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Synthesis and Antioxidant Activity of Some Schiff's Bases Fused With Tetrazole Ring

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ABSTRACT

A new series of Schiff's bases fused with tetrazole ring having the name (N-(substituted benzylidene)-2-amino tetrazole) were prepared through the reaction of 2-amino tetrazole with benzaldehyde and substituted benzaldehydes. The compounds (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).

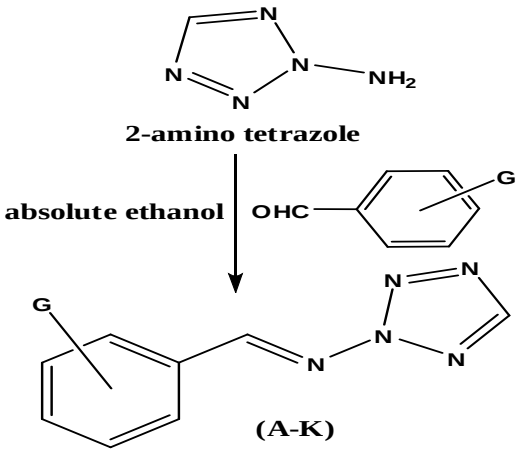
Keywords: Schiff's bases, Tetrazole, Activity, Antioxidant.

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], vasorelaxing [15], antiviral [16] and CNS dispersant [17] 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 [18], anticarcinogenic [19], antiviral [20], herbicidal [21] and antifungal [22] 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. Double-beam UV-VISIBLE spectrophotometer (UV 1700 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.



N-(substituted benzylidene)-2-amino tetrazole

Synthesis of N-(substituted benzylidene)-2-amino tetrazole: 0.01mol of 2-Amino tetrazole was dissolved in 50 mL absolute ethanol in a refluxing flask. Then 0.01mol benzaldehyde was slowly added to the refluxed mixture, the net mixture was refluxed for 6 h with stirring, the reflux was completed for another 2 h 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 70%, the melting point of the target molecule (A) was measured and found to be 143^{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 F.T.IR (KBr cm^{-1}) spectral data (stretching vibrations) and the physical properties of the compounds (A-K) are shown in Table 1, 2 and 3 respectively.

Table 1. The F.T.IR (KBr cm^{-1}) spectral data (stretching vibrations) for the compounds (A-K).

G	Compd.	O-H	C-H aromatic	C-H aliphatic	C=N	C=C aromatic
H	A	-	3100		1625	1605
p-Cl	B	-	3060		1620	1557
p-Br	C	-	3070		1622	1570
p-OCH_3	D	-	3020	2996-2875	1620	1569
p-NO_2	E	-	3600		1619	1501
p-OH	F	3300	3100		1620	1587
m-Cl	G	-	3045		1630	1537
m-Br	H	-	3055		1637	1550
m-OCH_3	I	-	3120	2986-2905	1629	1600
m-NO_2	J	-	3100		1624	1581
m-OH	K	3350	3025		1620	1528

Table 2. The ^{1}HNMR for the Some compounds

G	Compd.	Chemical shift ppm
p-Cl	B	8.92 tetrazole, 7.29 – 8.11 benzylidineimin
p-OCH_3	D	(7.50 -7.62), (7.39 -7.62), (7.06-7.29) benzylidineimin 8.92 terazole 3.83 aromatic C-OCH_3
p-NO_2	E	(8.52-7,62), (8.15-7.29), (9.56-8.11) benzylidineimin 8.92 tetrazole
p-OH	F	5.35 -5.00 aromatic C-OH, 8,92 tetrazole , (7.39 -7.62) , (7.46 -7.62), (7.02 -7.29) (9.56 -8.11) benzylidineimin
m-OCH_3	I	8.92 tetrazole, (7.25 -7.29), (7.62 -7.72), (7.08 -7.29) benzylidineimin 3.83 aromatic C-OCH_3
m-OH	K	(7.62 -7.72), (7.29 -7.58), (7.08 -7.29) benzylidineimin (5.35 -5.00) aromatic C-OH, 8.92 tetrazole

Table 3. The physical properties of the compounds (A-K).

G	Compd.	M.P.(^{o}C)	% Yield	IUPAC Name
H	A	143	70	N-benzylidene-2-amino tetrazole
p-Cl	B	167	65	N-(4-chloro benzylidene-2-amino tetrazole
p-Br	C	172	67	N-(4-bromo benzylidene-2-amino tetrazole
p-OCH_3	D	168	64	N-(4-methoxy benzylidene-2-amino tetrazole
p-NO_2	E	157	68	N-(4-nitro benzylidene-2-amino tetrazole
p-OH	F	188	77	N-(4-hydroxy benzylidene-2-amino tetrazole
m-Cl	G	164	56	N-(3-chloro benzylidene-2-amino tetrazole
m-Br	H	166	60	N-(3-bromo benzylidene-2-amino tetrazole
m-OCH_3	I	161	65	N-(3-methoxy benzylidene-2-amino tetrazole
m-NO_2	J	155	63	N-(3-nitro benzylidene-2-amino tetrazole
m-OH	K	175	78	N-(3-hydroxy benzylidene-2-amino 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. 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 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 min 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 (A-K). The authenticity of the product was confirmed by spectral data (F.T.IR) shown in table 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 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 (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 3 and 4 show the antioxidant properties of compounds (A-K). Note the standard deviation (SD) referred to (±) of at least three independent experiments was calculated and showed in the results.

Table 3. The antioxidant properties of compounds (A-K) against Fe^{+2}.

µmole Fe^{+2}/µmole tetrazole			
Compd.	G	50 µM	100 µM
A	H	0.0020±0.001	0.0030±0.001
B	*p*-Cl	0.0003±0.003	0.0022±0.002
C	*p*-Br	0.0043±0.002	0.0065±0.001
D	*p*-OCH_3	0.0060±0.001	0.0080±0.000
E	*p*-NO_2	0.0024±0.001	0.0044±0.001
F	*p*-OH	0.0200±0.001	0.0550±0.000
G	*m*-Cl	0.0009±0.001	0.0018±0.001
H	*m*-Br	0.0018±0.001	0.0040±0.001
I	*m*-OCH_3	0.0048±0.001	0.0057±0.001
J	*m*-NO_2	0.0020±0.002	0.0054±0.000
K	*m*-OH	0.0070±0.000	0.0095±0.002

Table 4. The antioxidant properties of compounds (A-K) against Cu^{+1}.

µmole Cu^{+1}/µmole tetrazole			
Compd.	G	50 µM	100 µM
A	H	0.27±0.001	0.40±0.000
B	*p*-Cl	0.29±0.002	0.45±0.001
C	*p*-Br	0.38±0.000	0.58±0.004
D	*p*-OCH_3	0.53±0.002	0.78±0.005
E	*p*-NO_2	0.45±0.002	0.50±0.002
F	*p*-OH	0.85±0.001	0.71±0.003
G	*m*-Cl	0.23±0.000	0.35±0.001
H	*m*-Br	0.31±0.004	0.40±0.001
I	*m*-OCH_3	0.43±0.002	0.41±0.000
J	*m*-NO_2	0.37±0.004	0.43±0.002
K	*m*-OH	0.48±0.001	0.69±0.001

APPLICATIONS

The prepared compounds using the metal ions Fe^{+3}, Cu^{+2}, using the ferrozine and 2,9-dimethyl-1,10-phenanthroline(neocuproine) are good antioxidants.

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