



Synthesis and antioxidant activity study of pyrazoline carrying an arylfuran/arylthiophene moiety

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Abstract: A novel series of *N*-acetyl-3-aryl-5-(5-(*p*/*o*-nitrophenyl)-2-furyl/
/thienyl)-substituted pyrazolines (**3a–o**) were synthesized by the reaction of
1-aryl-3-(5-(*p*/*o*-nitrophenyl)-2-furyl/thienyl)-2-propene-1-ones with hydrazine
hydrate in acetic acid medium. The structures of the newly synthesized com-
pounds were established by IR, ¹H-NMR, mass spectra and a single-crystal
X-ray study. The antioxidant activities of the synthesized compounds were
determined using the DPPH scavenging assay. The compounds **3a**, **3f**, **3h** and
3o showed moderate activity.

Keywords: *N*-acetyl-3,5-disubstituted pyrazoline; antioxidant activity; aryl-
furan; arylthiophene.

INTRODUCTION

Pyrazoline is an important five member heterocyclic compound containing nitrogen as the hetero atom. Several pyrazoline derivatives possess important pharmacological activities. Pyrazoline and their derivatives were found to possess a broad spectrum of biological activities, such as antitumor¹ and anti-inflammatory activities,² MAO-B inhibition³ and antioxidant⁴ activity. The derivatives of pyrazoline are used in applications such as dyestuffs, analytical reagents and as agrochemicals.⁵ Similarly, substituted furan/thiophene derivatives also exhibit significant biological activities, such as antibacterial, HIV-1 fusion inhibitions, antitumor, anti-inflammatory and antioxidant properties, *etc.*^{6–10} Prompted by these observations and in continuation of an ongoing search for biologically active heterocycles,^{11–14} the synthesis of a novel series of *N*-acetyl pyrazoline carrying an arylfuran/arylthiophene moiety is reported herein. These synthesized compounds were evaluated for their antioxidant activity. A few of the tested

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compounds showed significant antioxidant activity, when compared with the standard butylated hydroxytoluene (BHT).

EXPERIMENTAL

Materials, methods and instrumentation

All the employed chemicals were of analytical reagent (AR) grade and were obtained from Spectrochem and CDH. The formation of pyrazoline was confirmed by analytical IR, ^1H -NMR and mass spectra and single crystal X-ray data. IR spectra of the compounds were recorded on Thermo Nicolet Avatar 330-FTIR spectrophotometer. The melting points of the newly synthesized compounds were determined in open capillary tubes and are uncorrected. The ^1H -NMR spectra were recorded on a Bruker Avance-II 400 MHz NMR spectrometer using CDCl_3 as solvent and tetramethylsilane (TMS) as internal standard. All the chemical shift values are expressed on the δ scale downfield from TMS. The mass spectra were recorded on a Water-Micromass Q-ToF Micro LC mass spectrometer. Elemental analyses were realized on a Vario-El Elementar-III model analyzer. The X-ray crystallographic study of compound **3h** was performed on a Bruker X8 Proteum CCD diffractometer. The homogeneity of the compounds was controlled by thin layer chromatography using silica gel plates (Merck) using petroleum ether: ethyl acetate (9:1) as the mobile phase.

General procedure for the preparation of 1-aryl-3-(5-(p/o-nitrophenyl)-2-furyl/thienyl)-2-propene-1-ones (2a-o)

To a mixture of substituted acetophenone (0.01 mol) and substituted 5-arylfurfural/5-aryl thiophene-2-carboxaldehyde (0.01 mol) in ethanol (25 mL), 30% sodium hydroxide (5 mL) was added drop by drop under ice bath and the mixture was agitated for 4 h. The solid separated was filtered, washed thoroughly with water and recrystallized from ethanol-DMF solvent. The structures of the propenones are given in Table I.

General procedure for the preparation of N-acetyl-3-aryl-5-(5-(p/o-nitrophenyl)-2-furyl/thienyl) substituted pyrazolines (3a-o)

A mixture of chalcone (0.01 mol), hydrazine hydrate (0.05 mol) and glacial acetic acid (40 mL) was refluxed for 4 h. The resulting mixture was poured into ice cold water (100 mL) and allowed to settle. The solid that separated was collected by filtration, washed with cold water and then recrystallized from DMF-ethanol mixture. The structures of the newly synthesized pyrazolines are given in Table I.

Biological evaluation

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity was determined following the method of Mensor *et al.*¹⁵ using ethanol with DPPH as the control. The percentage radical scavenging activity, RSA, was determined using the following equation:

$$RSA = \frac{(A_c - A_s)}{A_c} \times 100$$

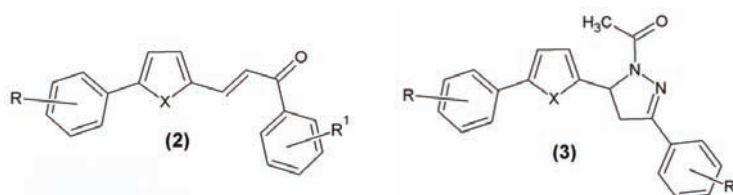
where A_c is the absorbance of the control and A_s is the absorbance of the sample. All the experiments were performed in triplicate; the results are expressed as mean $\pm$ standard deviation (SD).

Antioxidant activity

All synthesized compounds were screened for their antioxidant activity against the DPPH radical. A pre-screening of the various substituted pyrazolines **3a-o** was performed as a

preliminary evaluation. The compounds **3a**, **3d**, **3e**, **3f**, **3h**, **3n** and **3o** were taken for further screening. The compounds were dissolved in DMSO to obtain a solution of 0.001 mg mL⁻¹ concentration. From this stock solution, 0.2 mL was pipetted out and diluted to 2.5 mL with ethanol. Ethanol with DPPH was used as the control. The absorbance of these compounds was recorded at 518 nm. BHT was used as the standard for the antioxidant activity screening.

TABLE I. Structures of the synthesized 1-aryl-3-(5-(*p/o*-nitrophenyl)-2-furyl/thienyl)-2-propene-1-ones (**2a-o**) and *N*-acetyl-3-(substituted aryl)-5-(5-aryl-2-furyl/thienyl)pyrazolines (**3a-o**)



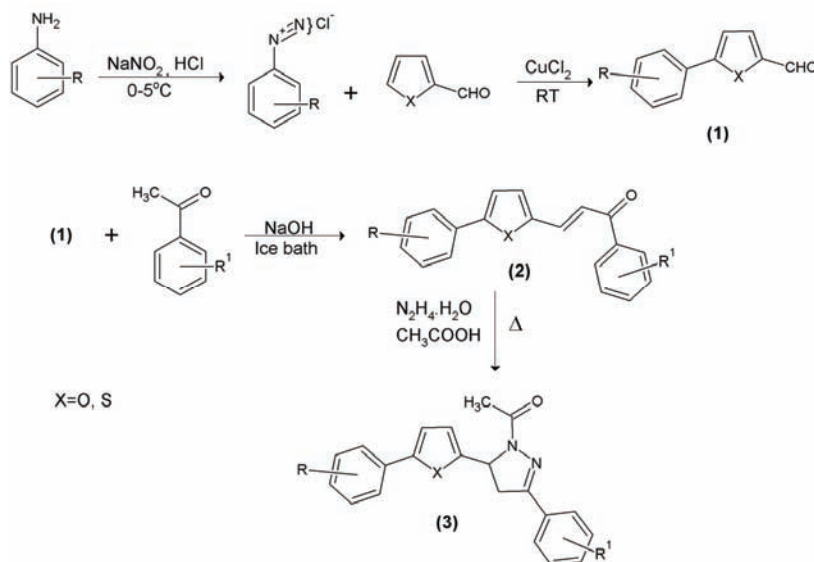
Compd.	R	R ¹	X
2a, 3a	<i>p</i> -NO ₂	<i>p</i> -CH ₃	O
2b, 3b	<i>p</i> -NO ₂	<i>p</i> -OCH ₃	O
2c, 3c	<i>p</i> -NO ₂	<i>p</i> -Cl	O
2d, 3d	<i>p</i> -NO ₂	<i>o,p</i> -Cl	O
2e, 3e	<i>p</i> -NO ₂	<i>p</i> -OH	O
2f, 3f	<i>p</i> -NO ₂	<i>p</i> -NO ₂	O
2g, 3g	<i>p</i> -NO ₂	<i>p</i> -NH ₂	O
2h, 3h	<i>o</i> -NO ₂	<i>p</i> -CH ₃	O
2i, 3i	<i>p</i> -NO ₂	<i>p</i> -CH ₃	S
2j, 3j	<i>p</i> -NO ₂	<i>p</i> -OCH ₃	S
2k, 3k	<i>p</i> -NO ₂	<i>p</i> -Cl	S
2l, 3l	<i>p</i> -NO ₂	<i>o,p</i> -Cl	S
2m, 3m	<i>p</i> -NO ₂	<i>p</i> -OH	S
2n, 3n	<i>p</i> -NO ₂	<i>p</i> -NO ₂	S
2o, 3o	<i>p</i> -NO ₂	<i>m</i> -NO ₂	S

RESULTS AND DISCUSSION

Chemistry

The 5-(*p/o*-nitrophenyl)furfural/2-thiophenecarboxaldehydes were obtained by the coupling of *p/o*-nitrobenzene-1-diazonium salt with furfural/2-thiophenecarboxaldehyde as per the reported procedure.¹⁶ 5-Arylfurfural/aryl-2-thiophenecarboxaldehyde **1** was condensed with various substituted acetophenone in the presence of sodium hydroxide to obtain a series of chalcones **2**. The obtained chalcones were treated with hydrazine hydrate in presence of glacial acetic acid medium to obtain the 3,5-disubstituted-*N*-acetylpyrazolines **3**.

The synthetic route for the compounds is outlined in Scheme 1. The analytical and spectral data of the prepared compounds are given in the Supplementary material to this paper.



Scheme 1. The schematic route for the synthesis of the *N*-acetyl-3-aryl-5-(substituted aryl-2-furyl/thienyl) pyrazolines.

The IR spectrum of compound **3b** showed an absorption band at 1646 cm^{-1} due to the *N*-acetyl carbonyl group. In the ^1H -NMR spectrum of compound **3b**, the three *N*-acetyl protons resonated at δ 2.4 ppm as a singlet. The methoxy protons appeared as a singlet at δ 3.8 ppm. The proton on the stereogenic carbon of the pyrazoline ring appeared as a doublet of doublet centred at δ 5.7 ppm ($J = 5.2$ and 12.0 Hz) integrating for one proton. The prochiral CH_2 protons of pyrazoline ring appeared as two distinct doublets of doublet centred at δ 3.4 ppm ($J = 5.2$ and 17.6 Hz) and at δ 3.6 ppm with coupling constants of 12.0 and 17.6 Hz. The C-3 and C-4 protons of the furan ring appeared as a doublet at δ 6.4 and 6.7 ppm in the ^1H -NMR spectrum of compound **3b**. The signal at δ 165.24 ppm was assigned to the carbonyl carbon. The C=N carbon appeared at δ 156.36 ppm. The C-5 carbon and the C-4 carbon of pyrazoline appeared at δ 75.2 and 68.3 ppm, respectively. The CH_3 carbon appeared at δ 12.5 ppm. The aromatic carbons resonated between δ 154.6–122.4 ppm. The mass spectrum of this compound showed the molecular ion peak (M^++1) at m/z 406.2 consistent with its molecular formula $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_5$. Moreover, in a typical example, the single crystal XRD of pyrazoline **3h** was recorded and it was in conformation with the proposed structure.¹⁷ The structure of compound **3h** determined from single crystal XRD data is given in Fig. 1 and the crystallographic results for the compound are summarized in Table II.

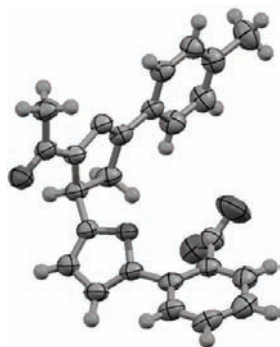


Fig. 1. The structure of compound **3h** determined from single crystal XRD data.

TABLE II. Summary of crystallographic results for the compound **3h**

Parameter	Value
Empirical formula	C ₂₂ H ₁₉ N ₃ O ₄
Formula weight	389.4
Description and colour	Block, brown
Temperature, K	298(2)
Wavelength, Å	0.71073
Crystal system, space group	Triclinic, P1
Unit cell parameters	$a = 7.6235(3) \text{ Å}$, $b = 10.5652(4) \text{ Å}$, $c = 13.1177(4) \text{ Å}$, $\alpha = 103.344(2)^\circ$, $\beta = 95.025(2)^\circ$, $\gamma = 108.221(2)^\circ$
Volume, Å ³	961.78(6)
Z, calculated density	2
Absorption coefficient, mm ⁻¹	0.094
Crystal size, mm	0.23×0.22×0.21

Antioxidant activity

All the synthesized compounds were screened for their antioxidant activity against the DPPH radical. The pre-screening of the various substituted pyrazolines **3a–o** was realized at different concentration level as a preliminary evaluation. The compounds **3a**, **3d**, **3e**, **3f**, **3h**, **3n** and **3o** were taken for further screening and tested at 0.2 mg. The percentage radical scavenging activities of the compounds were compared with that of the standard BHT at the same concentration.

The tested compounds showed antioxidant activity ranging from 26.82–63.68 %, whereas the standard BHT showed 97.60 % inhibition. Compounds **3a** and **3h** with a methyl substituent at the *para* position of the phenyl ring showed good activity compared to that of the standard. Similarly, compounds **3f** and **3o** with a nitro substituent at the *para* and *meta* positions, respectively, exhibited moderate activity. The title compound bearing a furan moiety showed significant activity, whereas the compound bearing a thiophene moiety exhibited the lowest inhibition towards the DPPH radical. A graphical representation of the results is given in Fig. 2.

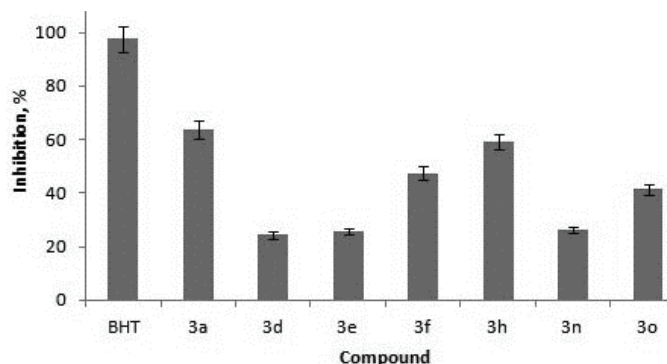


Fig. 2. The antioxidant activity of some of the synthesized pyrazolines. The error bars show the mean $\pm$ SD.

CONCLUSIONS

A novel series of pyrazoline derivatives containing a arylfuran/thiophene moiety were reported. The results of the antioxidant screening by the DPPH radical scavenging assay revealed that among the fifteen synthesized compounds, only pyrazoline **3a**, **3f**, **3h** and **3o** showed moderate antioxidant activity.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the prepared compounds are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА И АНТИОКСИДАТИВНА АКТИВНОСТ АРИЛФУРИЛ/ТИЕНИЛ СУПСТИТУИСАНИХ ДЕРИВАТА ПИРАЗОЛИНА

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Синтетисана је серија *N*-ацетил-3-арил-5-(5-(*p/o*-нитрофенил)-2-фурил/тиенил) супституисаних деривата пиразолина (**3a–o**), реакцијом између 1-арил-3-(5-(*p/o*-нитрофенил)-2-фурил/тиенил)-2-пропен-1-она са хидразин-хидратом у присуству сирћетне киселине. Структуре нових деривата су одређене помоћу ИС и NMR спектроскопије и масене спектрометрије и рендгенске структурне анализе монокристала. Испитане су антиоксидативне активности добијених једињења DPPH тестом. Деривати **3a**, **3f**, **3h** и **3o** показују умерену активност.

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