ELSEVIER

www.elsevier.nl/locate/farmac

Il Farmaco 55 (2000) 256–263

IL FARMACO

Studies on arylfuran derivatives☆ Part X. Synthesis and antibacterial properties of arylfuryl-Δ^2-pyrazolines

B. Shivarama Holla *, P.M. Akberali [1], M.K. Shivananda

Department of Chemistry, Mangalore University, Mangalagangotri 574 199, India

Received 20 May 1999; accepted 16 February 2000

Abstract

Arylfurylpropenones **3** were synthesized by Claisen–Schmidt condensation of arylfurfurals **1** with various substituted acetophenones **2**. Cyclocondensation of these arylfurylpropenones **3** with hydrazine hydrate and phenylhydrazine furnished 1H-pyrazolines **4** and *N*-phenylpyrazolines **6**, respectively. In order to study the structure–activity relationships, pyrazolines **4** were converted into their *N*-acetyl derivatives **5**. The antibacterial properties of the new pyrazoline derivatives were studied.

Keywords: Arylfurylpropenones; Arylfurylpyrazolines; Antibacterial activity

1. Introduction

Heterocyclic analogues of chalcones were prepared for biological studies [1–4]. Several 1,3,5-trisubstituted pyrazolines are reported to possess moderate antibacterial and antifungal activity [5]. Besides, a number of nitrofurylpyrazoline derivatives were found to possess antibacterial activity [6]. Some of them also find application as food preservatives, especially in preserving fish sausages. However, the use of nitrofurylpyrazolines as food preservatives has recently been discouraged owing to their toxicity [7]. One of the methods employed to reduce toxicity of nitrofuran drugs is to introduce arylfurans instead of nitrofurans [8]. Also, it is worthwhile to note that arylfuran-2-carboxaldehyde derivatives are found to exhibit antibacterial activity [9–11]. Keeping these observations in view and in continuation of our work on the synthesis of N-bridged heterocycles [12–15], we decided to undertake the synthesis of pyrazolines carrying an arylfuran substituent and to study their antibacterial activity.

With a view to study the structure–activity relationships, it was decided to introduce substitution at position 1 of the 3-aryl-5-(5-aryl-2-furyl)-4,5-dihydro-1*H*-pyrazoles (**4**). For the present study, two series of compounds viz., 1-acetyl-3-aryl-5-(5-aryl-2-furyl)-4,5-dihydropyrazoles (**5**) and 1-phenyl-3-aryl-5-(5-aryl-2-furyl)-4,5-dihydropyrazoles (**6**) were synthesized.

2. Chemistry

1-Aryl-3-(5-aryl-2-furyl)-2-propen-1-ones (**3**) were prepared by condensing 5-aryl-2-furalaldehydes (**1**) (R = NO_2, Cl, Br) with substituted acetophenones **2** in the presence of sodium hydroxide (Scheme 1). Compounds **3a**–**o** were treated with hydrazine hydrate to obtain 3-aryl-5-(5-aryl-2-furyl)-4,5-dihydropyrazoles (**4a**–**o**). This reaction probably involved the intermediate formation of hydrazones and subsequent addition of NH on the carbon–carbon double bond of the propenone moiety. Pyrazolines **4a**–**e**, **h**–**o** were further subjected to acetylation in the presence of acetic anhy-

☆ Presented at the National Seminar on Recent Trends in Organic Synthesis held at Kakatiya University, Warangal during February 18–19, 1997.

* Corresponding author. Tel.: +91-824-742262; fax: +91-824-742367.

E-mail address: root@mnglr.ernet.in (B. Shivarama Holla).

[1] Present address: Plama Laboratories Ltd., 120 A/B Industrial Area, Baikampady, New Mangalore 575 011, India.

0014-827X/00/$ - see front matter
PII: S0014-827X(00)00030-6

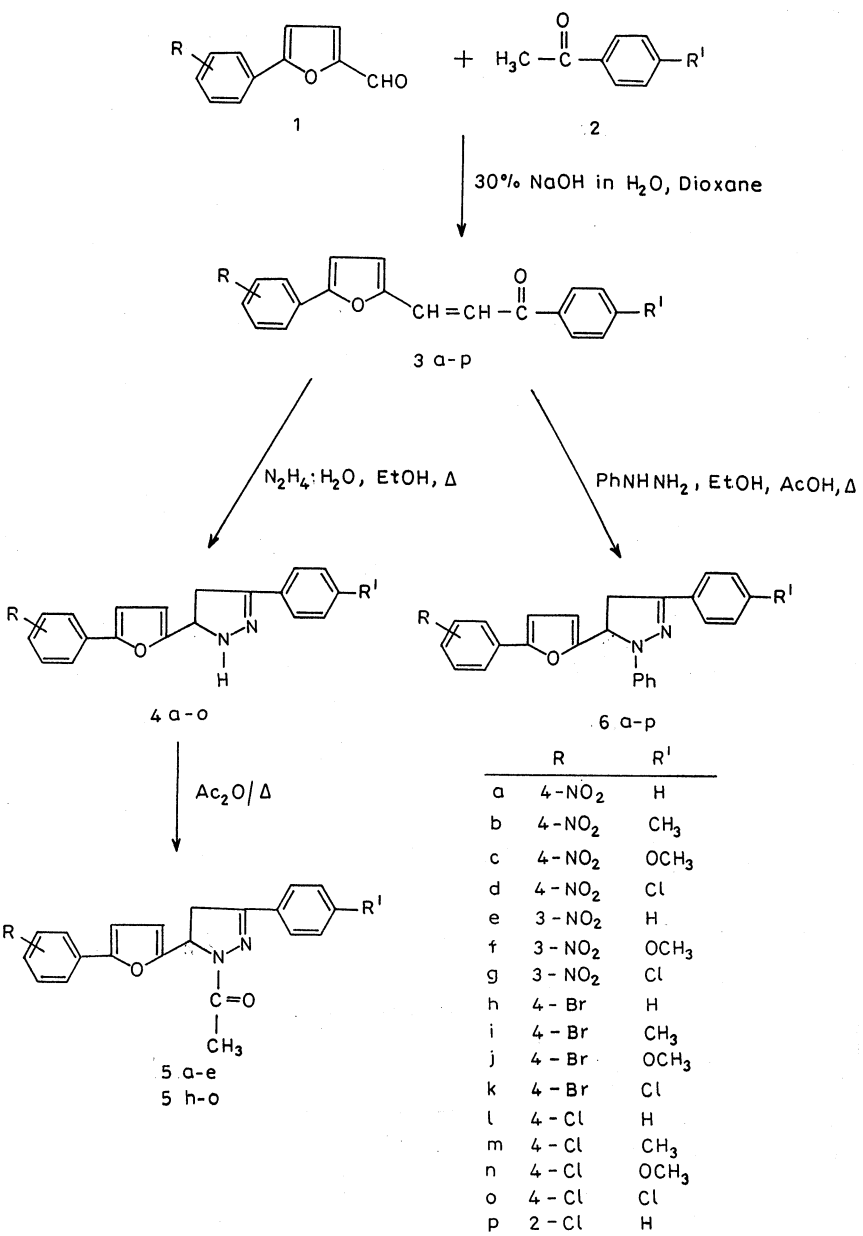
dride to afford 1-acetyl-3-aryl-5-(5-aryl-2-furyl)-4,5-dihydropyrazoles (**5a**–**e** and **h**–**o**). 1-Phenyl-3-aryl-5-(5-aryl-2-furyl)-4,5-dihydro-pyrazoles (**6a**–**p**) were prepared by refluxing the propenones **3** with phenylhydrazine in ethanol containing glacial acetic acid.

Condensation of **3** with phenylhydrazine can lead to two different pyrazolines **6** or **7**, as shown in Scheme 2. According to Baldwin's rules [16], the formation of *N*-phenylpyrazolines **7** involving a 5-*exo*-Trig. ring closure is preferred over the formation of *N*-phenylpyrazolines **6** involving a 5-*endo*-Trig. ring closure. However, in the present investigation, as the reaction is catalyzed by glacial acetic acid, *N*-phenylpyrazolines **6** are formed and their formation can be rationalized as shown in Scheme 3.

The formation of the derivatives **6**, instead of their regioisomers **7**, is favoured because hydrazines attack preferentially on the carbonyl group of α,β-unsaturated ketones, rather than the double bond, so that hydrazones formation is favoured.

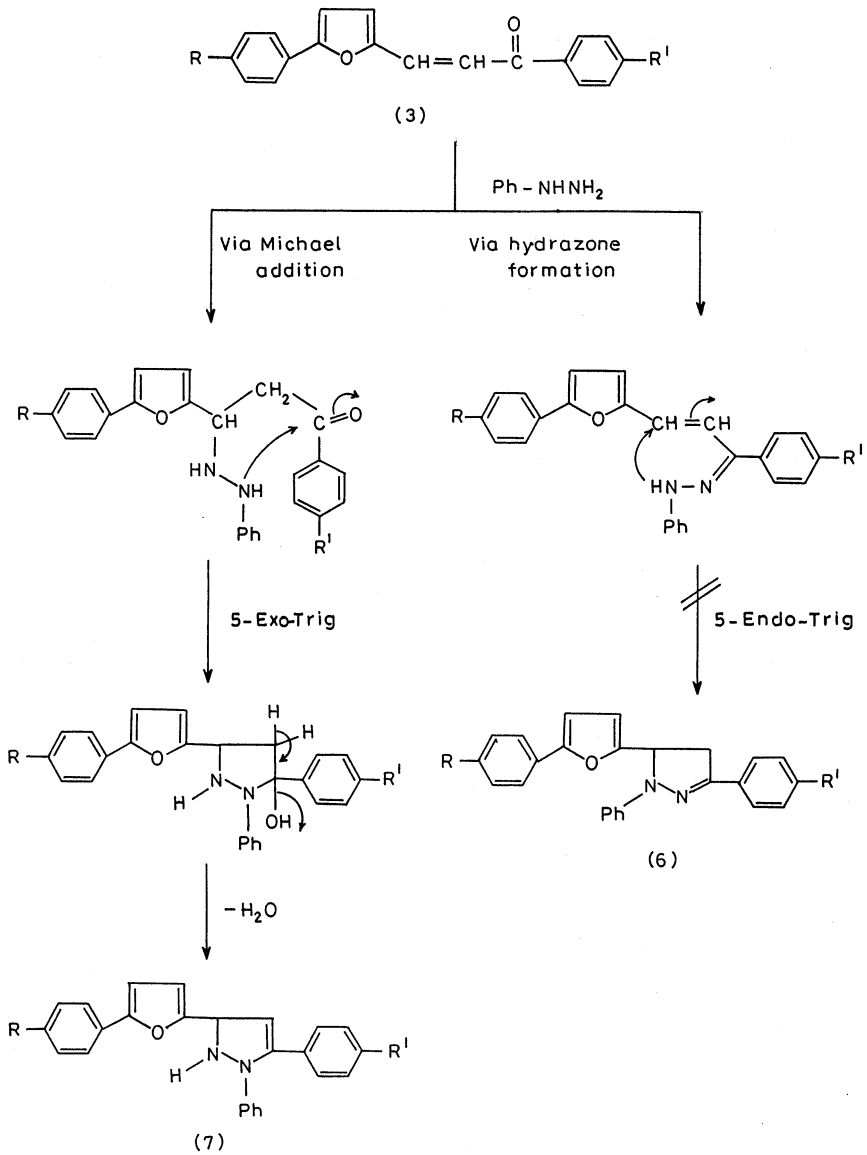
The physicochemical data (yield, melting point and molecular formula) for compounds **3**–**6** are given in Tables 1–4. Selected data (MS, IR, UV and ^{1}H NMR) are reported in Section 3. X-ray crystallographic analysis of compound **4b** unambiguously revealed the formation of the pyrazoline ring [17].

In the 270 MHz ^{1}H NMR spectrum of compound **4m**, the pyrazoline NH proton resonated at δ 10.2. The



	R	R'
a	4-NO_2	H
b	4-NO_2	CH_3
c	4-NO_2	OCH_3
d	4-NO_2	Cl
e	3-NO_2	H
f	3-NO_2	OCH_3
g	3-NO_2	Cl
h	4-Br	H
i	4-Br	CH_3
j	4-Br	OCH_3
k	4-Br	Cl
l	4-Cl	H
m	4-Cl	CH_3
n	4-Cl	OCH_3
o	4-Cl	Cl
p	2-Cl	H

Scheme 1.



Scheme 2.

CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at δ 3.1–3.4. The CH proton appeared as a doublet of doublets at δ 4.9 due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring ($J = 9.9$ and $J = 12.5$ Hz). The arylmethyl proton signal appeared at δ 2.5 as a singlet.

The mass spectrum of the compound **4c** showed a molecular ion peak at m/z 363 as base peak corresponding to the molecular formula $C_{20}H_{17}N_3O_4$ consistent with its structure. A M^+–N–NH peak was observed at m/z 334.

The mass spectrum of compound **5o** showed a molecular ion peak at m/z 398 corresponding to the molecular formula $C_{21}H_{16}Cl_2N_2O_2$. The M + 2 peak was observed at m/z 400. The base peak in this case was seen at m/z 43 corresponding to the CH_3–C=O moiety. The fragment ion peaks at m/z 355 and 357 could arise by the loss of CH_3CHO from the molecular ion. The fragmentation pattern is shown in Scheme 4.

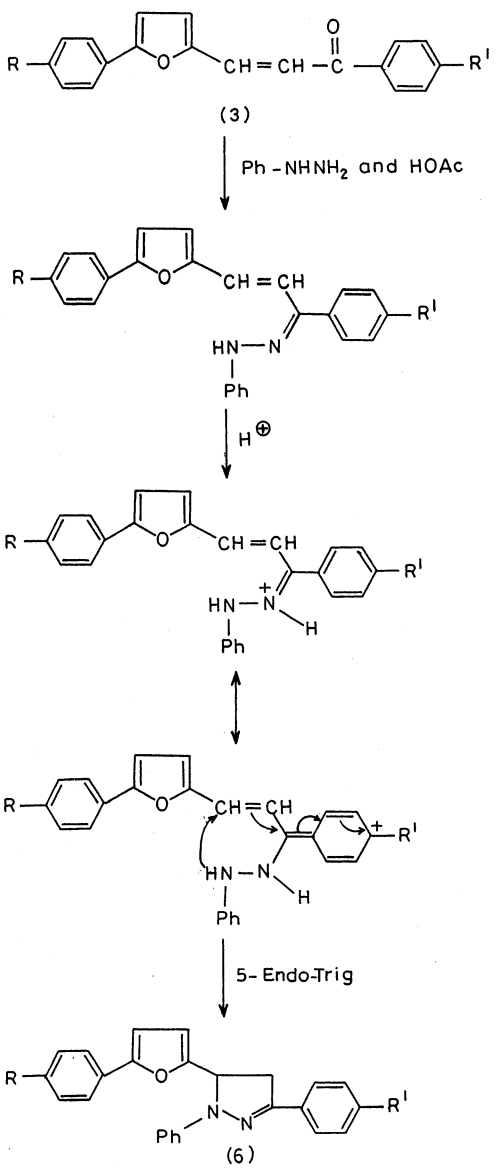
3. Experimental

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were carried out on Carlo Erba 1108 elemental analyzer and the results were within + 0.4% of the theoretical values. The UV spectra were recorded in dimethylformamide on a Beckman model-24 UV spectrophotometer. The IR spectra were recorded in Nujol mull on a Perkin–Elmer model 529. ^{1}H NMR spectra were recorded on a Bruker WH-270 pulsed FT NMR spectrometer or on a Perkin–Elmer R-32 (90 MHz) spectrometer using

DMSO-d_6 as solvent and tetramethylsilane as internal standard. Chemical shift values are given in (ppm) and coupling constants (J) in hertz. Mass spectra of some selected compounds were recorded on a JEOL JMS-D 300 mass spectrometer operating at 70 eV.

3.1. General procedure for the synthesis of 1-aryl-3-(5-aryl-2-furyl)-2-propen-1-ones (**3a–p**)

The suitably substituted acetophenones **2** (10 mmol) were dissolved in ethanol. Then, a solution of sodium hydroxide (5 ml, 30%) and suitable arylfurfuraldehydes **1** (10 mmol) in dimethylformamide(10 ml) was added to the resulting solution with continuous stirring. The clear solution so obtained was stirred for 4 h at room temperature and then allowed to stand overnight. The solid separated was filtered off, dried and recrystallized as indicated in Table 1, which also reports the yields, melting points and molecular formula.



Scheme 3.

Table 1
Physicochemical data of 1-aryl-3-(5-aryl-2-furyl)-2-propen-1-ones (**3a–p**) [a]

Comp.	M.p. (°C)	Yield (%)	Recrystallization solvent	Molecular formula
3a [b]	170	93	C	$C_{19}H_{13}NO_4$
3b	168	95	C	$C_{20}H_{15}NO_4$
3c	180	89	C	$C_{20}H_{15}NO_5$
3d	212	92	C	$C_{19}H_{12}ClNO_4$
3e	130–131	84	C	$C_{19}H_{13}NO_4$
3f	114–115	80	B	$C_{20}H_{15}NO_5$
3g	162–163	88	C	$C_{19}H_{12}ClNO_4$
3h [b]	137	96	C	$C_{19}H_{13}BrO_2$
3i	159	88	C	$C_{20}H_{15}BrO_2$
3j	193	98	C	$C_{20}H_{15}BrO_3$
3k	155	93	C	$C_{19}H_{12}BrClO_2$
3l [b]	131	97	C	$C_{19}H_{13}ClO_2$
3m	160	94	C	$C_{20}H_{15}ClO_2$
3n	175	95	C	$C_{20}H_{15}ClO_3$
3o	141	75	C	$C_{19}H_{12}Cl_2O_2$
3p	96–98	67	A	$C_{19}H_{13}ClO_2$

[a] Recrystallization solvent: (A) EtOH; (B) 1,4-dioxan; (C) EtOH + DMF.
[b] See Ref. [19]

Selected spectral data of this class of compounds are reported below.

3a: MS, m/z 319 [M^+], 273 [$M^+ - NO_2$]. IR (KBr) (cm^{-1}), 1649 (C=O str.), 1585 (C=C str.), 1572 (NO_2 asym.), 1338 (NO_2 sym.).

3b: Mass, m/z 333 [M^+, 80%] UV, λ_{max} 270 nm ($\varepsilon = 950$) and 400 nm ($\varepsilon = 4000$). IR (KBr) (cm^{-1}), 1668 (C=O str.), 1590 (C=C str.). ^{1}H NMR (90 MHz), δ 2.3 (s, 3H, Me), 6.8 (s, 1H, furan 3H, $J = 3$ Hz), 7.1–7.9 (m, 7H, ethylenic, furan 4H and aromatic

Table 2
Physicochemical data of 3-aryl-(5-aryl-2-furyl)-2-pyrazolines (**4a–o**)

Comp.	M.p. (°C)	Yield (%)	Molecular formula
4a	145	90	$C_{19}H_{15}N_3O_3$
4b	180	87	$C_{20}H_{17}N_3O_3$
4c	171	88	$C_{20}H_{17}N_3O_4$
4d	140	91	$C_{19}H_{14}ClN_3O_3$
4e	110–112	80	$C_{19}H_{15}N_3O_3$
4f	144–145	81	$C_{20}H_{17}N_3O_4$
4g	116–118	60	$C_{19}H_{14}ClN_3O_3$
4h	115	96	$C_{19}H_{15}BrN_2O$
4i	135	81	$C_{20}H_{17}BrN_2O$
4j	145	88	$C_{20}H_{17}BrN_2O_2$
4k	112	95	$C_{19}H_{14}BrClN_2O$
4l	125	87	$C_{19}H_{15}ClN_2O$
4m	134	89	$C_{19}H_{15}ClN_2O$
4n	126	90	$C_{19}H_{15}ClN_2O_2$
4o	114	87	$C_{19}H_{15}ClN_2O$

Table 3
Physicochemical data of 1-acetyl-3-aryl-(5-aryl-2-furyl)-2-pyrazolines (**5a**–**e** and **h**–**o**)

Comp.	M.p. (°C)	Yield (%)	Molecular formula
5a	190	85	$C_{21}H_{17}N_3O_4$
5b	184	89	$C_{22}H_{19}N_3O_4$
5c	191	86	$C_{22}H_{19}N_3O_5$
5d	255	86	$C_{21}H_{16}ClN_3O_4$
5e	115–117	89	$C_{21}H_{17}N_3O_4$
5h	151	88	$C_{21}H_{17}BrN_2O_2$
5I	152	91	$C_{22}H_{19}BrN_2O_2$
5j	139	82	$C_{22}H_{19}BrN_2O_2$
5k	150	95	$C_{21}H_{16}BrClN_2O_2$
5l	131	91	$C_{21}H_{17}ClN_2O_2$
5m	168	82	$C_{22}H_{19}ClN_2O_2$
5n	118	86	$C_{22}H_{19}ClN_2O_3$
5o	177	88	$C_{21}H_{16}Cl_2N_2O_2$

protons), 8.0–8.2 (d, 2H, *p*-nitrophenyl, $J = 8$ Hz), 8.3–8.5 (d, 2H, *p*-nitrophenyl, $J = 8$ Hz).

3c: Mass, m/z 349 [M^+, 100%]. IR (cm^{-1}), 1656 (C=O str.), 1599 (C=C str.), 1558 and 1331 (NO_2 asym. and sym.).

3d: Mass, m/z 353 [M^+], 307 [$M^+ - NO_2$]. IR (cm^{-1}), 1556(C=O str.), 1599 (C=C str.)

3f: Mass, m/z 349 [M^+, 100%]. IR (cm^{-1}), 1655 (C=O str.), 1598 (C=C str.). ^{1}H NMR (400 MHz, DMSO-d_6); δ 3.89 (s, 3H, OCH_3), 7.12 (d, 2H, Ar–H, $J = 8.79$ Hz), 7.24 (d, 1H, furyl proton, $J = 3.91$ Hz), 7.48 (d, 1H, furyl proton, $J = 3.4$ Hz), 7.58 (d, 1H, ethylenic, $J = 15.4$ Hz), 7.78–7.81 (d, 1H, ethylenic, $J = 15.63$ Hz), 8.16 (d, 2H, Ar–H, $J = 8.79$ Hz), 8.37–8.39 (m, 4H, *m*-nitrophenyl).

3k: IR (cm^{-1}), 1647 (C=O str.), 1590(C=C str.).

3l: IR (cm^{-1}), 1657 (C=O str.), 1587(C=C str.).

Table 4
Physicochemical data of 1-phenyl-3-aryl-(5-aryl-2-furyl)-2-pyrazolines (**6a**–**p**)

Comp.	M.p. (°C)	Yield (%)	Molecular formula
6a	155	80	$C_{25}H_{20}N_3O_3$
6b	173	86	$C_{26}H_{22}N_3O_3$
6c	159	84	$C_{26}H_{22}N_3O_4$
6d	185	80	$C_{25}H_{19}ClN_3O_3$
6e	130	88	$C_{25}H_{20}N_3O_3$
6f	145–150	98	$C_{26}H_{22}N_3O_4$
6g	160–165	89	$C_{25}H_{19}ClN_3O_3$
6h	140	82	$C_{25}H_{20}BrN_2O$
6i	179	86	$C_{26}H_{22}BrN_2O$
6j	168	85	$C_{26}H_{22}BrN_2O_2$
6k	143	88	$C_{25}H_{19}BrClN_2O$
6l	139	83	$C_{25}H_{20}ClN_2O$
6m	175	84	$C_{26}H_{22}ClN_2O$
6n	170	80	$C_{26}H_{22}ClN_2O_2$
6o	162	81	$C_{25}H_{19}Cl_2N_2O$
6p	120–121	80	$C_{25}H_{19}ClN_2O$

3n: UV, λ_{max} 315 nm ($\varepsilon = 845$) and 400 nm ($\varepsilon = 4000$). IR (cm^{-1}), 1647 (C=O str.), 1608 (C=C str.).

*3.2. General procedure for the synthesis of 3-aryl-5-(5-aryl-2-furyl)-2-pyrazolines (**4a**–**o**)*

To a solution of 1-aryl-3-(5-aryl-2-furyl)-2-propen-1-ones (**3a**–**o**) (10 mmol) in ethanol (10 ml), hydrazine hydrate (90%, 5 ml) was added dropwise. The reaction mixture was heated under reflux for 4 h and then cooled and poured onto crushed ice. The resulting 3-aryl-5-(5-aryl-2-furyl)-2-pyrazolines (**4a**–**o**) were collected by filtration and recrystallized from a mixture of dimethylformamide and ethanol. Physicochemical data of this class of compounds are given in Table 2. Selected spectral data are reported below.

4b: UV, λ_{max} 370 nm ($\varepsilon = 1531$), 270 nm ($\varepsilon = 1138$) and 290 nm ($\varepsilon = 1131$).

4c: Mass, m/z 363 [M^+, 100%], 334 [$M^+ - N_2H$, 13%], 214 (*p*-nitrophenylfuronitrile, 80%), 133 (*p*-methoxybenzonitrile, 21%), 348 [$M^+ - Me$, 6%], 334 [$M^+ - Et$, 4%], 333 [$M^+ - NO$, 11%], 305 [$M^+ - NO$ and CO, 17%].

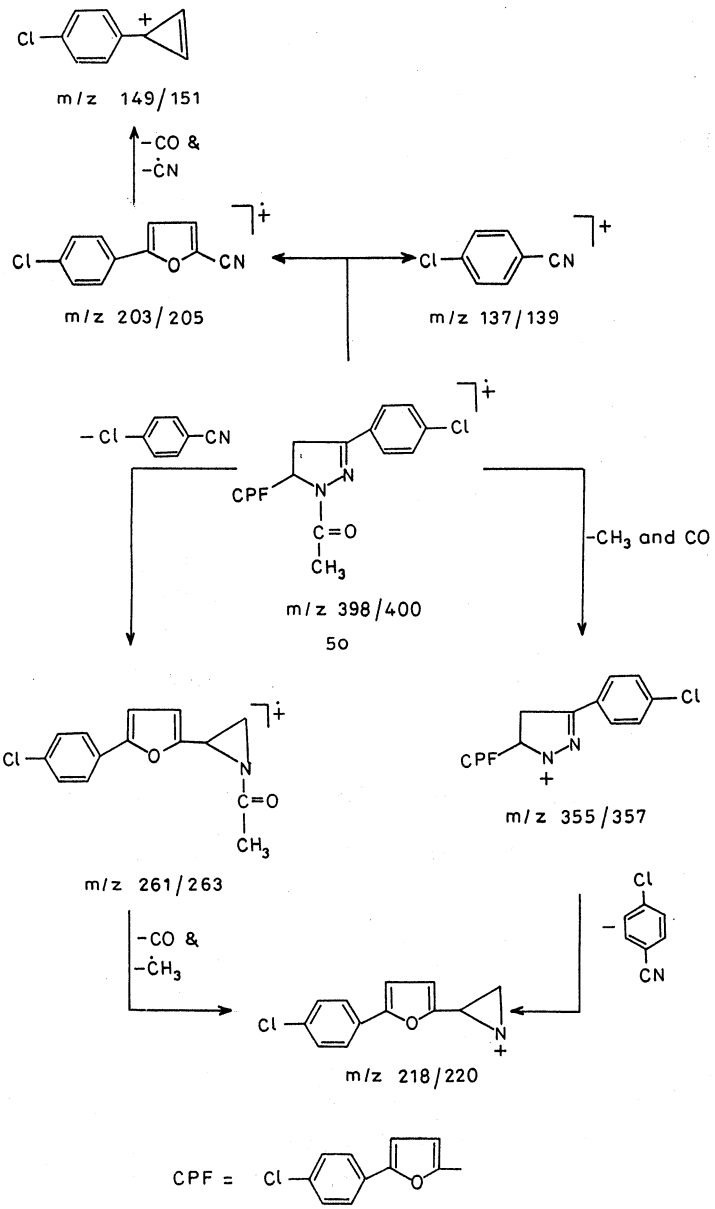
4e: Mass, m/z 333 [M^+, 95.6%], 304 [$M^+ - N_2H$, 12.8%], 214 (*m*-nitrophenylfuronitrile, 37%), 103 (benzonitrile, 13.6%), 303 [$M^+ - NO$, 9.7%], 275 [$M^+ -$ NO and CO, 6%]. ^{1}H NMR (270 MHz, DMSO-d_6); δ 2.9–3.5 (d, d, 2H, pyrazoline CH_2), 3.7 (s, 3H, OCH_3), 4.7–4.9 (d, d, 1H, pyrazoline CH), 6.4–8.2 (m, aromatic and furyl protons), 10.3 (s, 1H, NH).

4g: Mass, m/z 367/369 [M^+, 100%/34.3%], 338 [$M^+ - N_2H$, 6.4%], 214 (*m*-nitrophenylfuronitrile, 37.1%), 137/139 (*p*-chlorobenzonitrile, 10.4%/21.1%), 337 [$M^+ - NO$, 4.4%], 309 [$M^+ - NO$ and CO, 5.4%]. ^{1}H NMR (90 MHz, DMSO-d_6); δ 8.45 (s, 1H, NH), 7.5 (d, 2H, *p*-chlorophenyl, $J = 8.3$ Hz), 7.7 (d, 2H, *p*-chlorophenyl, $J = 8.3$ Hz), 8.1 (m, 4H, *m*-nitrophenyl), 7.2 (d, 1H, furyl proton, $J = 3.42$ Hz), 6.57 (d, 1H, furyl, $J = 3.42$ Hz), 4.95–5.03 (d, d, 1H, CH), 3.2–3.3 (d, d, 2H, CH_2).

4i: m/z 380/382 [$M^+/M+2$, 100%/99%], 351 [$M^+ -$ N – NH, 14.2%], 247/249 (*p*-bromophenylfuronitrile, 54.2%/8.5%), 117 (*p*-tolylcyanide, 19.9%). IR (cm^{-1}), 3230 (pyrazoline NH), 1600 (ring C=N), 1480 (ring N–N) ^{1}H NMR (270 MHz, DMSO-d_6); δ 2.2 (s, 3H, CH_3), 3.0–3.5 (d, d, 2H, pyrazoline CH_2), 4.7–4.9 (d, d, 1H, pyrazoline CH), 6.3–8.2 (m, aromatic and furyl protons), 10.3 (s, 1H, NH).

4j: IR (cm^{-1}), 3346 (pyrazoline NH), 1611 (C=N str.), 1518 (N–N str.). ^{1}H NMR (90 MHz); δ 3.1–3.6 (d, d, 2H, CH_2), 3.8 (s, 3H, OCH_3), 4.7–4.9 (d, d, 1H, CH), 10.3 (s, 1H, pyrazoline NH).

4m: 3300 (pyrazoline NH), 1590 (ring C=N), 1480 (ring N–N). ^{1}H NMR (270 MHz); δ 2.5(s, 3H, CH_3), 3.1–3.4 (d, d, 2H, CH_2), 4.9 (d, d, 1H, CH), 10.2 (s, 1H, NH), 6.4 (d, 1H, furyl proton, $J = 3.3$ Hz), 6.9 (d,



Scheme 4.

1H, furyl proton, $J = 3.3$ Hz), 7.2, 7.5 (d, d, 4H, *p*-tolyl, $J = 8.6$ Hz), 7.5, 7.7 (d, d, 4H, *p*-chlorophenyl, $J = 8.3$ Hz).

4n: δ 3.7 (s, 3H, OCH_3), 2.8–3.6 (d, d, 2H, CH_2), 4.7–4.9 (d, d, 1H, CH), 10.3 (s, 1H, NH), 6.2 (d, 1H, furyl proton, $J = 3.3$ Hz), 6.4 (d, 1H, furyl proton, $J = 3.3$ Hz), 6.9, 7.2 (d, d, 4H, aromatic, $J = 8.6$ Hz), 7.4, 7.6 (d, d, 4H, *p*-chlorophenyl, $J = 8.6$ Hz).

*3.3. General procedure for the synthesis of 1-acetyl-3-aryl-5-(5-aryl-2-furyl)-2-pyrazolines (**5a–e**, **h–o**)*

A solution of 3-aryl-5-(5-aryl-2-furyl)-2-pyrazolines (**4a–e**, **h–o**) (10 mmol) in acetic anhydride (10 ml) was refluxed for 3 h. The reaction mixture was cooled and poured onto crushed ice to decompose the excess acetic anhydride. The solid material so obtained was collected by filtration and recrystallized from a mixture of dimethylformamide and ethanol. Physicochemical data of these *N*-acetylpyrazolines are given in Table 3. Selected spectral data are reported below.

5b: Mass, *m/z* 389 [M^+, 100%], 346 [$M^+ - Ac$, 72.7%], 330 (346-Me, 72.7%), 318 [$M^+ - 43 - N_2$, 63.6%], 117 (*p*-tolylcyanide, 7.2%), 214 (*p*-nitrophenylfuronitrile, 15.1%), 43 (Ac, 90%). UV, λ_{max} 370 nm ($\varepsilon = 2956$), 300 nm ($\varepsilon = 2275$). IR (cm^{-1}), 1668 (C=O str.), 1600 (C=N str.), 1506 and 1332 (NO_2 asym. and sym.), 1510 (N–N str.). ^1H NMR (90 MHz); δ 3.1–3.9 (d, d, 2H, CH_2), 5.5–5.7 (d, d, 1H, CH), 2.4 (s, 3H, CH_3CO), 2.2 (s, 3H, CH_3).

5c: UV, λ_{max} 300 nm ($\varepsilon = 2982$), 380 nm ($\varepsilon = 2015$). IR (cm^{-1}), 1668 (C=O str.), 1600 (C=N str.), 2854 (OCH_3 str.), 1515 and 1338 (NO_2 asym. and sym. str.), 1500 (N–N str.).

5i: UV λ_{max} 300 nm ($\varepsilon = 3500$).**5j**: UV, λ_{max} 300 nm ($\varepsilon = 3500$). IR (cm^{-1}), 1670 (C=O), 1600 (C=N), 1500 (N–N str.), 2852 (OCH_3 str.). ^{1}H NMR; δ 2.4 (s, 3H, CH_3CO), 3.7 (s, 3H, OCH_3), 3.1–3.6 (d, d, 2H, CH_2), 5.5–5.7 (d, d, 1H, CH), 6.3 (d, 1H, furyl protons, $J = 3.3$ Hz), 6.4 (d, 1H, furyl protons, $J = 3.3$ Hz), 6.7–7.6 (m, aromatic protons).

5n: Mass, m/z 398 [M^+, 100%], 400 [$M + 2$], 355/357 [$M^+ - CH_3CHO$], 43 (Ac). ^{1}H NMR (270 MHz), 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3CO), 3.5 (d, d, 1H, CH_2), 3.9 (d, d, 1H, CH_2), 5.6–5.8 (d, d, 1H, CH), 6.4 (d, 1H, furyl proton, $J = 3.3$ Hz), 6.9 (d, 1H, furyl proton, $J = 3.3$ Hz), 7.3 (d, 2H, *p*-tolyl, $J = 8.6$ Hz), 7.5 (d, 2H, *p*-tolyl, $J = 8.6$ Hz), 7.6 (d, 2H, *p*-chlorophenyl, $J = 8.6$ Hz), 7.8 (d, 2H, *p*-chlorophenyl, $J = 8.6$ Hz).

5o: IR (cm^{-1}), 1650 (C=O str.), 1600 (C=N str.), 1510 (N–N str.).

*3.4. General procedure for the synthesis of 1-phenyl-3-aryl-5-(5-aryl-2-furyl)-2-pyrazolines (**6a–p**)*

To a solution of 1-aryl-3-(5-aryl-2-furyl)-2-propen-1-ones (**3a–p**) (10 mmol) in ethanol (10 ml), phenylhydrazine (1 ml) was added. The reaction mixture was then treated with glacial acetic acid (5 ml). The resulting mixture was heated under reflux for 6 h on a water bath. The precipitated solid was filtered and recrystallized from a mixture of dimethylformamide and ethanol. Physicochemical data of this class of compounds are given in Table 4. Selected spectral data are reported below.

Table 5
Antibacterial activity of arylfurylpyrazolines **4–6**

Comp.	Minimum inhibitory concentration (μg/ml)			
	E. coli	*S. aureus*	*B. subtilis*	*P. aeruginosa*
4c	4.2	9.2	9.4	9.3
4e	12.5	25.0	6.0	12.5
4f	6.0	25.0	6.0	12.5
4g	12.5	25.0	12.5	12.5
4j	5.0	11.4	12.8	12.6
4n	5.0	10.7	14.0	13.1
5c	4.4	9.3	9.7	8.9
5e	6.0	12.5	6.0	6.0
5n	4.4	9.0	9.3	9.2
6c	3.3	7.7	7.8	7.5
6j	4.0	8.7	10.2	10.1
6n	4.5	10.2	10.9	10.0
Furacin	6.0	12.5	12.5	12.5

6b: Mass; 6b, m/z 423 [M^+, 75%], 91 ($C_6H_5N^+$, 10%), 332 [$M^+ - 91$, 20%]; ^{1}H NMR (90 MHz), δ 3.1–3.9 (d, d, 2H, CH_2), 5.25 (d, d, 1H, CH), 6.2–7.9 (m, 11H, aromatic and furylprotons), 8.1 (d, 2H, *p*-nitrophenyl, $J = 8$ Hz), 8.3 (d, 2H, *p*-nitrophenyl, $J = 8$ Hz), 2.2 (s, 3H, tolyl-CH_3).

6h: Mass, m/z 442/444 [$M^+/M + 2$, 15%], 91 ($C_6H_5N^+$, 100%), 350 [$M^+ - 91$, 20%]. ^{1}H NMR (90 MHz); δ 3.1 (d, d, 1H, CH_2, $J = 11$ Hz), 3.8 (d, d, 1H, CH_2, $J = 11$ Hz), 5.25 (d, d, 1H, CH, $J = 6$ Hz), 6.1 (d, 1H, furan 3H, $J = 3$ Hz), 6.4 (d, 1H, furan 4H, $J = 3$ Hz), 6.6–7.7 (m, aromatic protons).

4. Antibacterial activity

Some selected arylfurylpyrazolines (**4**), *N*-acetylpyrazolines (**5**) and *N*-phenylpyrazolines (**6**) were screened for their in vitro antibacterial activity against *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa*. Their minimum inhibitory concentrations (MIC values) were determined by serial dilution method [18]. Nitrofurazone (Furacin) was used as the standard drug for comparison. The results of such studies are reported in Table 5.

The screening data indicate that compounds **4–6c**, **4–6j** and **4–6n** carrying *p*-nitro, *p*-bromo and *p*-chlorophenylfuryl groups, respectively, showed a similar degree of antibacterial activities against *E. coli* and *S. aureus* compared with the standard drug. The antibacterial activity of the remaining compounds were not encouraging, although most compounds manifested moderate antibacterial activity. Thus, it was concluded that some of the compounds of the series proved to be promising antibacterial agents and hence deserve further pharmacological investigation.

Acknowledgements

The authors are thankful to Head, RSIC, CDRI Lucknow, Head, RSIC, IIT Madras and Director, SIF, IISc, Bangalore for providing microanalysis, IR, NMR and mass spectral data. Two of the authors (P.M.A. and M.K.S.) are grateful to UGC and CSIR, New Delhi, respectively, for the award of research fellowships to them.

References

[1] D.N. Dhar, The Chemistry of Chalcones and Related Compounds, Wiley, New York, 1981.
[2] K.B. Raut, S.H. Wender, J. Org. Chem. 25 (1960) 50.
[3] Z.S. Ariyan, H.J. Suschitzky, J. Chem. Soc. (1961) 2242.
[4] A. Jurasek, V. Knoppava, M. Danderova, J. Kovac, Reinprecht, Tetrahedron 34 (1978) 1883.

[5] A.M. Fahmy, K.M. Hassan, A.A. Khalaf, R.A. Ahmed, Synthesis of Some New β-lactams, 4-Thiazolidinones and Pyrazolines, Indian J. Chem. 26B (1987) 884; Chem. Abstr. 109 (1988) 92871.
[6] N. Hiroshi, S. Akira, I. Masumi, Acetylpyrazolines, Japan (Kokai), 139 (1970) 7012; Chem. Abstr. 73 (1970) 25457z.
[7] S. Arain, T. Matsuda, Bull. Jpn. Soc. Sci. Fisheries 32 (1966) 655.
[8] A. Krutosikova, R. Frimm, J. Kovac, L. Ebringer, Substituted-5-(5-phenyl-2-furfurylidene)rhodanines, Czech., 145 (1972) 021; Chem. Abstr. 78 (1973) 29758z.
[9] T.I. Vozyakova, A.F. Oleinik, K.Y. Novitskii, V. Nauchn, Study in the Arylfuran Series, Konf. Khim. Teknol. Furanovykh Soedin. (1978) 100; Chem. Abstr. 92 (1980) 180897.
[10] A.F. Oleinik, K.Y. Novitskii, V. Nauchn, Study in the Arylfuran Series, Konf. Khim. Teknol. Furanovykh Soedin. (1978) 37; Chem. Abstr. 92 (1980) 180892.
[11] B.S. Holla, P.M. Akberali, Studies on Arylfuran Heterocycles. Part 1. Synthesis of 6-(5-aryl-2-furyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles, J. Indian Chem. Soc. 68 (1991) 171.
[12] B.S. Holla, P.M. Akberali, Studies on arylfuran heterocycles. Part 2. Synthesis and antibacterial activity of 2-amino/2-arylamino-4-[5-(*p*-nitrophenyl)-2-furyl]-thiazoles, J. Indian Chem. Soc. 68 (1991) 341.
[13] B.S. Holla, M.K. Shivananda, P.M. Akberali, S. Baliga, S. Safeer, Studies on arylfuran derivatives. Part VI. Synthesis, characterization and antibacterial properties of 6-(5-aryl-2-furyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and 6-(5-nitro-2-furyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles, Farmaco 51 (1996) 785.
[14] B.S. Holla, K.V. Udupa, Synthesis, spectral studies and biological activities of some N-bridged heterocycles derived from 3-arylaminomethyl-4-amino-5-mercapto-1,2,4-triazoles, Farmaco 47 (1992) 305.
[15] B.S. Holla, B. Kalluraya, K.R. Sridhar, E. Drake, L.M. Thomas, K.K. Bhandary, M.J. Levine, Synthesis, structural characterization, crystallographic analysis and antibacterial properties of some nitrofuryl triazolo[3,4-*b*]-1,3,4-thiadiazines, Eur. J. Med. Chem. 29 (1994) 301.
[16] J.E. Baldwin, Chem. Commun. (1976) 734.
[17] B.S. Holla, P.M. Akberali (unpublished results).
[18] E.J. Stokes, G.L. Ridgway, Clinical Bacteriology, fifth ed., Edward Arnold, 1980, p. 226.
[19] R. Frimm, J. Kovac, E. Zavodska, Furan derivatives-VII. α,β-Unsaturated furan ketones, Zb. Pr. Chem. Fak. SVST. (1967) 41; Chem. Abstr. 69 (1968) 106364m.