European Journal of Chemistry 7 (3) (2016) 363-367

European Journal of Chemistry

Journal webpage: www.eurjchem.com

One-pot pseudo five-component synthesis and antioxidant evaluation of 4,4'-(aryl-methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)

Moustafa Ahmed Gouda [1,2,*], Majed Musallam Mutlaq Al-Balawi [1] and Ameen Ali Abu-Hashem [3,4]

[1] *Department of Chemistry, Faculty of Science and Arts, Taibah University, Ulla, 41411, Kingdom of Saudi Arabia*
[2] *Chemistry Department, Faculty of Science, Mansoura University, Mansoura 35516, Egypt*
[3] *Department of Photochemistry, National Research Center, Dokki, Giza 12622, Egypt*
[4] *Department of Chemistry, Faculty of Science, Jazan University, Jazan, 45142, Kingdom of Saudi Arabia*

** Corresponding author at: Department of Chemistry, Faculty of Science and Arts, Taibah University, Ulla, 41411, Kingdom of Saudi Arabia. Tel.: +2.050.6432235. Fax: +2.050.2246781. E-mail address: dr_mostafa_chem@yahoo.com (M.A. Gouda).*

ARTICLE INFORMATION

DOI: 10.5155/eurjchem.7.3.363-367.1474

Received: 09 July 2016
Received in revised form: 20 July 2016
Accepted: 23 July 2016
Published online: 30 September 2016
Printed: 30 September 2016

KEYWORDS

Arylmethylene
Bis-pyrazol-5-ol
Michael reaction
One pot reaction
Antioxidant activity
Tandem Knoevenagel reaction

ABSTRACT

A simple method for the synthesis of some 4,4'-(aryl-methylene)*bis*(3-methyl-1*H*-pyrazol-5-ol) derivatives via a one-pot pseudo five-component reaction of phenyl hydrazine, ethyl acetoacetate and aldehydes in acetic acid is reported. The prepared compounds were characterized by elemental analyses and spectral data. Some of the synthesized compounds were screened for their antioxidant activity using 2,2'-azino-*bis*(3-ethyl benzothiazoline-6-sulfonic acid (ABTS) method; all the investigated compounds showed similar and higher antioxidant activity than ascorbic acid and exhibited high protection against DNA damage induced by the bleomycin iron complex.

Cite this: *Eur. J. Chem.* **2016**, *7(3)*, 363-367

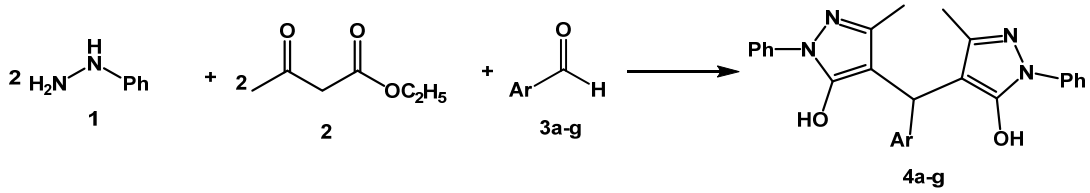
1. Introduction

Oxidative stress results in oxidative alteration of biological macromolecules such as lipids, proteins and nucleic acids. It is considered to play a pivotal role in the pathogenesis of aging and degenerative diseases [1-3]. In order to cope with an excess of free radicals produced upon oxidative stress, human bodies have developed sophisticated mechanisms for maintaining redox homeostasis. These protective mechanisms include scavenging or detoxification of reactive oxygen species (ROS), blocking ROS production, sequestration of transition metals, as well as enzymatic and non-enzymatic antioxidant defenses produced in the body, that is, endogenous [4,5] and others supplied with the diet, namely, exogenous ones. Among them, dietary polyphenols have been widely studied for their strong antioxidant capacities and other properties by which cell functions are regulated [6].

Among the heterocyclic ring systems, pyrazolone derivatives have a wide range of unique biological activities. Some of the pyrazolone derivatives are included in many of the comercialized drugs for brain ischemia, [7] and myocardial ischemia [8]. Among them, *bis*(pyrazolyl)methanes (BPMs) such as 4,4'-(aryl-methylene)-*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) have a broad spectrum of approved biological activity, being used as anti-inflammatory [9], gastric secretion stimulatory [10], antidepressant [11], antibacterial [12], and antifilarial agents [13]. Moreover, these compounds have been applied as fungicides [14], pesticides [15], insecticides [16], dyestuffs [17], and chelating as well as extracting reagents for different metal ions [18].

Numerous synthetic methods have been reported for the preparation of 4,4'-(aryl-methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) under classical or modified conditions [19-31]. However, some of these methods suffer from expensive reagents, low yield, prolonged reaction time and use of toxic organic solvents, and tedious workup procedures. Thus, a search for new reagents and the development of new methods are still of practical importance. In this regard, we decided to explore the possibility of synthesizing 4,4'-(aryl-methylene)*bis*(3-methyl-1-phenyl-pyrazol-5-ol) via a novel, one-pot, multi-component condensation of phenyl hydrazine (2 equiv.), ethyl acetoacetate (2 equiv.) and aromatic aldehydes (1 equiv.) in 50% acetic acid in order to evaluate their anti-oxidant activities.

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.7.3.363-367.1474



Product	Ar	Time (hr)	Yield (%) [a]
4a	Phenyl	7	77
4b	4-Methoxyphenyl	6	83
4c	4-Chlorophenyl	6	81
4d	2-Thienyl	6	74
4e	4-Bromophenyl	7	77
4f	4-Florophenyl	6	83
4g	4-Nitrophenyl	6	81

[a] Isolated yield after recrystallization.

Scheme 1

2. Experimental

2.1. Instrumentation

All melting points are recorded on Gallenkamp electric melting point apparatus and are uncorrected. The IR spectra ν (cm^{-1}) (KBr) were recorded on a Perkin Elmer Infrared Spectrophotometer Model 157. The ^1H NMR spectra were obtained on a JEOL Spectrophotometer at 500 MHz, using TMS as an internal reference and DMSO-d_6 as solvent and were carried out in the National Research Center, Dokki, Giza, Egypt. Elemental analyses (C, H, and N) were carried out at the Microanalytical Center of Cairo Univ., Giza, Egypt.

2.2. Synthesis

Typical procedure for the synthesis of 4,4'-(substituted-methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**4a**-**g**): A mixture of phenylhydrazine (2.1 g, 20 mmol), ethyl aceto-acetate (2.6 g, 20 mmol) in 20 mL acetic acid (50%) was refluxed for 10 min then aromatic aldehydes namely; benzal-dehyde (1.06 g, 10 mmol), 4-methoxybenzaldehyde (1.36 g, 10 mmol), 4-chlorobenzaldehyde (1.41 g, 10 mmol) thiophene-2-carboxaldehyde (1.12 g, 10 mmol), 4-bromobenzaldehyde (1.83 g, 10 mmol),4-florobenzaldehyde (1.24 g, 10 mmol) or 4-nitrobenzaldehyde (1.51 g, 10 mmol) was added. The mixture was heated over a water bath at 90 °C for an appropriate time (Scheme 1). The formed precipitate was filtered, dried and recrystallized from ethanol to give compound **4a**-**g**.

4,4'-(Phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4a**): Reaction time: 7 h. Color: White powder. Yield: 77%. M.p.: 172-173 °C [Lit. [32], 174 °C]. FT-IR (KBr, ν, cm^{-1}): 3138 (NH), 3059 ($CH_{arom.}$), 3030 (br, OH), 1573 (C=N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 6H, $2CH_3$), 4.91 (s, 1H, C*H*-Ph), 7.13-7.66 (m, 15H, ArH), 12.47 (s, 1H, OH), 13.90 (s, 1H, OH). Anal. calcd. for $C_{27}H_{24}N_4O_2$: C, 74.29; H, 5.54; N, 12.84. Found: C, 74.32; H, 5.59; N, 12.86%.

4,4'-(4-Methoxy-phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4b**): Reaction time: 6 h. Color: White crystal. Yield: 83%. M.p.: 163-165 °C [Lit. [33], 160-161 °C]. FT-IR (KBr, ν, cm^{-1}): 3138 (NH), 3059 ($CH_{arom.}$), 3035 (br, OH), 1578 (C=N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 2.46 (s, 6H, $2CH_3$), 3.85 (s, 3H, OCH_3), 4.84 (s, 1H, C*H*-$C_6H_4OCH_3$), 7.08-7.64 (m, 14H, ArH), 12.62 (s, 1H, OH), 13.85 (s, 1H, OH). Anal. calcd. for $C_{28}H_{26}N_4O_3$: C, 72.09; H, 5.62; N, 12.01. Found: C, 71.98; H, 5.68; N, 12.03%.

4, 4'-(4-Chloro-phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4c**): Reaction time: 6 h. Color: White crystal. Yield: 81%. M.p.: 206-208 °C [Lit. [32], 208 °C]. FT-IR (KBr, ν, cm^{-1}): 3050 (br, OH), 1581 (C=N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 2.30 (s, 6H, $2CH_3$), 4.88 (s, 1H, C*H*-C_6H_4Cl), 7.20-7.66 (m, 14H, ArH), 12.69 (s, 1H, OH), 14.00 (s, 1H, OH). Anal. calcd. for $C_{27}H_{23}ClN_4O_2$: C, 68.86; H, 4.92; N, 11.90. Found: C, 68.76; H, 5.82; N, 11.80%.

4,4'-(2-Thienylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4d**): Reaction time: 6 h. Color: White crystal. Yield: 74%. M.p.: 289-190 °C [Lit. [34], 190-192 °C]. FT-IR (KBr, ν, cm^{-1}): 3080 (br, OH), 1595 (C=N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 2.32 (s, 6H, $2CH_3$), 5.13 (s, 1H, C*H*-C_4H_3S), 6.75-7.82 (m, 13H, ArH), 12.63 (s, 1H, OH), 14.01 (s, 1H, OH). Anal. calcd. for $C_{25}H_{22}N_4O_2S$: C, 67.85; H, 5.01; N, 12.66. Found: C, 67.38; H, 4.99; N, 12.25.

4,4'-((4-Bromo-phenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4e**): Reaction time: 7 h. Color: White crystal. Yield: 77%. M.p.: 185-186 °C [Lit. [35], 183-184 °C]. FT-IR (KBr, ν, cm^{-1}): 3062 (br, OH), 1595 (C=N), 602 (C-Br). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 2.31 (s, 6H, $2CH_3$), 4.92 (s, 1H, C*H*-C_6H_4Br), 7.17-7.69 (m, 14H, ArH), 12.58 (s, 1H, OH), 13.89 (s, 1H, OH). Anal. calcd. for $C_{27}H_{23}BrN_4O_2$: C, 62.92; H, 4.50; N, 10.87: Found: C, 63.02; H, 4.42; N, 10.78

4,4'-((4-Fluoro-phenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4f**): Reaction time: 6 h. Color: White crystal. Yield: 83%. M.p.: 180-181 °C [Lit. [35], 182-184 °C]. FT-IR (KBr, ν, cm^{-1}): 3065 (br, OH), 1599 (C=N), 753(C-F). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 6H, $2CH_3$), 5.34 (s, 1H, C*H*-C_6H_4F), 7.18-7.71 (m, 14H, ArH), 11.43 (s, 1H, OH), 13.91 (s, 1H, OH). Anal. calcd. for $C_{27}H_{23}FN_4O_2$: C, 71.35; H, 5.10; N, 12.33: Found: C, 71.24; H, 5.02; N, 12.24%.

4,4'-((4-Nitro-phenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4g**): Reaction time: 6 h. Color: Yellow crystal. Yield: 81%. M.p.: 218-220 °C [Lit. [36], 219-220 °C]. FT-IR (KBr, ν, cm^{-1}): 3067 (OH), 1601 (C=N), 1479, 1346 (NO_2). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 6H, $2CH_3$), 5.12 (s, 1H, C*H*-$C_6H_4NO_2$), 7.24-8.18 (m, 14H, ArH), 12.65 (s, 1H, OH), 13.87 (s, 1H, OH). Anal. calcd. for $C_{27}H_{23}N_5O_4$: C, 67.35; H, 4.81; N, 14.54: Found: C, C, 67.27; H, 4.73; N, 14.47%.

2.3. Biological evaluation

2.3.1. ABTS screening assay [37]

Antioxidant activities were evaluated from the bleaching of ABTS derived radical cations. The radical cation derived from ABTS [2,2'-azino-*bis*(3-ethyl benzothiazoline-6-sulfonic acid)] was prepared by reaction of ABTS (60 mL) with MnO_2 (3 mL, 25 mg/mL) in 5 mL aqueous buffer solution (pH = 7). After shaking the solution for a few minutes, it was centrifuged and filtered. The Absorbance (A control) of the resulting green-blue solution (ABTS radical solution) was recorded at λ_{max} 734 nm. The absorbance (A test) was measured upon the addition

of 20 mL of 1 mg/mL solution of the tested sample in spectroscopic grade MeOH:Buffer (1:1, *v*:*v*) to the ABTS solution. The inhibition ratio (%) was calculated using the following Equation (1):

$$(\%)\ \text{Inhibition} = [A\ (\text{control}) - A\ (\text{test})\ /A\ (\text{control})] \times 100 \quad (1)$$

Ascorbic acid (20 mL, 2 mM) solution was used as a standard antioxidant (positive control). Blank sample was run using solvent without ABTS (Table 1).

Table 1. ABTS Antioxidant activity assay of the new compounds.

Compound [a]	Absorbance of samples (λ)	% Inhibition [b]
Control of ABTS	0.500	0
Ascorbic acid	0.061	87.8
Pyrazole V	0.055	89.0
4a	0.056	88.2
4b	0.060	88.0
4c	0.068	86.4
4d	0.059	88.2

[a] ABTS: The method used for antioxidant activity.
[b] (%) Inhibition = [A(control) – A(test) / A(control)] × 100.

2.3.2. Bleomycin-dependent DNA damage assay [38,39]

To the reaction mixtures in a final volume of 1.0 mL, the following reagents at the final concentrations stated were added: DNA (0.2 mg/mL), bleomycin (0.05 mg/mL), $FeCl_3$ (0.025 mM), magnesium chloride (5 mM), KH_2PO_4/KOH buffer pH = 7.0 (30 mM) and ascorbic acid (0.24 mM) or the test fractions diluted in MeOH to give a concentration of (0.1 mg/mL). The reaction mixtures were incubated in a water-bath at 37 °C for 1 h. At the end of the incubation period, 0.1 mL of ethylenediaminetetraacetic acid (EDTA) (0.1 M) was added to stop the reaction (the iron EDTA complex is unreactive in the bleomycin assay). DNA damage was assessed by adding 1 mL 1% (*w*:*v*) thiobarbituric acid (TBA) and 1 mL of 25% (*v*:*v*) hydrochloric acid (HCl) followed by heating in a water-bath maintained at 80 °C for 15 min. The chromogen formed was extracted into 1-butanol, and the absorbance was measured at 532 nm.

3. Results and discussion

3.1. Chemistry

The synthetic strategies adopted to obtain the target compounds are depicted in Scheme 1. Multicomponent reactions (MCR) of phenyl hydrazine hydrate (**1**) (2 equiv.), ethyl acetoacetate (**2**) (2 equiv.) and aldehydes (**3**) (1 equiv.) in acetic acid (50%) afforded 4,4'-(aryl-methylene)-*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s (**4**) (Scheme 1).

The possible mechanism for the synthesis of compound **4a-g** is representing in Scheme 2. Protonation of ethyl acetoacetate (EAA) **2** by acetic acid generates the enol **I**. electrophilic attraction of phenylhydrazine **1** to the enol (**I**) afforded the ammonium salt (**II**), hydronium ion transfer take place to form the oxonium ion (**III**). Cyclization of compound **III** afforded the pyrazolium ion (**IV**) which loss proton to convert into pyrazole (**V**). Protonation of compound **V** by acetic acid generates the enol (**VI**) which reacts with the aldehydic carbonyl to form six-membered cyclic transition state (**VII**) and increases the electrophilicity of the aldehyde carbonyl group and makes it more susceptible to nucleophilic attack in an intramolecular fashion to form the intermediate (**VIII**). The intermediate **VIII** subsequently abstracts the proton from acetic acid and generates the enolate aldol cation (**IX**) which interact with compound **V** to generate the enol form (**VI**) to complete the catalytic cycle. The aldol **X** on dehydration results in the formation of 4-arylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**XI**) which reacted with acetic acid to form the cation **XII**, condensation with compound **VI** to form the corresponding *bis*-enolate cation (**XIII**), which subsequently loss proton and form the target of compound **4a-g.** The products **4a-g** were characterized by IR and ^{1}H NMR analysis. For example, the ^{1}H NMR spectra of compound **4b** indicated the presence of three singlet signals at δ 2.46, 3.85, 4.89 ppm due to $2CH_3$, OCH_3 and arylmethylene protons, respectively, and a broad two singlet signal at δ 12.62 and 13.85 ppm reminiscent of two enolisable OH groups. The IR spectra of compound **4b** indicated peaks at 3035 cm^{-1} due to OH and 1581 cm^{-1} due to C= N functional groups.

3.2. Biological evaluation

3.2.1. ABTS antioxidant assay

The synthesized compounds were screened for their antioxidant activity using ABTS method which reported by Lissi *et al*. [37]. The antioxidant activity assay employed here is one of the several assays that depends on measuring the consumption of stable free radicals i.e. evaluate the free radical scavenging activity of the investigated component. The methodology assumes that the consumption of the stable free radical (X') will be determined by reactions as followed:

$$XH + Y' \rightarrow X' + YH \quad (2)$$

Total antioxidant potential of resinous exudates from Heliotropium species, and a comparison of the ABTS methods. The rate and/or the extent of the process measured in terms of the decrease in X' concentration, would be related to the ability of the added compounds to trap free radicals. The decrease in color intensity of the free radical solution due to scavenging of the free radical by the antioxidant material is measured calorimetrically at a specific wavelength. The assay employs the radical cation derived from 2,2'-azino-*bis*(3-ethyl-benzthiazoline-6-sulfonic acid) (ABTS) as stable free radical to assess antioxidant potential of the investigated compounds. All the investigated compounds showed similar and higher antioxidant activity than ascorbic acid as shown in the results in Table 1 [40,41].

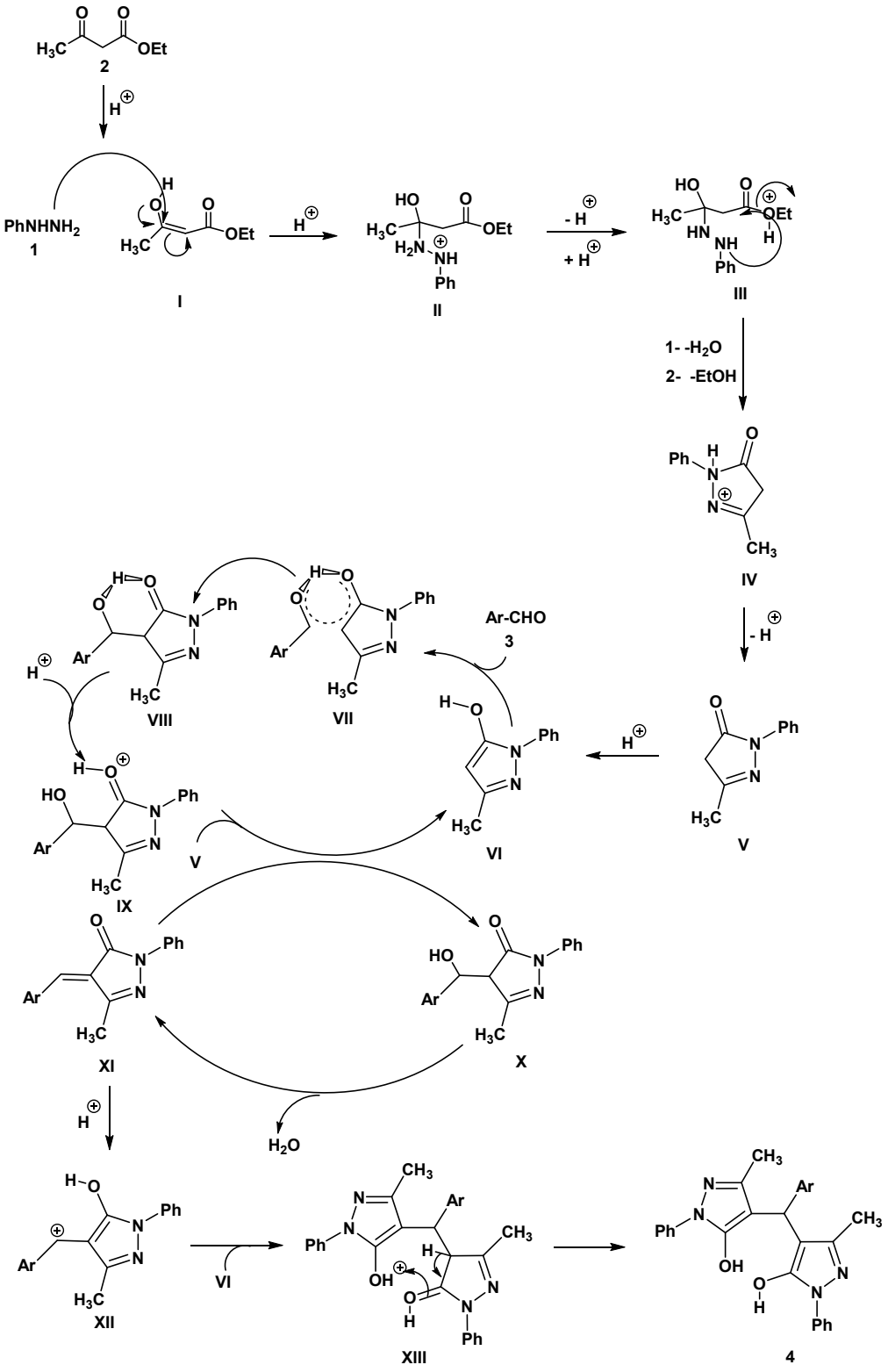
3.2.2. Bleomycin-dependent DNA damage assay

The bleomycin is a family of glycopeptide antibiotics that was used routinely as antitumor agents. The bleomycin assay was adopted for assessing the pro-oxidant effects of food antioxidants. The antitumor antibiotic bleomycin binds iron ions and DNA. The bleomycin iron complex degrades DNA that, upon heating with thiobarbituric acid (TBA), yields a pink chromogen. Upon the addition of suitable reducing agents antioxidants compete with DNA and diminish chromogen formation [38-41].

The protective activity against DNA damage induced by bleomycin iron complex was examined in order to show the action of the investigated compounds. The results in Table 2 showed that compounds all the investigated compounds showed similar and higher antioxidant activity than ascorbic acid and exhibited high protection against DNA damage induced by the bleomycin iron complex, thus, diminishing chromogen formation between the damaged DNA and TBA molecules.

Table 2. Bleomycin dependent-DNA damage of the investigated compounds.

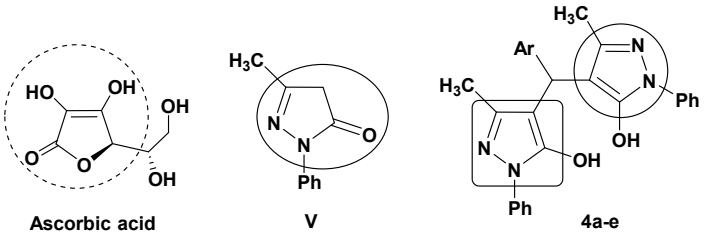
Compound	Absorbance of samples
Ascorbic acid	0.062
Pyrazole V	0.061
4a	0.062
4b	0.067
4c	0.074
4d	0.065



Scheme 2

By comparing the results obtained for the antioxidant properties of the compounds reported in this study with their structures, the following structure activity relationships (SAR's) were postulated (Scheme 3).

(i) Pyrazole **V** (Scheme 3) is more potent than ascorbic acid which may be attributed to the replacement of furan moiety with the pyrazole. These results are in agree with that reported by Metwally *et al.* [41].



Scheme 3

(ii) All the investigated compounds showed similar and higher antioxidant activity than ascorbic acid which may be attributable to presence of pyrazole moiety.

(iii) All the investigated compounds showed nearly similar antioxidant activity so arylmethylene have no effect on activity.

(iv) Compound **4a** more potent than compound **4b**, **4c** and **4d** which may be due to replacement of phenyl moiety by methoxyphenyl, chlorophenyl and thienyl (Scheme 3).

4. Conclusions

We have developed a simple and efficient method for the synthesis of 4,4'-(aryl-methylene)*bis*(1-phenyl-pyrazol-5-ol) using acetic acid. The short reaction times, one-pot, multi-component condensation reaction, simple workup, good yields, and mild reaction conditions.

References

[1]. Gutteridge, J. M. C. *Free Radic. Res. Commun*. **1993**, *19*, 141-158.
[2]. Kehrer, J. P. *Crit. Rev. Toxicol*. **1993**, *23*, 21-48.
[3]. Becker, L. B. *Cardiovasc. Res*. **2004**, *61*, 461-470.
[4]. Hayes, J. D.; McLellan, L. I. *Free Radic. Res.* **1999**, *31*, 273-300.
[5]. Masella, R.; Di Benedetto, R.; Vari, R.; Filesi, C.; Giovannini, C. *J. Nutr. Biochem.* **2005**, *16*, 577-586.
[6]. Hartmann, R. E.; Shah, A.; Fagan, A. M.; Schwetye, K. E.; Parsadanian, M.; Schulman, R. N.; Finn, M. B.; Holtzman, D. M. *Neurobiol. Dis*. **2006**, *24*, 506-515.
[7]. Elguero, J. In Comprehensive Heterocyclic Chemistry: Pyrazoles and their Benzo Derivatives, Vol. 5, ed. by Katritzky, A. R. and Rees, C. W., Pergamon Press, Oxford, 1984, 167-303.
[8]. Kessler, P.; Aybek, T.; Neidhart, G.; Dogan, S.; Lischke, V.; Bremerich, D. H.; Byhahan, C. *J. Cardiothorac. Vasc. Anesth.* **2005**, *19*, 32-39.
[9]. Sugiura, S.; Ohno, S.; Ohtani, O.; Izumi, K.; Kitamikado, T.; Asai, H.; Kato, K. *J. Med. Chem.* **1977**, *20*, 80-85.
[10]. Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J. *J. Med. Chem*. **1985**, *28*, 256-260.
[11]. Mahajan, R. N.; Havaldar, F. H.; Fernandes, P. S. *J. Indian Chem. Soc.* **1991**, *68*, 245-246.
[12]. Chauhan, P. M. S.; Singh, S.; Chatterjee, R. K. *Ind. J. Chem. , Sect. B: Org. Chem. Incl. Med. Chem*. **1993**, *32*, 858-861.
[13]. Singh, D.; Singh, D. *J. Ind. Chem. Soc.* **1991**, *68*, 165-167.
[14]. Londershausen, M. *Pestic. Sci.* **1996**, *48*, 269-292.
[15]. The Chemistry of Synthetic Dyes and Pigments; H. A. Lube (Ed.); American Chemical Society: Washington, DC, 1970
[16]. Garnovskii, A. D.; Uraev, A. I.; Minkin, V. I. *Arkivoc* **2004**, *3*, 29-41.
[17]. Pavlov, T.; Goleneva, A. F.; Lesnov, A. E.; Prokhorova, T. S. *Pharm. Chem. J*. **1998**, *32*, 370-372.
[18]. Buzykin, I.; Lonshchakova, T. I. *Russ. Chem. B*+ **1971**, *20*, 2224-2226.
[19]. Li, L.; Ma, H.; Wang, Y. M.; Meng, J. B. *Chem. J. Chin. Univ.* **1995**, *12*, 1903-1910.
[20]. Bai, J.; Lu, J.; Wang, Z. J.; Gan, H. Y.; Ma, H. R. *Chin. J. Org. Chem*. **2004**, *6*, 616-620.
[21]. Shi, D. Q.; Chen, J.; Wu, B. N.; Zhuang, Q. Y.; Wang, X. S. *Chin. J. Org. Chem.* **2005**, *25*, 405-408.
[22]. Wang, W.; Wang, S. X.; Qin, X. Y.; Li, J. T. *Synth. Commun*. **2005**, *9*, 1263-1269.
[23]. Elinson, M. N.; Dorofeev, A. S.; Nasybullin, R. F.; Nikishin, G. I. *Synthesis* **2008**, *12*, 1933-1937.
[24]. Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M.; *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4501-4503.
[25]. Niknam, K.; Saberi, D.; Sadegheyan, M.; Deris, A. *Tetrahedron Lett.* **2010**, *51*, 692-694.
[26]. Zang, H.; Su, Q.; Mo, Y.; Cheng, B. *Ultrason. Sonochem.* **2011**, *18*, 68-72.
[27]. Babaie, M.; Sheibani, H. *Arab. J. Chem*. **2011**, 4, 159-162.
[28]. Sobhani, S.; Hasaninejad, A. R.; Maleki M. F; Parizi Z. P. *Synth. Commun.* **2012**, *42*, 2245-2255.
[29]. Sobhani, S.; Safaei, E.; Hasaninejad, A. R.; Rezazadeh, S. *J. Organomet. Chem*. **2009**, *694*, 3027-3031.
[30]. Gouda, M. A. *J. Heterocyclic Chem*. **2016**, *53*, 356-376.
[31]. Hassankhani, A. *J. Mex. Chem. Soc.* **2015**, *59(1)*, 1-4.
[32]. Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata. N. *J. Med. Chem.* **2007**, *50*, 5053-5056.
[33]. Porai-Koshits, A. E.; Porai-Koshits, B. A.; Lipina, N. G. *Zh. Obshch. Khim*. **1956**, *26*, 872-877.
[34]. Ahluwalia, V. K.; Sharma, P.; Goyal, B. A. *Indian J. Chem. B* **1997**, *36*, 1059-1061
[35]. Hasaninejad, A.; Zare, A.; Shekouhy, M. Golzar, N. *Org. Prep. Proced. Int.* **2011**, *43*, 131-137.
[36]. Karimi-Jaberi, Z.; Pooladian, B.; Moradi, M.; Ghasemi, E. *Chin. J. Catal*. **2012**, *33*, 1945-1949
[37]. Lissi, E. A.; Modak, B.; Torres, R.; Esocbar, J.; Urzua, A. *Free Radic. Res.* **1999**, *30(6)*, 471-477.
[38]. Gutteridge, J.; Rowley, D.; Halliwell, B. *Biochem. J.* **1981**, *199*, 263-265.
[39]. Abdel-Wahab, B. F.; El-Ahl A. A.; Badria F. A *Chem. Pharm. Bull.* **2009**, *57*, 1348-1351
[40]. Gouda, M. A. *J. Heterocyclic. Chem.* **2015**, DOI: 10.1002/jhet.2576.
[41]. Metwally, M. A.; Gouda, M. A.; Harmal, A. N.; Khalil, A. M. *Eur. J. Med. Chem*. **2012**, *56*, 254-62.