{C}$) were recorded on hot stage Gallen Kamp melting point apparatus and were uncorrected. The records were done in the Department of Chemistry/ College of Science/ Babylon University. The procedure for the synthesis of A1, A, and B was reported elsewhere [17].

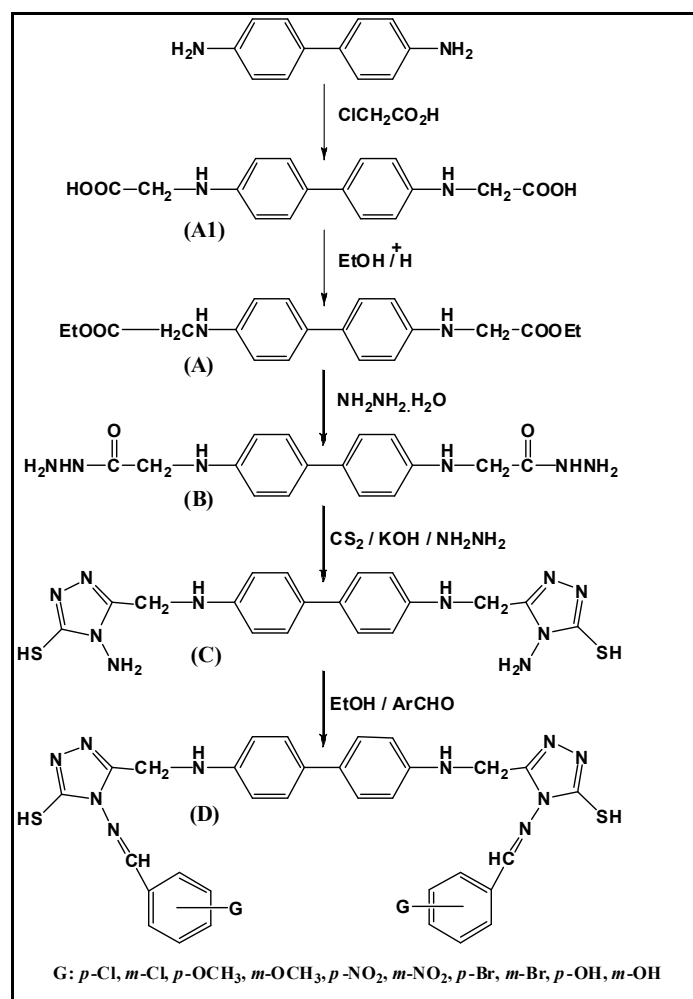
1) Synthesis of C:

A mixture of B 0.01 mol, potassium hydroxide (0.03 mol), and (0.03 mol) carbon disulfide was dissolved in absolute ethanol and refluxed for 4 hour in a water bath. Then the excess carbon disulfide was removed by distillation. Hydrazine hydrate 0.03 was added to the solution and refluxed for 8 hours. Acidification by 20% HCl produced white precipitate; the product (73% yiled) was recrystallized from ethanol.

2) Synthesis of D0-D10:

The compound C 0.01 mol was dissolved in refluxed absolute ethanol (75 ml), benzaldehyde (0.04 mole) was slowly added to the refluxed mixture, the net mixture was refluxed for 9 hours, after cooling to room temperature the mixture was filtered and the precipitate was dried and recrystallized from ethanol, the

percentage yield was (75%), the melting point of the target molecule (D0) was measured and found to be (185°C). The same reaction was carried out to different substituted benzaldehydes (G: *p*-Cl, *m*-Cl, *p*-OCH₃, *m*-OCH₃, *p*-NO₂, *m*-NO₂, *p*-Br, *m*-Br, *p*-OH, *m*-OH). The F.T.IR (KBr cm⁻¹) stretching vibrations and the physical properties of the compounds (D0-D10) are shown in Table (2-1) and (2-2) respectively.



Scheme 1. Synthesis of compounds D0-D10

Table (2-1): The F.T.IR (KBr cm⁻¹) stretching vibrations for the compounds (D0-D10).

G	Compd.	O-H	N-H	C-H aromatic	C-H aliphatic	C=N	C=C aromatic
-	A1	-	3210	3020	2960-2840	-	1530
-	A	-	3316	3023	2960-2875	-	1568
-	B	-	3260	3103	2930-2859	-	1540
-	C	-	3215	2096	2956-2896	1620	1557
H	D0	-	3218	3029	2940-2857	1628	1548
<i>p</i> -Cl	D1	-	3256	3058	2930-2860	1625	1543
<i>p</i> -Br	D2	-	3278	3073	2998-2851	1624	1521
<i>p</i> -OCH ₃	D3	-	3290	3081	2945-2856	1626	1550
<i>p</i> -NO ₂	D4	-	3310	3056	2971-2875	1620	1531
<i>p</i> -OH	D5	3421	3287	3070	2976-2820	1622	1520
<i>m</i> -Cl	D6	-	3281	3041	2967-2840	1627	1530
<i>m</i> -Br	D7	-	3301	3035	2951-2900	1623	1550
<i>m</i> -OCH ₃	D8	-	3289	3020	2980-2910	1625	1600
<i>m</i> -NO ₂	D9	-	3261	3090	2973-2880	1627	1581
<i>m</i> -OH	D10	3382	3240	3043	2995-2915	1621	1528

Table (2-2): The physical properties of the compounds (D0-D10).

G	Compd.	Melting point (°C)	% Yield
H	D0	185	75
<i>p</i> -Cl	D1	203	70
<i>p</i> -Br	D2	207	72
<i>p</i> -OCH ₃	D3	201	75
<i>p</i> -NO ₂	D4	200	75
<i>p</i> -OH	D5	230	76
<i>m</i> -Cl	D6	202	66
<i>m</i> -Br	D7	199	72
<i>m</i> -OCH ₃	D8	204	68
<i>m</i> -NO ₂	D9	195	70
<i>m</i> -OH	D10	223	75

¹HNMR spectrum of compound D0 exhibited multiplets in the region at δ 7.3 ppm for 6 aromatic protons and δ 7.6 ppm for 4 aromatic protons, two proton of the –CH olefin groups is observed at δ 8.1 ppm. Two protons of the –SH groups is observed at δ 3 ppm. Two protons of the –CH₂ group is observed at δ 4.32 ppm, two protons present in NH groups are observed at δ 4.00 ppm. Also, δ 6.49 ppm for 4 aromatic protons, and δ 7.26 ppm for 4 aromatic protons were exhibited.

¹HNMR spectrum of compound D1 exhibited multiplets in the region at δ 7.3 ppm for 4 aromatic protons and δ 7.6 ppm for 4 aromatic protons, two proton of the –CH olefin group is observed at δ 8.1 ppm. Two protons of the –SH groups is observed at δ 3 ppm. Two protons of the –CH₂ group is observed at δ 4.32 ppm, two protons present in NH groups are observed at δ 4.00 ppm. Also, δ 6.49 ppm for 4 aromatic protons, and δ 7.26 ppm for 4 aromatic protons were exhibited.

¹HNMR spectrum of compound D2 exhibited multiplets in the region at δ 7.5 ppm for 8 aromatic protons and δ 8.1 ppm for 2 olefinic protons. The protons of the –SH groups are observed at δ 3 ppm as a singlet. Two proton of the –CH₂ group is observed at δ 4.32 ppm, two protons present in NH groups are observed at δ 4.00 ppm. In addition, 8 aromatic protons appeared at δ 6.49 ppm, and δ 7.26 ppm for 4 respectively.

¹HNMR spectrum of compound D3 exhibited multiplets in the region at δ 3.73 ppm for 2 protons of the –CH₃ groups and δ 6.8 ppm for 4 of the –CH aromatic group. Four proton of the –CH aromatic groups are observed at δ 7.5 ppm, and two proton of the –CH olefinic groups are observed at δ 8.1 ppm. Two protons of the –SH groups are observed at δ 3 ppm, and four proton of the –CH₂ groups are observed at δ 4.32 ppm. Two protons of NH groups are observed at δ 4.00 ppm, also, δ 6.49 ppm for four aromatic protons, and δ 7.26 ppm for four aromatic protons were observed.

¹HNMR spectrum of compound D4 exhibited multiplets in the region at δ 8.2 ppm for 2 of the –CH aromatic groups, 2 proton of the –CH aromatic groups are observed at δ 7.9 ppm. Two proton of the –CH aromatic group is observed at δ 7.6 ppm, and two protons of the –CH aromatic group is observed at δ 8.0 ppm. Two protons of the –CH olefinic group is observed at δ 8.1 ppm, and two proton of the –SH groups are observed at δ 3 ppm. Also, two proton of methylene groups are observed at δ 4.32 ppm. Two protons of NH groups are observed at δ 4.00 ppm of compound. Besides that, 8 aromatic protons were appeared at δ 6.49, and δ 7.26 ppm respectively.

¹HNMR spectrum of compound D5 exhibited multiplets in the region at δ 5 ppm for –OH groups, 2 proton of the –CH aromatic group is observed at δ 6.8 ppm. Four proton of the –CH aromatic group is observed at δ 7.4 and 8.0 ppm, and two proton of the –CH olefinic groups is observed at δ 8.1 ppm. Also, two proton of the –SH groups is observed at δ 3 ppm, and two proton of the –CH₂ groups are observed at δ 4.32 ppm. In addition, two protons of NH is observed at δ 4.00 ppm, and 8 aromatic protons appeared at δ 7.26 and δ 6.49 ppm respectively.

¹HNMR spectrum of compound D6 exhibited multiplets in the region at δ 7.3-7.2 ppm for 4 aromatic protons, 4 proton of the –CH aromatic group is observed at δ 7.5-7.6 ppm. Two proton of the –CH olefinic group is observed at δ 8.1 ppm, and two proton of the –SH groups is observed at δ 3 ppm. Also, two proton of

the $-\text{CH}_2$ groups are observed at δ 4.32 ppm, and two protons of NH is observed at δ 4.00 ppm. In addition, 8 aromatic protons observed at δ 7.26 ppm and at δ 6.49 ppm respectively.

^1H NMR spectrum of compound D7 exhibited multiplets in the region at δ 7.8-7.6 ppm for 6 aromatic protons and at δ 7.2 ppm for 2 aromatic protons. Two proton of the $-\text{CH}$ olefinic group is observed at δ 8.1 ppm, two proton of the $-\text{SH}$ groups are observed at δ 3 ppm as a singlet. Two proton of the $-\text{CH}_2$ groups are observed at δ 4.328 ppm, and two protons for NH groups are observed at δ 4.00 ppm. Also, at δ 6.49 ppm for 4 aromatic protons, and at δ 7.26 ppm for 4 aromatic protons.

^1H NMR spectrum of compound D8 exhibited multiplets in the region at δ 3.73 ppm for 6 protons of the $-\text{CH}_3$ groups and at δ 7.2 ppm for 4 of the $-\text{CH}$ aromatic group. Four protons of the $-\text{CH}$ aromatic groups are observed in the region at δ 6.8-7.1 ppm. Also, two protons of the $-\text{CH}$ olefinic groups is observed at δ 8.1 ppm, and two protons of the $-\text{SH}$ groups are observed at δ 3 ppm. Two protons of the $-\text{CH}_2$ groups are observed at δ 4.32 ppm, and two protons of NH are observed at δ 4.00 ppm. Besides that, at δ 6.49 ppm for 4 aromatic protons, δ 7.26 ppm for 4 aromatic protons.

^1H NMR spectrum of compound D9 exhibited multiplets in the region at δ 8.2-8.6 ppm for 4 of the $-\text{CH}$ aromatic group, two proton of the $-\text{CH}$ aromatic group is observed at δ 7.6 ppm, and two proton of the $-\text{CH}$ aromatic group is observed at δ 8.0 ppm. Two proton of the $-\text{CH}$ olefinic groups are observed at δ 8.1 ppm, two protons of the $-\text{SH}$ groups are observed at δ 3 ppm, and two proton of the $-\text{CH}_2$ groups are observed at δ 4.32 ppm. Also, two protons of NH are observed at δ 4.00 ppm, δ 6.49 ppm for 4 aromatic protons, and δ 7.26 ppm for 4 aromatic protons.

^1H NMR spectrum of compound D10 exhibited multiplets in the region at δ 5 ppm for 2 of the $-\text{OH}$ groups, 2 proton of the $-\text{CH}$ aromatic group is observed at δ 6.8 ppm, and two proton of the $-\text{CH}$ aromatic group is observed at δ 7.1 ppm. Two proton of the $-\text{CH}$ olefinic groups are observed at δ 8.1 ppm, two protons of the $-\text{SH}$ groups are observed at δ 3 ppm, and two proton of the $-\text{CH}_2$ groups are observed at δ 4.32 ppm. Also, two protons of NH is observed at δ 4.00 ppm, and at δ 6.49 ppm for 4 aromatic protons, and at δ 7.26 ppm for 4 aromatic protons.

3) Ferric ion antioxidant activity:

The antioxidant activity of the compounds (D0-D10) was measured by using ferrozine [12]. The reduction of (Fe^{+3}) by triazole ring was studied at pH 5.5, due to low solubility of iron at physiological pH, the reaction mixture contained 50 mM sodium acetate buffer (pH 5.5). 1 mM ferrozine, 50 μM of tested compounds and 100 μM of $\text{Fe}(\text{NO}_3)_3$. The reaction was started by the addition of $\text{Fe}(\text{NO}_3)_3$ and the increase of absorbance at 562 nm after 3 minutes was recorded, Fe_{+2} concentration was determined by using an extinction coefficient for $[\text{Fe}(\text{ferrozine})_3]^{+2}$ complex which is equal to $27.9 \times 10^3 \text{ M}^{-1} \cdot \text{cm}^{-1}$ [13].

4) Copper ion antioxidant activity:

The antioxidant properties of compounds (D0-D10) was measured by using 2,9-dimethyl-1,10-phenanthroline (neocuproine) [14], an indicator molecule that binds specifically to the reduced form of copper (Cu^{+1} but not the oxidized form Cu^{+2}) [15]. The reaction mixture contained (20 mM) $\text{KH}_2\text{PO}_4/\text{KOH}$ buffer (pH 7.4), 200 μM $\text{Cu}(\text{NO}_3)_2$, 600 μM 2,9-dimethyl-1,10-phenanthroline, 50 μM of the tested compounds. The mixtures were incubated at room temperature for 120 minutes and then the absorbances were recorded at 455 nm. The copper concentration was determined by using an extinction coefficient for $[\text{Cu}(\text{neocuproine})_2]^{+1}$ complex which is $7.2 \times 10^3 \text{ mM}^{-1} \cdot \text{cm}^{-1}$ [14].

Results and Discussion:

The synthesis of Schiff's bases was done starting from the reaction of benzidine with chloroacetic acid in absolute ethanol and potassium hydroxide forming (A1), the final was reacted with ethanol absolute in strong acid medium to give the ester derivative (A) and the ester derivative was reacted with hydrazine in absolute ethanol to give the acid hydrazide (B) and (B) reacts with CS_2/KOH and NH_2NH_2 in two steps to form (C) derivative and the later reacted with different aldehydes shown in Scheme in absolute ethanol to give the series (D0-D10). The authenticity of the products was confirmed by spectral data (^1H -NMR) and (F.T.IR). The antioxidant activities of the prepared compounds are assessed by the extent of conversion of the Fe^{+3} and Cu^{+2} to the reduced form Fe^{+2} and Cu^{+1} . The antioxidant activity of putative antioxidant has been attributed to various

mechanisms, among which are prevention chain initiation, binding of transition metal ion catalyst, decomposition of peroxides, prevention of continued hydrogen abstraction, reductive capacity and radical scavenging. The compounds give different antioxidant activities[16]. Schiff's bases (D0-D10) studied show higher reducing capacity for copper ions than for iron ions, this can be attributed to the standard reduction and oxidation potentials of the metals, the standard reduction potential of the $\text{Cu}^{+2}/\text{Cu}^{+1}$ (0.15 V) which is much lower than that for $\text{Fe}^{+3}/\text{Fe}^{+2}$ (0.77 V). Tables (3-1) and (3-2) show the antioxidant properties of compounds (D0-D10).

Table (3-1): The antioxidant activity of compounds (D0-D10) against Fe^{+2} .

mol Fe^{+2} / mol D0-D10		
Compound	Substitution	50 μM
D0	H	0.0018
D1	<i>p</i> -Cl	0.0023
D2	<i>p</i> -Br	0.0042
D3	<i>p</i> -OCH ₃	0.0050
D4	<i>p</i> -NO ₂	0.0032
D5	<i>p</i> -OH	0.0302
D6	<i>m</i> -Cl	0.0016
D7	<i>m</i> -Br	0.0033
D8	<i>m</i> -OCH ₃	0.0044
D9	<i>m</i> -NO ₂	0.0021
D10	<i>m</i> -OH	0.0123

Table (3-2): The antioxidant activity of compounds (D0-D10) against Cu^{+1} .

mol Cu^{+1} / mol D0-D10		
Compound	Substitution	50 μM
D0	H	0.31
D1	<i>p</i> -Cl	0.22
D2	<i>p</i> -Br	0.28
D3	<i>p</i> -OCH ₃	0.41
D4	<i>p</i> -NO ₂	0.35
D5	<i>p</i> -OH	0.81
D6	<i>m</i> -Cl	0.18
D7	<i>m</i> -Br	0.31
D8	<i>m</i> -OCH ₃	0.43
D9	<i>m</i> -NO ₂	0.37
D10	<i>m</i> -OH	0.63

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