UV-Vis assisted Synthesis and Antioxidant Properties of some bis-(Schiff's bases) fused with bi(1,3,4-thiadiazole) rings

Mutaz A. Ali [1], Mustafa K. Shneshil [2], Waseela abdul redah abdul razak [2], Rana A,Hammza [1]

[1] *Department of Chemistry, College of Science, Al-Nahrain University.*

[2] *Department of Chemistry, College of Education for pure Science, Diyala University.*

Abstract

A new series of di Schiff's bases fused with bi(1,3,4-thiadiazole) rings having the name (2,2'-bis-N-(substitutedbenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)) were prepared through the reaction of oxalic acid with phosphorus oxychloride followed by hydrolysis reaction, the product was directly reacted with benzaldehyde and substituted benzaldehydes. The compounds (0-10) were identified using the analytical and spectral means using (Uv-Vis spectroscopy), the antioxidant properties were measured to the prepared compounds using the metal ions (Fe^{+3}, Cu^{+2}), ferrozine and 2,9-dimethyl-1,10-phenanthroline (neocuproine) as indicators, the compound (5) reveals the highest activity through this work.

Introduction:

Heterocyclic synthesis has emerged as powerful technique for generating new molecules useful for drug discovery[1]. Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs [2].

Several thiadiazoles compounds are reported to possess, antibacterial [3], antifungal [4], Anti-inflammatory [5], antidepressant [6], analgesic [7] and hypoglycemic activities [8]. Several thiadiazole derivatives are found to possess antitubercular [9], antimicrobial [9] and anti-inflammatory [9] activities.

Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities[10]. Thiadiazole moiety acts as "hydrogen binding domain" and "two-electron donor system". It also acts as a constrained pharmacophore[11]. Many drugs containing thiadiazole nucleus are available in the market such as acetazolamide, methazolamide, sulfamethazole[11]. Thiadiazole can act as the bio-isosteric replacement of the thiazole moiety. So it acts like third and fourth generation cephalosporins, hence can be used in antibiotic preparations. Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. They occur in nature in four isomeric forms. 1,2,3- thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. The 1,3,4-thiadiazole isomer of thiadiazole series and its dihydro-derivatives provide a bulk of literature on thiadiazole[12]. A glance at the standard reference work shows that more work has been carried out on the 1,3,4-thiadiazole than all other isomers combined. Members of this ring system have found their way into such diverse application as pharmaceuticals, oxidation inhibitors, cyanine dyes, & metal complexing agents[13]. The literature review showed that the thiadiazole nuclei have antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radio protective, and anti-leishmanial activities[13].

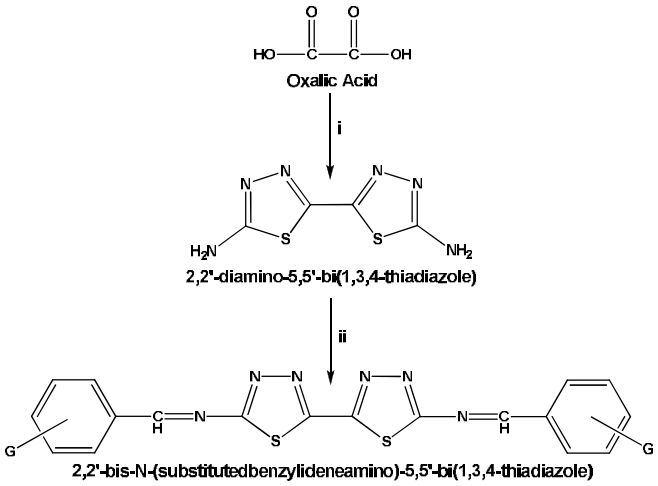
In this work we are synthesized new derivatives of Schiff's bases fused with 1,3,4-thiadiazole ring. Antioxidants are extensively studied for their capacity to protect organisms and cells from damage induced by oxidative stress. Scientists in various disciplines have become more interested in new compounds, either synthesized or obtained from natural sources, which could provide active compounds to prevent or reduce the impact of oxidative stress on cells [15].

Experimental and Methods:

The synthesis of the target molecule is shown in the sequences of reactions depicted in the following Scheme. The F.T.IR spectral data were recorded on F.T.IR-8300 Fourier Transform Infrared Spectrophotometer *SHIMADZU* using potassium bromide disc, Double-beam UV-VISIBLE spectrophotometer (UV 1650 CP), *SHIMADZU* was used to measure the absorbance of the prepared compounds. Melting points (^{o}C) were recorded on hot stage Gallen Kamp melting point apparatus and were uncorrected.

The chemical names follow the IUPAC nomenclature. Some starting materials were purchased from (Kunshan Yalong trading Co., LTD), E-mail: sales@yalongchina.net and were used without purification.

All the recordings were recorded at the Department of Chemistry, College of Science, Al-Nahrain University.



i) Thiosemicarbazide , $POCl_3$, H_2O , KOH.
ii) Benzaldehyde and substituted benzyldehyde , Ethanol (absolute) solvent.

1) Synthesis of 2,2'-diamino-5,5'-bi(thiadiazole):
A mixture of appropriate oxalic acid (0.01mol) and (0.02mol) of thiosemicarbazide with (10mL) of phosphorus oxychloride was refluxed gently for (3 hrs.). After cooling (50mL) of water was added, the mixture was then refluxed for (7hrs.) and filtered, neutralized with some crystals of potassium hydroxide. The precipitate was washed with water and recrystallized from (ethanol 50% - water 50%) to give the desired product.

2) Synthesis of 2,2'-bis-N-(substitutedbenzylideneamino)-5,5'-bi(1,3,4-thiadiazole):
2,2'-diamino-5,5'-bi(1,3,4-thiadiazole) (0.005 mole) was dissolved in refluxed absolute ethanol (50 ml), benzaldehyde (0.01 mole) was slowly added to the mixture, the mixture was refluxed for (6 hrs.) with stirring, the reflux was completed for another (2 hrs) until no more precipitate formed, after cooling to room temperature, the mixture was filtered and the precipitate was dried, the percentage yield was (65%), the melting point of the target molecule was measured and found to be (192^{o}C). The same reaction was carried out to different substituted benzaldehydes (G: H, *p*-Cl, *p*-Br, *p*-OCH_3, *p*-NO_2, *p*-OH, *m*-Cl, *m*-Br, *m*-OCH_3, *m*-NO_2, *m*-OH). The F.T.IR (KBr cm^{-1}) spectral data (stretching vibrations) for the compounds (0-10) are shown below in Table (2-1) and the physical properties of the compounds (0-10) are shown in Table (2-2).

Table (2-1): The F.T.IR (KBr cm^{-1}) spectral data (stretching vibrations) for the compounds (0-10).

G	Compd.	O-H	C-H aromatic	C-H aliphatic	C=N	C=C aromatic
H	0	-	3150		1620	1600
p-Cl	1	-	3090		1610	1556
p-Br	2	-	3050		1630	1550
p-OCH_3	3	-	3100	2980-2840	1610	1563
p-NO_2	4	-	3120		1615	1600
p-OH	5	3350	3160		1625	1607
m-Cl	6	-	3000		1620	1541
m-Br	7	-	3050		1635	1540
m-OCH_3	8	-	3048	2972-2865	1619	1600
m-NO_2	9	-	3122		1610	1560
m-OH	10	3380	3122		1626	1570

Table (2-2): The physical properties of the compounds (0-10).

G	Compd.	M.P.(^{o}C)	% Yield	IUPAC Name
H	0	192	65	2,2'-bis-N-benzylideneamino-5,5'-bi(1,3,4-thiadiazole)
p-Cl	1	204	70	2,2'-bis-N-(4-chlorobenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)
p-Br	2	210	70	2,2'-bis-N-(4-bromobenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)
p-OCH_3	3	207	75	2,2'-bis-N-(4-methoxybenzylideneamino) -5,5'-bi(1,3,4-thiadiazole)
p-NO_2	4	203	60	2,2'-bis-N-(4-nitrobenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)
p-OH	5	240	65	2,2'-bis-N-(4-hydroxybenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)
m-Cl	6	201	65	2,2'-bis-N-(3-chlorobenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)
m-Br	7	204	70	2,2'-bis-N-(3-bromobenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)
m-OCH_3	8	210	65	2,2'-bis-N-(3-methoxybenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)
m-NO_2	9	200	55	2,2'-bis-N-(3-nitrobenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)
m-OH	10	225	65	2,2'-bis-N-(3-hydroxybenzylideneamino)-5,5'-bi(1,3,4-thiadiazole)

3) Ferric ion (Fe^{+3}) antioxidant properties (reducing activity):

The antioxidant properties of the prepared compounds containing 1,3,4-thiadiazole ring to reduce (Fe^{+3} to Fe^{+2}) were measured by using ferrozine [16]. The reduction of (Fe^{+3}) by 1,3,4-thiadiazole 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, 100 μM of tested compounds and 100 μM of $Fe(NO_3)_3$. The reaction was started by the addition of $Fe(NO_3)_3$ and the increase of absorbance at 562 nm after 3 minutes was recorded, Fe^{+2} concentration was determined by using an extinction coefficient for $Fe[(ferrozine)_3]^{+2}$ complex which is equal to 27.9×10^3 M^{-1} $.cm^{-1}$ [17].

Copper ion (Cu^{+2}) antioxidant properties (reducing activity):

The antioxidant properties of the prepared compounds containing 1,3,4-thiadiazole ring to reduce (Cu^{+2} to Cu^{+1}) were measured by using 2,9-dimethyl-1,10-phenanthroline (neocuproine) [18], an indicator molecule that binds specifically to the reduced form of copper (Cu^{+1} but no the oxidized form Cu^{+2}) [19]. The reaction mixture contained (20 mM) KH_2PO_4/KOH buffer (pH 7.4), 200 μM $Cu(NO_3)_2$, 600 μM 2,9-dimethyl-1,10-phenanthroline, 50, 100 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 $Cu[(neocuproine)_2]^{+2}$ complex which is 7.2×10^3 M^{-1} $.cm^{-1}$, that was determined by reducing Cu^{+2} with ascorbate [18].

Results and Discussion:

The synthesis of 2,2'-bis-N-(substitutedbenzylideneamino)-5,5'-bi(1,3,4-thiadiazole) was achieved by the reaction of oxalic acid with phosphorus oxychloride, the product after that was hydrolyzed and treated then with crystals of potassium hydroxide, and then was reacted with benzaldehyde and substituted benzaldehyde to form the target molecules (0-10). The authenticity of the product was confirmed by spectral data (F.T.IR) shown in Table (2-1). The antioxidant properties 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 properties of compounds were studied at different concentrations. 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 [19,20]. The compounds (3 and 5) reveal the highest antioxidant activity this is attributed to the presence of hydroxyl group, thiadiazoles (0-10) 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 Cu^{+2}/Cu^{+1} (0.15 V) which is much lower than that for Fe^{+3}/Fe^{+2} (0.77 V). Tables (3-1) and (3-2) show the antioxidant properties of compounds (0-10).

Note the standard deviation (SD) referred to (±) of at least three independent experiments was calculated and showed in results.

TABLE (3-1): The antioxidant properties of compounds (0-10) against Fe^{+2}.

μmole Fe^{+2}/μmole 1,3,4-thiadiazole			
Compd.	G	50 μM	100 μM
0	H	0.0080±0.001	0.0095±0.001
1	*p*-Cl	0.0004±0.002	0.0012±0.002
2	*p*-Br	0.0046±0.002	0.0055±0.001
3	*p*-OCH_3	0.0066±0.001	0.0070±0.000
4	*p*-NO_2	0.0030±0.001	0.0040±0.001
5	*p*-OH	0.0300±0.001	0.0650±0.002
6	*m*-Cl	no effect	0.0010±0.002
7	*m*-Br	0.0020±0.001	0.0030±0.001
8	*m*-OCH_3	0.0050±0.001	0.0060±0.001
9	*m*-NO_2	0.0022±0.002	0.0041±0.000
10	*m*-OH	0.0018±0.000	0.0225±0.002

TABLE (3-2): The antioxidant properties of compounds (0-10) against Cu^{+1}.

μmole Cu^{+1}/μmole 1,3,4-thiadiazole			
Compd.	G	50 μM	100 μM
0	H	0.20±0.001	0.30±0.000
1	*p*-Cl	0.19±0.002	0.28±0.001
2	*p*-Br	0.42±0.000	0.56±0.004
3	*p*-OCH_3	0.40±0.002	0.58±0.005
4	*p*-NO_2	0.32±0.002	0.40±0.002
5	*p*-OH	0.70±0.001	0.88±0.003
6	*m*-Cl	0.12±0.000	0.20±0.001
7	*m*-Br	0.20±0.004	0.30±0.001
8	*m*-OCH_3	0.33±0.002	0.38±0.000
9	*m*-NO_2	0.25±0.004	0.36±0.002
10	*m*-OH	0.50±0.001	0.59±0.001

References

1. Hermakens PH, Ottenheijm HC, Rees DC. Solid-phase organic reactions II: A review of literature. Nov 95 nov 96.*Tetrahedron* 1997; 53: 5643.
2. Gordon E, Barrett RW, Dower WJ, Foder SP. Applications of combinatorial technologies to drug discovery. 2. Combinatorial organic synthesis, library screening strategies, and future directions. *J Med Chem* 1994; 37:1485.
3. Kirilmis C, Ahmedzade M, Süleyman S, Koca M, Kizirgil A. Synthesis and antimicrobial activity of some novel derivatives of benzofuran: Part 2. The synthesis and antimicrobial activity of some novel 1-(1-benzofuran-2-yl)-2-mesitylethanone

derivatives. *Euro. J. Med. Chem.*, 2008, 43, 300-308.
4. Shazia N. Aslam, Philip C. Stevenson, Sara J. Phythian, Nigel C. Veitch, David R. Hall. Synthesis of cicerfuran, an antifungal benzofuran, and some related analogues. *Tetrahedron*, 2006, 62, 4214-4226.
5. Balasaheb Y. Mane, Y.S.Agasimundin, B. Shivkumar, Devanand B. Shinde. Microwave-assisted synthesis of benzofuran analogs of fenamates as non-steroidal antiinflammatory agents. *J. Chil. Chem. Soc*., 2009, 54(1), 77-79.
6. Malik WU, Mahesh VK, Raishighani M. Synthesis and biological evaluation of of some benzofuran derivative. *Indian J.Chem*, 1971, 9, 655.
7. Fry DJ, Ficken EG, Burrows RW. *Brit.*, 1969, 1, 168495.
8. Brady BA, Kennedy JA, Süllivan WI. The configuration of aurones. *Tetrahedron*, 1973, 29, 359-362.
9. Manna K, Agarwal YK, Srinivasan KK. Synthesis and biological evaluations of new benzofuran isoxazole derivatives as potential antitubercular, antibacterial and antifungal agents. *Indian J. Hetero. Chem.*, 2008, 18, 87-88.
10. Cerutti, P.A.,. Oxidant stress andcarcinogenesis. European J. Clinical Investigation, 1991, 21(1): 1-5.
11. Halliwell, B.,. Antioxidants and Human Disease. A General Introduction. *Nutrition Reviews*, 1997, 55(1): S44-S49.
12. Pietta, P.G.,. Flavonoids as antioxidant. *Journal of Natural Products*, 2000, 63: 1035-1042.
13. Cerutti, P.A.,. Oxy-radicals and cancer. Lancet, 1994, 344(8926): 862-863.
14. Ames, B.N., L.S. Gold and W.C. Willett,. The causes and prevention of cancer. Proceedind of the National Academy of Sciences, 1995, 92(12): 5258-5265.
15. Hussain, H. H.; Babic, G.; Durst, T.; Wright, J. S.; Flueraru, M.; Chichirau, A.; Chepelev, L. L., *J. Org. Chem.*, 2003, 68, 7023-7032.
16. Lurdes, M.; Fernandez, M. T.; Santos, M.; Rocha, R.; Florêncio, M. H.; Jennings, K. R., *Free Rad. Res.*, 2002, 36, 1199-1208.
17. Stooky, L. L., *Anal. Chem.*, 1970, 42, 779-781.
18. Proudfoot, J. M.; Croft, K. D.; Puddey, I. B.; Beilin, L. J., *Free Rad. Biol. Med.*, 1997, 23, 720-728.
19. Simpson, J. A.; Narita, S.; Gieseg, S.; Gebicki, J. M; Dean, R. T., *Biochem. J.*, 1992, 282, 621-624.
20. Yildirim, A.; Mavi, A.; Kara, A. A., *J. Agri. Food Chem.*, 2001, 49, 4083-4089.

الملخص

تم في هذا البحث تحضير مركبات (قواعد شف) جديدة ثنائية مرتبطة بثنائي حلقة (4,3,1–ثاياديازول) bi(1,3,4–thiadiazole) والمسماة (2,2'–di–N–substituted benzylideneamino–5,5'–bi(1,3,4–thiadiazole)) وذلك من خلال مفاعلة حامض الأوكزاليك مع أوكسي كلوريد الفوسفور ثم تحلل الناتج مائياً، وتمت مفاعلة الناتج بعد ذلك مع البنزالديهايد وعدة مركبات من البنزالديهايد المعوض وتم تشخيص المركبات بالوسائل التحليلية والطيفية باستخدام (Uv–Vis spectroscopy)، وتم قياس فعالية هذه المركبات (0–10) كمضادات للأكسدة بأستخدام أيونات (Fe^{+3}، Cu^{+2}) وذلك بأستخدام كاشف الفيروزين و كاشف 9,2–ثنائي مثيل–10,1– فينانثرولين (نيوكبروين)، أظهر المركب (5) أعلى فعالية كمضاد للأكسدة من خلال هذا البحث.