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Research Article

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Synthesis, characterization and comparative antimicrobial studies of some novel chalcones and pyrazolines containing naphthofuryl substituents

Shet Prakash M[1] , V. P. Vaidya[*2], K. M. Mahadevan[2], M. K. Shivananda[1], P. A. Suchetan[1], B. Nirmala[1] and Madavi Sunitha[1]

[1]*Department of Chemistry, University College of Science, Tumkur University, Tumkur, Karnataka, India*
[2]*Department of Chemistry, Kuvempu University, Shankaraghatta, Shimoga, Karnataka, India*

ABSTRACT

Prompted by the varied biological activities of chalcones, pyrazolines and naphthofurans, a series of 1-aryl-3-[(3-substituted)-2-naphthofuryl]-2-propen-1-ones ***(3a-f)*** *were prepared by condensing 3-substituted-naphthofuran-2-carboxaldehyde****(1a-b)*** *with substituted acetophenones* ***(2a-c)*** *in the presence of sodium hydroxide. Compounds* ***(3a-f)*** *were then treated with hydrazine hydrate to afford 3-substituted aryl-5-(3-substituted-2-naphthofuryl)-2-pyrazolines* ***(4a-f.)*** *The structures of these novel compounds were confirmed on the basis of elemental analysis and spectral data. All the title compounds were screened for their antimicrobial activities. The screening data indicated that tested compounds showed moderate antimicrobial activit;y, but were found to be less than the standard drugs. A comparative study of antimicrobial activity of chalcones and pyrazolines is done.*

Key words: Naphtho[2,1-b]furan**;** chalcones*;* 2-pyrazolines; antifungal activity; antibacterial activity.

INTRODUCTION

Naphthofurans possess a broad range of biological activities that are constituents of important natural products [1-7]. The chemistry of chalcones has been recognized as an important field of study. Some substituted chalcones and their derivatives including heterocyclic analogues are reported to possess interesting biological properties, which are detrimental to the growth of microbes, tubercle bacilli, malarial parasites and intestinal worms. Some of these chalcones are found to exhibit inhibitory action on several enzymes, fungi and herbaceous plants. The synthesis and biological activities of various chalcones and their derivatives has been reviewed by Dhar [8-13]. Pyrazolines constitute an important class of heterocycles which were found to display broad spectrum of biological activities such as pesticidal, anti-inflammatory, antiarthritic, antidepressant and antiviral and also they are found to possess bactericidal, insecticidal, fungicidal, anaesthetic, analgesic and antidiabatic activities. 2-Pyrazolines possessing aryl substituents at positions 1,3 and 5 exhibit fluorescence properties. Many pyrazolines also find use as polymer intermediates in industry, hence much importance is given to the synthesis and structural aspect of pyrazolines as witnessed by continued activity in this area. Besides, fluorinated pyrazolines find application as antifertility, antibacterial and antifungal agents[14-21]. In view of the various biological activities of chalcones, pyrazolines and napthofurans, it was contemplated to synthesize various novel chalcones and pyrazolines carrying naphthofuryl ring and to compare their antimicrobial activities.

EXPERIMENTAL SECTION

Melting points were determined in open glass capillaries and were found uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded in KBr on a Perkin Elmer Spectrometer. ^{1}H NMR spectra were recorded on Brucker 300 MHz instrument in DMSO-d_6 as solvent and TMS as an internal standard.

The compounds **(2a-b)** were prepared by the reduction of corresponding esters **(1a-b).** Compounds **(3a-b)** were prepared by Dess-Martin oxidation of **(2a-b).** 1-Aryl-3-[(3-substituted)-2-naphthofuryl]-2-propen-1-ones **(5a-f)** were prepared by condensing 3-substituted-naphthofuran-2-carboxaldehyde **(3a-b)** with substituted acetophenones **(4a-c)** in the presence of sodium hydroxide. Compounds **(5a-f)** were then treated with hydrazine hydrate to afford 3-substituted aryl-5-(3-substituted-2-naphthofuryl)-2-pyrazolines **(6a-f)** (**Scheme-1**). The purity of these compounds was monitored by TLC. The melting points of these compounds were determined and were uncorrected.

All the title compounds were screened for their antimicrobial activities according to tube dilution method [22]. All the newly synthesized chalcones (**5a-f**) were screened for their *in vitro* antimicrobial activities against Gram positive bacteria viz., *Staphyllococcus aureus* and Gram negative bacteria viz., *E.coli* and fungi viz., *C. albicans* and *A.niger* at concentrations of 2.0 mg.

The sequence of the reactions is depicted in the Scheme 1.

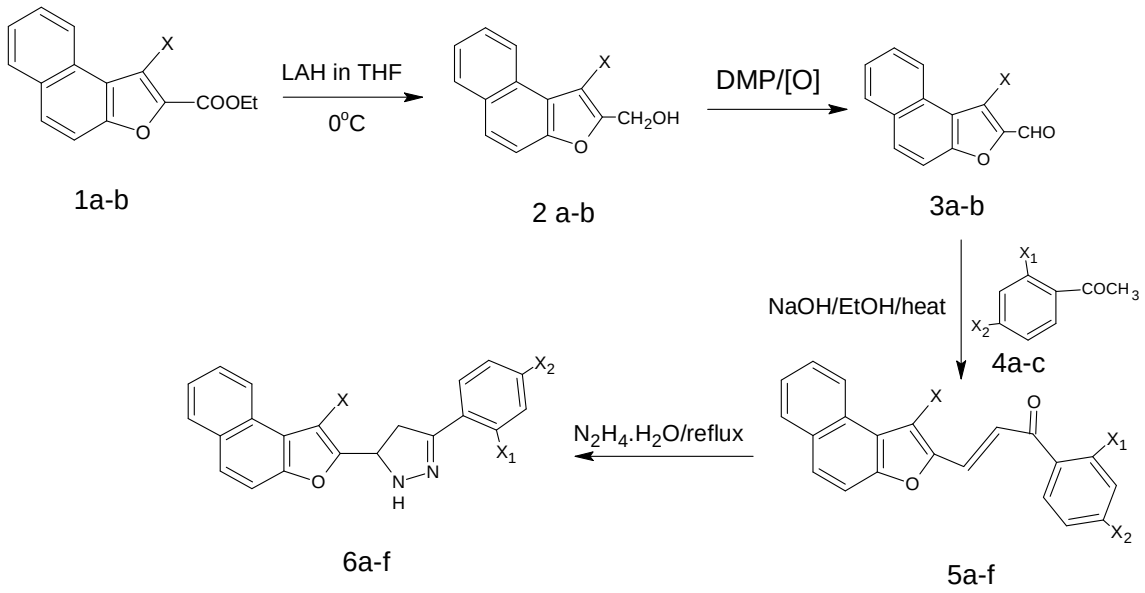
Synthesis of ethyl naphtofuran-2-carboxylate and 3-bromo ethyl naphtofuran-2-carboxylate (1a-b)
Ethyl naphthofuran-2-carboxylate was prepared by using 2-hydroxy-1-naphthaldehyde. This compound on reaction with ethyl chloroacetate in presence of anhydrous potassium carbonate and DMF resulted in the formation of ethyl 3-naphthofuran-2-carboxylatye **4**, in good yield. The compound **1a** was brominated by using bromine in acetic acid with stirring to obtain the compound **1b**.

Reduction of compounds (1a-b) to corresponding alcohol (2a-b)
40 mmol of LAH in THF was taken and to this the solution of 10 mmol of compounds **(1a-b)** in THF was added slowly with continuous stirring at 0^0C. Stirring was continued for 2hrs.The completion of reaction was monitored by TLC. The reaction mixture was quenched with ammonium chloride solution. The product was extracted in THF and recrystallized by using alcohol.

The Dess-Martin Oxidation of (2a-b) to corresponding aldehyde (3a-b)
10 mmol of alcohol **(2a-b)** was taken in MDC and Dess-Martin reagent (20 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was worked up with saturated solution of sodium carbonate. The compounds were recrystallized from DMF.

Synthesis of *1-aryl-3-[(3-substituted)-2-naphthofuryl]-2-propen-1-ones (5a-f) :*
To an alcoholic solution of 3-substituted-naphthofuran-2-carboxaldehyde **(3a-b),** substituted acetophenones **(4a-c)** were added with stirring in presence of 10% solution of sodium hydroxide. The resulting mixture was refluxed for about 1 hr. The reaction mixture was cooled and the solid separated was filtered, dried and recrystallized from DMF. The purity of these compounds was checked by TLC.

Synthesis of *3-substituted aryl-5-(3-substituted-2-naphthofuryl)-2-pyrazolines(6a-f):*
To an alcoholic solution of above chalcones **(5a-f)** (10 mmol), hydrazine hydrate (10 mmol) was added with stirring and the resulting mixture was heated under reflux for 2hr. The reaction mixture was then cooled and poured into ice-cold water. The solid separated was filtered, dried and recrystallized from DMF. The purity of these compounds was checked by TLC.



SCHEME-1

Table 1: Physical characterization data of compounds (2a-b)

Compd.	X	Molecular formula	M.P. (^{0}C)	Yield (%)	Elemental Analysis (%) Calculated (Found) C	H	O	Br
2a	H	$C_{13}H_{10}O_2$	190	85	78.78 (78.6)	5.85 (5.7)	16.16 (16.10)	-
2b	Br	$C_{13}H_9$ Br O_2	129	82	56.31 (56.26)	3.24 (3.21)	11.55 (11.50)	28.88 (28.78)

Table 2: Physical characterization data of compounds (3a-b)

Compd.	X	Molecular formula	M.P. (^{0}C)	Yield (%)	Elemental Analysis (%) Calculated (Found) C	H	O	Br
3a	H	$C_{13}H_8O_2$	258	78	79.59 (79.50)	4.08 (4.10)	16.32 (16.24)	-
3b	Br	$C_{13}H_7$ Br O_2	185	80	56.72 (56.70)	25.45 (25.10	11.63 (11.10)	29.09 (28.89)

Table 3: Physical characterization data of compounds (5a-f)

Compd.	X	X1	X2	Molecular formula	M.P. (^{0}C)	Yield (%)	Elemental Analysis (%) Calculated (Found) C	H	F
5a	H	H	H	$C_{21}H_{14}O_2$	270	82	84.56 (84.67)	4.69 (4.78)	-
5b	H	F	H	$C_{21}H_{13}FO_2$	>300	75	79.66 (79.76)	4.10 (4.16)	2.84 (2.78)
5c	H	F	F	$C_{21}H_{12}F_2O_2$	>300	78	75.45 (75.56)	3.60 (3.74)	11.37 (11.34)
5d	Br	H	H	$C_{21}H_{13}BrO_2$	>300	92	66.84 (66.75)	3.44 (3.41	--
5e	Br	F	H	$C_{21}H_{12}BrFO_2$	>300	88	63.79 (63.67)	3.84 (3.81)	4.81 (4.75)
5f	Br	F	F	$C_{21}H_{12}BrF_2O_2$	>300	87	61.01 (61.13)	0.24 (0.23)	9.20 (9.15)

Table 4: Physical characterization data of compounds (6a-f)

Compd.	X	X1	X2	Molecular formula	M.P. (^{0}C)	Yield (%)	Elemental Analysis (%) Calculated (Found) C	H	N
6a	H	H	H	$C_{21}H_{16}N_2O$	128	82	88.76 (88.5)	5.12 (5.01)	8.97 (8.70)
6b	H	F	H	$C_{21}H_{15}FN_2O$	173	85	76.36 (76.18)	4.54 (4.21)	8.48 (8.23)
6c	H	F	F	$C_{21}H_{14}F_2N_2O$	106	78	64.45 (63.76)	4.02 (4.00)	8.04 (7.91)
6d	Br	H	H	$C_{21}H_{15}BrN_2O$	152	79	64.45 (63.98)	3.83 (3.76)	7.16 (7.01)
6e	Br	F	H	$C_{21}H_{14}BrFN_2O$	174	83	61.61 (60.90)	3.42 (3.38)	6.84 (6.79)
6f	Br	F	F	$C_{21}H_{13}BrF_2N_2O$	165	68	59.01 (58.98)	3.04 (2.99)	6.55 (6.46)

Table 5: Antimicrobial activity screening data at 2 mg concentration of chalcones *1-aryl-3-[(3-substituted)-2-naphthofuryl]-2-propen-1-ones (5a-f)*

	Antibacterial activity		Antifungal activity	
Compd.	*Staphyllococcus aureus*	*Escherichia coli*	*A.niger*	*C.albicans*
5a	0.0	0.2	0.0	0.0
5b	0.0	0.0	0.0	0.0
5c	0.1	0.2	2.5	1.1
5d	0.0	0.0	0.0	0.0
5e	1.2	1	0.8	1.3
5f	0.0	0.0	0.0	0.0

Table 6: Antimicrobial activity screening data at 2 mg concentration of *pyrazolines , 3-substituted aryl-5-(3-substituted-2-naphthofuryl)-2-pyrazolines(6a-f)*

	Antibacterial activity		Antifungal activity	
Compd.	*Staphyllococcus aureus*	*Escherichia coli*	*A.niger*	*C.albicans*
6a	0.2	0.0	0.0	0.2
6b	0.3	0.0	0.0	0.0
6c	0.0	0.0	0.0	0.0
6d	0.2	0.0	0.0	0.0
6e	0.0	0.0	0.0	0.0
6f	0.8	0.7	0	0.6

RESULTS AND DISCUSSION

The structures of the newly synthesized compounds **(2a-b), (3a-b), (5a-f)** and **(6a-f)** were confirmed on the basis of elemental analysis and spectral data.

The formation of alcohol **(2a-b)** from ester **(1a-b)** was confirmed by mass, IR and NMR. In the mass spectrum of **2a**, the molecular ion peak appeared at m/z 197. The IR spectrum of **2a** has shown broad absorption band corresponding to alcoholic -OH group and disappearance of the peak corresponding to carbonyl group of ester. In the NMR spectrum of **2a,** the –OH proton signal appeared as a singlet at δ, 5.53. Two protons of CH_2 group appeared as a singlet at δ, 4.66. The seven protons of the naphthofuran ring appeared in the aromatic range of δ, 7.39-8.27.

The formation of aldehyde **(3a-b)** from alcohol **(2a-b)** was confirmed by IR and NMR. The IR spectrum of **3a** has shown a strong absorption band corresponding to carbonyl group and absence of the peak corresponding to –OH group of alcohol. In the NMR spectrum of **3a,** the aldehydic proton signal appeared at δ, 9.89. The seven protons of the naphthofuran ring appeared in the aromatic range of δ, 7.61-8.63.

In the IR spectrum of compound (**5a**), C=O stretching frequency appeared at 1680 cm^{-1} and the C=C stretching frequencies appeared at 1602 cm^{-1} respectively. In the IR spectra of the title compound (**6a**), the absorption band

corresponding to C=O stretching frequency disappeared and the NH stretching frequency observed at 3300 cm^{-1} . The ^1H NMR (400 M Hz) spectrum of the compound (5**a**) showed two doublets at δ, 6.5-6.7 corresponding to two olefinic protons of chalcones and the remaining twelve aromatic protons appeared in the range δ, 6.9-7. The mass spectrum of compound (**5a**) showed a molecular ion peak at m/z 298 consistent with its molecular formula $C_{21}H_{14}O_2$ thus confirming the formation of chalcone.

In the ^1H NMR(400 M Hz) spectrum of the compound (**6d**), the NH proton appeared as a singlet at δ, 3.87.The CH and CH_2 protons of the pyrazoline ring appeared as two doublets at δ, 7.12-7.29. The remaining nine aromatic protons of the naphthofuran ring appeared as a multiple at δ, 7.31-7.96 and the remaining two more aromatic protons appeared as two singlets at δ, 8.84 and 9.34 respectively. The mass spectrum of compound (**6d**) showed a molecular ion peak at m/z 391 consistent with its molecular formula $C_{21}H_{15}BrN_2O$ thus confirming the formation of pyrazoline.

Antimicrobial activity

The screening data indicated that all the synthesized chalcones did not show any appreciable antimicrobial activity. The results of Antimicrobial activity are shown in Table 3. All the newly synthesized pyrazolines (**6a-f**) were screened for their *in vitro* antimicrobial activities against Gram positive bacteria viz., *Staphyllococcus aureus* and Gram negative bacteria viz., *E.coli* and fungi viz., *C.albicans* and *A.niger* at concentrations of 2.0 mg.. The screening data indicated that all the synthesized pyrazolines did not show any appreciable antimicrobial activity. The results of antimicrobial activity are shown in Table 4.

CONCLUSION

Four series of novel compounds, **(2a-b), (3a-b), (5a-f)** and **(6a-f)** were prepared, characterized and their antimicrobial activities were studied. All the synthesized chalcones and pyrazolines did not show any appreciable antimicrobial activity.

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