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Synthesis and Antioxidant Activity of 1-(1,2,3,4-Tetrazol-2-yl-Diazenyl) -4-(Substituted Benzylideneamino)

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ABSTRACT

A series of Schiff's bases fused with tetrazole ring having the name 1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(substituted benzylideneamino) benzene were prepared through the reaction of 2-amino tetrazole hydrochloric acid and sodium nitrite and the product was reacted with aniline, then the final product was reacted with benzaldehyde and substituted benzaldehydes. The compounds 3(a-k) were identified using the analytical and spectral means, the antioxidant properties were measured to the prepared compounds using the metal ions (Fe^{+3}, Cu^{+2}), using the ferrozine and 2,9-dimethyl-1,10-phenanthroline (neocuproine).

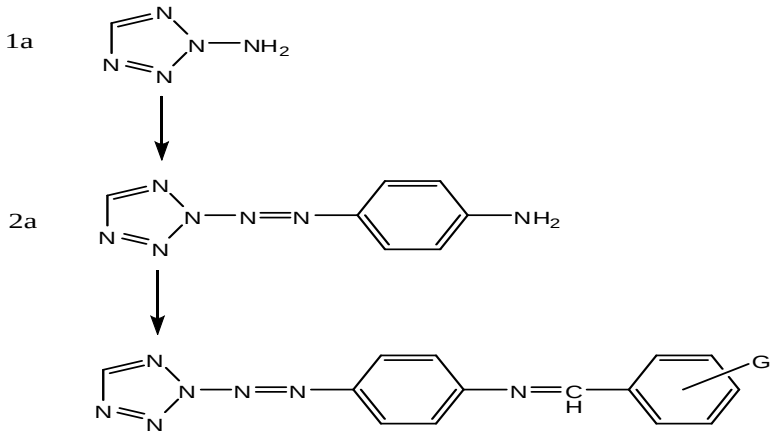
Keywords: Schiff's bases, tetrazole ring, 1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(substituted benzylidene amino) benzene.

INTRODUCTION

Nitrogen containing heterocyclic are one of the most extensively synthesized and screened compounds as they show diverse pharmacological activities. The development of tetrazole chemistry has been largely associated with wide scale of applications of these classes of compounds in medicine, biochemistry, agriculture and also large number of medicinally important tetrazole heterocyclic incorporated drugs approved by the FDA [1]. Tetrazoles and their derivatives are important constituents of pharmacologically active synthetic compounds. The tetrazole nucleus also occurs in the structure of numerous naturally occurring compounds which have been associated with a broad spectrum of biological activities [2]. The fusion of Schiff's bases with the tetrazole ring is known to increase the biological activity [3]. The tetrazole group, which is considered as a carboxylic group pharm core, possesses a wide range of biological activities. Several substituted tetrazoles have been shown to possess anti-inflammatory [4-5], antimalarial [6], anticancer [7], antifungal [8-11], anticonvulsant [12], antibacterial [13-14,15], vaso relaxing [16], antiviral [17] and CNS dispersant [18] activities. The tetrazole functionality plays an important role in medicinal chemistry, primarily due to its ability to serve as bioequivalent of the carboxylic acid group. Heterocyclic synthesis of tetrazole derivatives is obviously an important task in modern medicinal chemistry. They have been associated with a broad spectrum of various biological activities. The Schiff's bases derived from thiocarbohydrazide are known to exhibit diverse activities like antibacterial [19], ant carcinogenic [20], antiviral [21], herbicidal [22] and antifungal [23] activities.

MATERIALS 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. Proton Nuclear Magnetic Resonance (^{1}HNMR), using Varian VnmrJ 400 spectrometer (400 MHz) and tetramethylsilane (TMS). 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.



Synthesis of 4-(1,2,3,4-tetrazol-2-yl-diazenyl) aniline(2a) : 0.01mol of 2-Amino tetrazole was dissolved in slightly acidified distilled water, to it a mixture of 0.01 mol of HCl and $NaNO_2$ was added and the reaction was occupied in ice bath, then 0.01 mol of aniline was added, a bright yellow precipitate was formed and filtered.

Synthesis of 1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(substituted benzylideneamino) benzene 3(a-k) : 0.01 mol of 4-(1,2,3,4-Tetrazol-2-yl-diazenyl) aniline was dissolved and refluxed with 50 mL absolute ethanol, 0.01 mol of benzaldehyde was slowly added to the refluxed mixture.The net mixture was refluxed for 8 h with stirring, the reflux was completed for another two hours until no more precipitate formed.After cooling to room temperature the mixture was filtered and the precipitate was dried and recrystallized from ethanol.The percentage yield was 66%.The melting point of the target molecule (3) was measured and found to be (196^{o}C). The same reaction was carried out to different substituted benzaldehydes (G: *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 spectral data and the physical properties of the compounds 3(a-k) are shown in table 1,2 and 3 respectively.

Table 1. The physical properties of the compounds 3(a-k).

G	Compd.	m.p.(^{o}C)	% Yield	IUPAC Name
H	3a	196	66	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(benzylideneamino) benzene
p-Cl	3b	179	78	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(4-chloro benzylideneamino) benzene
p-Br	3c	198	59	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(4-bromo benzylideneamino) benzene
p-OCH_3	3d	184	69	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(4-methoxy benzylideneamino) benzene
p-NO_2	3e	176	70	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(4-nitro benzylideneamino) benzene
p-OH	3f	210	73	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(4-hydroxy benzylideneamino) benzene
m-Cl	3g	180	60	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(3-chloro benzylideneamino) benzene
m-Br	3h	189	61	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(3-bromo benzylideneamino) benzene
m-OCH_3	3i	170	68	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(3-methoxy benzylideneamino) benzene
m-NO_2	3j	182	64	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(3-nitro benzylideneamino) benzene
m-OH	3k	203	73	1-(1,2,3,4-tetrazol-2-yl-diazenyl)-4-(3-hydroxy benzylideneamino) benzene

Table 2. The F.T.IR (KBr cm^{-1}) spectral data (stretching vibrations) for the compounds 3(a-k).

G	Compd.	O-H	C-H aromatic	C-H aliphatic	C=N	C=C aromatic
H	3a	-	3074		1615	1600
p-Cl	3b	-	3110		1610	1550
p-Br	3c	-	3112		1614	1560
p-OCH_3	3d	-	3024	2990-2866	1620	1580
p-NO_2	3e	-	3100		1610	1581
p-OH	3f	3320	3103		1613	1554
m-Cl	3g	-	3055		1610	1546
m-Br	3h	-	3065		1611	1588
m-OCH_3	3i	-	3122	2993-2902	1612	1659
m-NO_2	3j	-	3080		1620	1563
m-OH	3k	3340	3065		1613	1566

Table 3. The ^1H NMR Spectral Data of Compounds 3(a-k).

G	Compd.	Chemical Shift ppm
H	3a	6.7-7.1(4H, m, Ar-H), 7.7-7.9(4H, m, Ar-H), 8.5 (1H, s, CH=N), 9.1(1H, s) tetrazole
p-Br	3c	6.9-7.2(4H, m, Ar-H), 7.6-7.8(4H, m, Ar-H), 8.6 (1H, s, CH=N), 9.1(1H, s) tetrazole
p-OCH_3	3d	6.8-7.0(4H, m, Ar-H), 7.5-7.7(4H, m, Ar-H), 8.5 (1H, s, CH=N), 9.0(1H, s) tetrazole,4.1(3H, s, OCH_3)
p-OH	3f	6.7-6.9(6H, m, Ar-H), 7.8-7.9(4H, d Ar-H), 8.4 (1H, s, CH=N), 8.9(1H, s) tetrazole,9.7(3H, s, OH)
m-Cl	3g	6.6-6.7(4H, m, Ar-H), 7.5-7.6(3H, d Ar-H),7.9(1H, d Ar-H) 8.5 (1H, s, CH=N), 9.1(1H, s) tetrazole
m-NO_2	3j	6.8-6.9(4H, m, Ar-H), 7.9(1H, d Ar-H),8.1(3H, d Ar-H) 8.6 (1H, s, CH=N), 9.0(1H, s) tetrazole

Ferric ion (Fe^{+3}) antioxidant properties (reducing activity) : The antioxidant properties of the prepared compounds containing tetrazole ring to reduce (Fe^{+3} to Fe^{+2}) were measured by using ferrozine [23]. The reduction of (Fe^{+3}) by tetrazole 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. 1mM 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 min 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} [24].

Copper ion (Cu^{+2}) antioxidant properties (reducing activity) : The antioxidant properties of the prepared compounds containing tetrazole ring to reduce (Cu^{+2} to Cu^{+1}) were measured by using 2,9-dimethyl-1,10-phenanthroline (neocuproine) [25], an indicator molecule that binds specifically to the reduced form of copper (Cu^{+1} but no the oxidized form Cu^{+2}) [26]. The reaction mixture contained 20 mM KH_2PO_4/KOH buffer pH 7.4, 200µM $Cu(NO_3)_2$, 600 µM 2,9-dimethyl-1,10-phenanthroline, 50, 100µM 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 $Cu(neocuproine)_2^{+1}$ complex which is 7.2×10^3 mM^{-1} cm^{-1} [25].

RESULTS AND DISCUSSION

The synthesis of N-(substituted benzylidene)-2-amino tetrazole was achieved by the reaction of 2-amino tetrazole with benzaldehyde and substituted benzaldehydes to form the target molecules 3(a-k).The authenticity of the product was confirmed by spectral data (F.T.IR) shown in table 2. 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 the 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 [27].
Tetrazoles 3(a-k) 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 (4) and (5) show the antioxidant properties of compounds 3(a-k).

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

Table 4. The antioxidant properties of compounds 3(a-k) against Fe^{+2}.

μmole Fe^{+2}/μmoletetrazole			
Compd.	G	50 μM	100 μM
3a	H	0.0031±0.001	0.0450±0.001
3b	*p*-Cl	0.0018±0.002	0.0029±0.001
3c	*p*-Br	0.0039±0.001	0.0060±0.001
3d	*p*-OCH_3	0.0059±0.001	0.0079±0.000
3e	*p*-NO_2	0.0031±0.001	0.0056±0.001
3f	*p*-OH	0.0251±0.001	0.0579±0.001
3g	*m*-Cl	0.0011±0.002	0.0025±0.001
3h	*m*-Br	0.0022±0.001	0.0051±0.001
3i	*m*-OCH_3	0.0030±0.001	0.0048±0.002
3j	*m*-NO_2	0.0019±0.001	0.0033±0.001
3k	*m*-OH	0.0120±0.001	0.0175±0.001

Table 5. The antioxidant properties of compounds 3(a-k) against Cu^{+1}.

μmole Cu^{+1}/μmole tetrazole			
Compd.	G	50 μM	100 μM
3a	H	0.20±0.001	0.42±0.001
3b	*p*-Cl	0.30±0.000	0.66±0.001
3c	*p*-Br	0.33±0.001	0.53±0.001
3d	*p*-OCH_3	0.48±0.002	0.82±0.002
3e	*p*-NO_2	0.42±0.001	0.75±0.002
3f	*p*-OH	0.78±0.001	0.97±0.001
3g	*m*-Cl	0.32±0.001	0.58±0.001
3h	*m*-Br	0.39±0.002	0.62±0.001
3i	*m*-OCH_3	0.40±0.002	0.71±0.000
3j	*m*-NO_2	0.36±0.001	0.46±0.001
3k	*m*-OH	0.69±0.001	0.82±0.001

REFERENCES

[1] L.V.Myznikov, A.Hrabalek, G.I. Koldobskii. Drugs in tetrazole series, *Chem. Het. Comp.***2007**, 43, 1-9.

[2] H.I.El-Subbagh, S.M.Abu-Zaid, M.A.Mahran, F.A.Badria, A.M.Alofaid, *J. Med.Chem.* **2000**, 43, 2915-2921.

[3] R. Gupta, A.K.Gupta, S. Paul ,Synthesis of new 4-(4,5-diphenyl-1h-imidazol-2-yl)tetrazolo[1,5-a]quinolines from tetrazolo[1,5-a]quinolines. *Ind. J. Chem*. **2000**, 39B, 847.

[4] A.M. Farghaly, A.A.Bekhit, J.Y.Park, Arch, *Pharm. Pharm. Med. Chem.* **2000**,333, 53–57.

[5] A.A.Bekhit, O.A. El-Sayed, E.Aboulmagd, J.Y. Park Tetrazolo[1,5-a]quinoline as a potential promising new scaffold for the synthesis of novel anti-inflammatory and antibacterial agents, *Eur. J. Med. Chem*. **2004**; 39: 249-55.

[6] R.Vlabhov, St. Parushev, J.Vlahov, P.Nickel, G. Snatzke, Synthesis of some new quinolinederivatives-potential antimalarial drugs, *Pure. Appl. Chem*. **1990**, 62(7), 1303-06.

[7] L.Dalla Via, O.Gia, V.Gasparotto, M.G.Ferlin, Discovery of a new anilino-3Hpyrrolo[3,2-f] quinoline derivative as potential anti-cancer agent, *Eur. J. Med. Chem.* **2007**, XX, 1-6.

[8] K. Sharma, P.S.Fernandes, A facile route to the synthesis of substituted 2- hydrazinoquinolines and its ring closer reaction and their biological activity, *Ind. J. Het.Chem*. Oct-Dec **2005**, 15,161-168.

[9] S.P.Rajendra, R.Karvembu, Synthesis and antifungal activities of schiff bases derived from 3-amino-2H-pyrano[2,3-b]quinoline-2-ones, *Ind. J. Chem*. Jan **2002**; 41B, 222-224.

[10] A.H.Kategaonkar, R.U.Pokalwar, S.S.Sonar, V.U.Gawali, Synthesis in vitro antibacterial and antifungal evaluations of new a-hydroxyphosphonate and new a-acetoxyphosphonatederivatives of tetrazolo [1,5-a] quinoline, *Eur. J. Med. Chem*. **2010**, 45, 1128–1132.

[11] M.Gupta, S.Paul, R.Gupta, The one pot synthesis of antifungal active 9-substituted-3-aryl-5H,13aH-quinolino[3,2-f][1,2,4]triazolo[4,3-b],[1,2,4]triazepines, *Ind. J. Chem*. Apr **2010**, 42B, 475-481.

[12] Z.Zie, K. Chai, H. Piao, K.Kwak, Z.Quan, Synthesis and anticonvulsant activity of 7-alkoxyl-4,5-dihydro-[1,2,4]triazolo [4,3-a]quinolines, *Bioorg. Med. Chem. Lett*. **2005**, 15, 4803-05.

[13] R. Gupta, A.K.Gupta,S. Paul , Microwave-assisted synthesis and biological activities of some 7/9-substituted-4-(3-alkyl/aryl-5,6-dihydro-s-triazolo[3,4-b][1,3,4] thiadiazole-6-yl)-tetrazolo[1,5-α] quinolines, *Ind. J. Chem.* Nov **2000,** 39B, 847-852.

[14] S.Bawa, S. Kumar, Synthesis of schiff's bases of 8-methyl-tetrazolo[1,5-a]quinoline as potential anti-inflammatory and antimicrobial agents, *Ind. J. Chem*. Jan **2009**, 48B, 142-145.

[15] M.G.Ferlin,G. Chiarelotto, F.Antonucci, L.Caparrotta,G. Froldi , Mannich bases of 3Hpyrrolo[3,2-f]quinoline having vasorelaxing activity. *Eur. J. Med. Chem*. **2002**, 37, 427-434.

[16] C.Benard, F. Zouhiri, M.Normand-Bayle, M.Danet, D.Desmaele, H. Leh, Linker-modified quinoline derivatives targeting HIV-1 integrase: synthesis and biological activity, *Bioorg.Med. Chem. Lett*. **2004**, 14, 2473-76.

[17] J.S. Shukla,S. Saxena. *Indian Drugs*. **1980**, 18, 15.

[18] M.A. Baseer, V.D. Jadhav, R.M. Phule, Y.V.Archana, Y.B.Vibhute, *Orient. J. Chem.* **2000**, 16, 553.

[19] B.Moubaraki, K.S. Murray, J.D.Ranford, X.Y.Xu. *Chem. Commun*., **1998**, 353.

[20] T.A.Blumenkopf, J.A. Harrington, C.S.Koble, D.D.Bankston, R.W.Morrsion, E.C.Bigham,V.L. T.Spector, *J. Med. Chem*, **1992**, 16, 2306.

[21] P. Pathak,V.S. Jolly, K.P. Sharma. *Orient. J. Chem*, **2000**, 16, 161.

[22] Z.H.Chohan, H. Pervez, K.M.Khan, C.T. Supuran, *J. Enzyme Inhib. Med. Chem*, **2005**, 20, 81.

[23] L.L.Stooky, *Anal. Chem.*, **1970**, 42, 779-781.

[24] J. M. Proudfoot, K.D.Croft, I.B.Puddey, L.J. Beilin, *Free Rad. Biol. Med*., **1997**, 23, 720-728.

[25] J.A.Simpson, S. Narita, S.Gieseg, J.M.Gebicki, R.T. Dean, *Biochem. J*., **1992**, 282, 621-624.
[26] A.Yildirim, A.Mavi, A.A. Kara, *J. Agri. Food Chem*., **2001**, 49, 4083-4089.
[27] M.A. Hossain, S.K. Shaha and F.Aziz, Antioxidant potential study of some synthesized Nheterocycles, *Bangla. Med. Res. Counc. Bull*, **2009**, 35, 49-52.