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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL CHALCONE AND PYRAZOLINE DERIVATIVES

SOWJANYA MUDIMELA[1*], KUMUDHA DHAMOTHARASWAMY[1], PRAVEENA KATIKALA[1], VISHWANATH BOGDA ANANTHARAMAIAH[1]

[1]Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore, Karnataka, India

***Corresponding Author: Sowjanya Mudimela, Aditya BIPER, Bangalore, Karnataka, India; E Mail: psowjusatish@gmail.com**

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ABSTRACT

A series of some novel chalcones and pyrazolines were synthesized and evaluated against bacterial strains such as *S.aureus, E.coli, P.aeroginosa* and *B.subtilis* and fungal strains like *C.albicans*, *S.cerevisiae*. In the present investigation, substituted chalcones **(3a-f)** were synthesized by condensing 3-acetyl-2,5-dimethyl thiophene **(1)** with substituted aromatic aldehydes **(2)**. Then **(3a-f)** were treated with phenyl hydrazine **(4)** to yield substituted pyrazolines **(5a-f)**. All the synthesized compounds were characterized by spectral analysis [IR, H-NMR, Mass]. All the compounds were screened for their antibacterial and antifungal activity, Zone of Inhibition (ZOI) was determined and most of the compounds were shown significant activity against bacteria when compared to fungal organisms.

Keywords: Antibacterial, Antifungal, Chalcones, Pyrazolines, Spectral Analysis

INTRODUCTION

Chalcones, trans-1, 3-diaryl-2-propen-1-ones are α, β-unsaturated ketones consisting of two aromatic rings (ring A and B) having diverse array of substituents. Chalcones have been recently the subject of great interest due to broad spectrum of pharmacological activities, including antioxidant [1,5], antibacterial [2], antileishmanial [7], anticancer [3], antiangiogenic [4], anti-inflammatory [5], antifungal [6], anti-malarial [7] properties. Considerable attention has been focused on pharmacologically-interesting heterocyclic systems like pyrazolines owing to their pharmacological activities, which include anti-tumor [8], anti-inflammatory [9], antioxidant [9], antimicrobial[9], anti-parasitary [10], anticonvulsant [11], antimicrobial [12], antimalarial [13], inflammatory arthritis [14], antidepressant [15], anticancer [16], antioxidant [17], antiamoebic [18], cytotoxic [19], antinociceptive [20], antimycobacterial [21] and antihepatotoxic [22] properties. Taking these observations into an account in the present work some novel chalcones and pyrazolines were synthesized **(Of Scheme-I)** and characterized. The various substitutents and physical data of the synthesized compounds are given in **Table-1 and 2.**

MATERIALS AND METHODS

All the chemicals were procured from Sigma-Aldrich and were of LR grade. Melting points of the synthesized compounds were recorded on Metler Fp-51 instrument and are uncorrected. The Infra-Red spectra were recorded on Perkin Elmer Model 283B and Nicolet-740 FT-IR instruments and values are given in cm^{-1}. Proton Magnetic Resonance spectra were recorded on Varian Gemini-200, Varian Gemini-400, Avance 300 MHz and Ux-NMR instrument. The samples were made in CCl_4/Chloroform-d (1:1) or DMSO-d6 using tetramethylsilane (TMS) as the internal standard and are given in the δscale. A mass spectrum was recorded on VG Micromass 7070H (ESI and EI) and was given in mass units (m/z). The purity of the synthesized compounds was determined by thin layer chromatography (TLC), performed on precoated silica gel-60 F254 (0.5mm) glass plates.

Chemistry

Synthesis of 1-(2, 5dimethylthiophen-3yl)-3-(substituted aryl / heteroaryl)-prop-2-en-1-ones(3a-f):

To a solution of 3-acetyl,2,5-dimethylthiophene **(1)** in ethanol, a solution of KOH(4:1), taken in a RB flask and various substituted aromatic aldehydes **(2)** (2:1) were added. The mixture was kept at room temperature for 24hr.On acidification with 1:1 HCl, the chalcones precipitated out were filtered and recrystallized using suitable solvents.

1-(2,5-dimethylthiopen-3-yl)-3-(4-nitropenyl)prop-2-en-1-one (3a)

IR (KBr, cm^{-1}): 1653 cm^{-1} (C=O), 679 cm^{-1} (C-S), 839cm^{-1} (C-N); **^{1}H NMR (DMSO-d6):** δ 2.5 (s, 3H, CH_3), δ 2.75 (s, 3H, CH_3), δ 7.1(s, H, Ar- H), δ 7.4(d, H, =CH), δ 7.7 (t, 3H, Ar- H of thiophene), δ 8.25 (d, 2H, Ar- H); **[M+H] m/z :** 288

3-(2-chloro-5-nitrophenyl)- 1- (2,5-dimethyl thiophen-3-yl) prop- 2- en - 1-one (3b)

IR (KBr, cm^{-1}): 1658 cm^{-1} (C=O), 699 cm^{-1} (C-S), 1268 cm^{-1} (C-N); **^{1}H NMR (DMSO-d6):** δ 2.5 (s, 3H, CH_3), δ 2.75 (s, 3H, CH_3), δ 7.1(s, H, Ar- H), δ 7.4(d, H, =CH), δ 7.65 (d, H, Ar-H), δ 8.05 (d, H, Ar- H), δ 8.6 (s, H, H-thiophene); **[M+H] m/z :** 321.

1-(2,5-dimethylthiophene-3-yl)-3-(3-methyl-1-phenylpyrazolidine-3-yl)prop-2-en-1-one(3c)

IR (KBr, cm^{-1}): 1642 cm^{-1}(C=O), 650 cm^{-1} (C-S), 999 cm^{-1} (C-N); **^{1}H NMR (DMSO-d6):**

δ 2.4 (s, 3H, CH_3), δ 2.5 (s, 3H, CH_3), δ 2.7 (s, 3H, CH_3), δ 7.5(d, H, =CH), δ 7.4 (t,2(Ar-H), 1- H(pyrazole ring), Ar-H), δ 7.7 (m, 3H, Ar- H), δ 8.15 (s, H, H-thiophene ring); **[M+H] m/z :** 323.

3-(benzo[d][1,3]dioxol-5-yl)-1-(2,5-dimethylthiophen-3-yl)prop-2-en-1-one(3d)

IR (KBr, cm^{-1}): 1643 cm^{-1} (C=O), 1356 cm^{-1} (C-O), 608 cm^{-1} (C-S); **^{1}H NMR (DMSO-d6):** δ 2.45 (s, 3H, CH_3), δ 2.75 (s, 3H, CH_3), δ 6(s,2H,O-CH_2-O) δ 7.1(t,4H,3H(Ar-H)& 1H(=CH)), δ 7.6 (d, H, Ar-H(thiophene ring)). **[M+H] m/z:** 287.

3-(3,4-dimethoxypenyl)-1-(2,5-dimethylthiophene-3-yl)prop-2-en-1-one(3e)

IR (KBr, cm^{-1}): 1651 cm^{-1} (C=O), 1258 cm^{-1} (C-O), 682 cm^{-1} (C-S); **^{1}H NMR (DMSO-d6):** δ 2.45 (s, 3H, CH_3), δ 2.75 (s, 3H, CH_3), δ 3.95(s,6H,2(O-CH_3)) δ 7.1(m,3H,(Ar-H)), δ 7.3(s, H, =CH), δ 7.7 (d, H, Ar-H(thiophene ring)).**[M+H] m/z:**302

1-(2,5-dimethylthiopen-3-yl)-3-(4-methyl-3-nitrophenyl)prop-2-en-1-one (3f)

IR (KBr, cm^{-1}): 1557 cm^{-1} (C=O), 1525 cm^{-1} (N-O);**^{1}H NMR (DMSO-d6):** δ 2.41 (s, 3H, CH_3), δ 2.64 (s, 3H, CH_3), δ 7.54(d,H,(Ar-H)), δ 7.64 (d,H,=CH), δ 8.09 (d, H, Ar-H(thiophene ring)) δ 8.43 (d,H,(Ar-H). **[M+H] m/z:** 301.

Synthesis of 3-(2, 5-dimethylthiophen-3yl)-5-(substituted aryl)-1-phenyl-4,5-dihydro-1*H*-pyrazoles(5a-f):

In a RB flask, a mixture of Phenyl hydrazine hydrochloride (144mg) in ethanol (20ml), pyridine (0.3ml) and the (3a-f) were added and refluxed on water bath for 4-6hrs.The excess solvent was removed by vacuum and the product was recrystallized.

3-(2,5-dimethylthiophen-3-yl)-5-(4-nitophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (5a)

IR (KBr, cm^{-1}): 1598 cm^{-1} (C=N), 1249 cm^{-1} (C-N), 691 cm^{-1} (C-S); **^{1}H NMR (DMSO-d6):** δ 2.24 (s, 3H, CH_3), δ 2.5 (s, 3H, CH_3), δ 6.3(d,H,H_B-CH_2), δ 6.5(d,H,H_A-CH_2), δ 6.9(d,H,H_C-CH), δ 7.1(s,H,(Ar-H)), δ 8.15 (d, 2H, Ar-H(thiophene ring)). **[M+H] m/z:** 377.

5-(2-chloro-5-nitrophenyl) -3-(2,5-dimethyl thiophen-3-yl)-1-phenyl-4,5-dihydro-1H-pyrazole (5b)

IR (KBr, cm^{-1}): 1516 cm^{-1} (C=N), 692 cm^{-1} (C-S), 1249 cm^{-1} (C-N); **^{1}H NMR (DMSO-d6):** δ 2.3 (s, 3H, CH_3), δ 2.75 (s, 3H, CH_3), δ 6.65(d,H,H_B-CH_2), δ 6.55(d,H,H_A-CH_2), δ 6.9(d,H,H_C-CH), δ 7.1(d,2H,(Ar-H)), δ 8.5 (s, H, Ar-H(thiophene ring)).**[M+H] m/z:** 412.

3-(2,5-dimethyl thiophene-3-yl)-5-(3-methyl-1-phenyl pyraolidine-3-yl)-1-penyl -4,5-dihydro-1H-pyrazole (5c)

IR (KBr, cm^{-1}): 1598 cm^{-1} (C=N), 689 cm^{-1} (C-S), 1154 cm^{-1} (C-N); **^{1}H NMR (DMSO-d6):** δ 2.4 (t, 6H, 2CH_3), δ 3.7(d,H,H_B-CH_2), δ 3.1(d,H,H_A-CH_2), δ 5.15(d,H,H_C-CH), δ 6.8 (d, H, Ar-H(thiophene ring)), δ 7.1(d,2H,(Ar-H)). **[M+H] m/z:** 411.

5-(1,3-benzodioxol-5-yl)-3-(2,5-dimethylthiophen-3-yl)-1-phenyl-4,5-dihydro-1H-pyrazol (5d)

IR (KBr, cm^{-1}): 1596 cm^{-1} (C=N), 1251cm^{-1} (C-O), 689 cm^{-1} (C-S); **^{1}H NMR (DMSO-d6):** δ 2.45 (d, 3H, CH_3), δ 2.7 (d, 3H, CH_3), δ 3.1(d,H,H_B-CH_2), δ 3.75(s,H,H_A-CH_2), δ 5.1(s,H,H_C-CH), δ 5.9 (d,2H,O-CH_2) δ 7.1(m,4H, (Ar-H)), δ 7.4 (s, H, Ar-H(thiophene ring)). **[M+H] m/z:** 376.

3-(2,5-dimethylthiophene-3-yl)-5-(3,4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (5e)

IR (KBr, cm^{-1}): 1598 cm^{-1} (C=N), 1236 cm^{-1} (C-O), 696 cm^{-1} (C-S); **^{1}H NMR (DMSO-d6):** δ 2.45 (s, 3H, CH_3), δ 2.75 (s, 3H, CH_3), δ 2.9 (d, H, -CH), δ 3.6(s,6H,2(O-CH_3)), δ 5.1 (s, H, Ar-H(thiophene ring)), δ 6.6(d,2H,(Ar-H)), δ 6.8(m, 5H, ,(Ar-H**));** **[M+H] m/z :** 393

3-(2,5-dimethylthiophen-3-yl)-5-(4-methyl-3-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole(5f)

IR (KBr, cm^{-1}): 1529 cm^{-1} (C=N), 1110 cm^{-1} (C-N), 688 cm^{-1} (C-S); **^{1}H NMR (DMSO-d6):** δ 2.4 (s, 3H, CH_3), δ 2.6 (s, 3H, CH_3), δ 3.1(d,H,H_B-CH_2), δ 3.85(d,H,H_A-CH_2), δ 5.25(t,H,H_C-CH), δ 7.54(d,H,(Ar-H)), δ 8.0 (s, H, Ar-H(thiophene ring)); **[M+H] m/z :** 390.

Antimicrobial Activity

All the compounds were screened for their in-vitro antimicrobial activity against *B.subtilis*, *S.aureus* (Gram-positive) and *E.coli, P.aeroginosa* (Gram-negative) and antifungal activity against *C.albicans*, *S.cerevisiae* by disc diffusion method. The Zone of Inhibition (ZOI) was determined by using Tetracycline and Fluconazole as a standard for antibacterial and antifungal activity respectively. The results are given in the Table-**3.**

Scheme-I

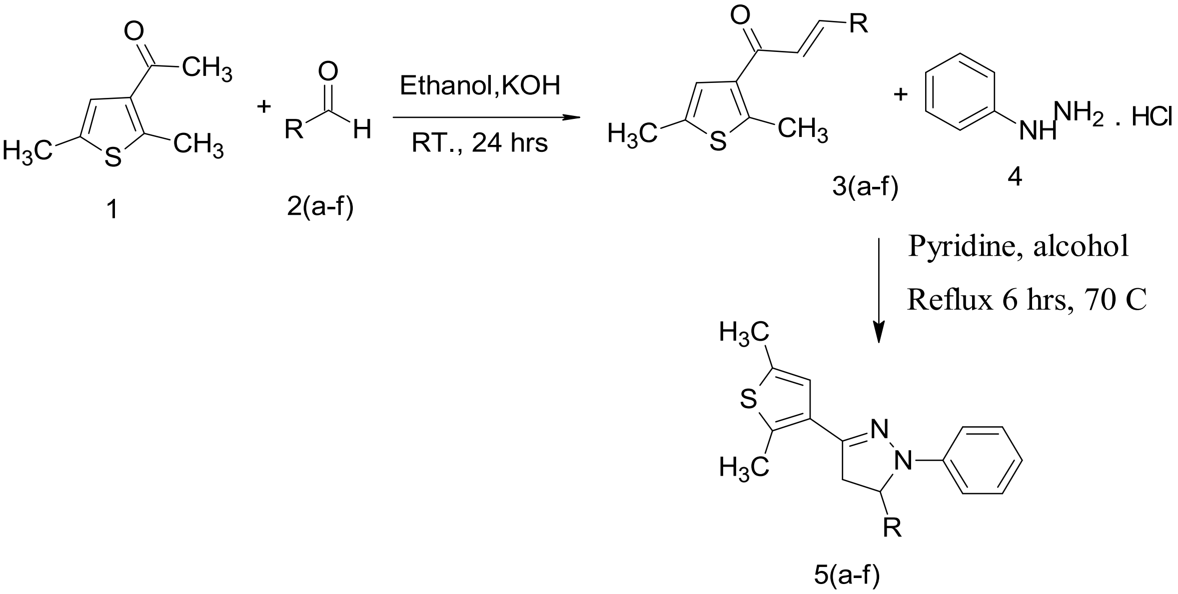


Table 1: Substitutents of the title compounds (3a-f, 5a-f)

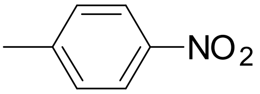
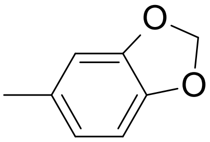
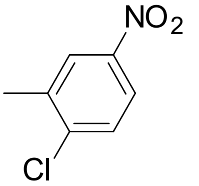
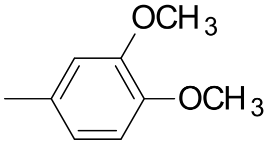
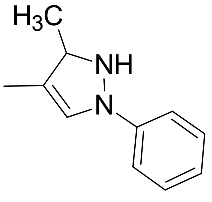
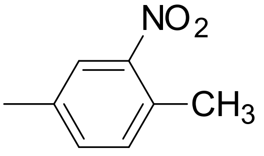
Compd Code	R	Compd Code	R
3a,5a		**3d,5d**	
3b,5b		**3e,5e**	
3c,5c		**3f,5f**	

Table 2: Physicochemical characterization of the synthesized compounds (3a-f, 5a-f):

Compound	Molecular Weight	Molecular Formula	Melting Point (°C)	% Yield	R_f Value
3a	**287**	$C_{15}H_{13}O_3NS$	**190-192°C**	**83%**	**0.88**
3b	**321**	$C_{15}H_{12}O_3ClNS$	**120-122°C**	**85%**	**0.90**
3c	**324**	$C_{19}H_{20}SN_2O$	**110-112°C**	**78%**	**0.79**
3d	**286**	$C_{16}H_{14}O_3S$	**90-92°C**	**76%**	**0.86**
3e	**302**	$C_{17}H_{18}O_3S$	**110-112°C**	**83.5%**	**0.85**
3f	**301**	$C_{16}H_{15}O_3NS$	**100-102°C**	**86%**	**0.82**
5a	**377**	$C_{21}H_{19}O_2SN_3$	**80-83°C**	**82%**	**0.92**
5b	**411**	$C_{21}H_{18}O_2N_3SCl$	**110-113°C**	**87.2%**	**0.79**
5c	**412**	$C_{25}H_{22}N_4S$	**130-133°C**	**72%**	**0.80**
5d	**376**	$C_{22}H_{20}N_2O_2S$	**90-92°C**	**77.8%**	**0.77**
5e	**392**	$C_{23}H_{24}O_2SN_2$	**126-129°C**	**80%**	**0.82**
5f	**390**	$C_{22}H_{20}O_2SN_3$	**110-113°C**	**84.2%**	**0.84**

Table -3: Antibacterial and Antifungal Activity of the synthesized compounds (3a-f), (5a-f):

Antibacterial activity					Antifungal activity	
Zone of Inhibition(mm)						
Compd Code	Gram Positive Organisms		Gram Negative Organisms		Antifungal Organisms	
	B.Subtilis	*S.aureus*	*E.coli*	*P.aeroginosa*	*C.albicans*	*S.cervisiae*
3a	15	10	14	11	14	10
3b	10	8	9	8.4	12	14
3c	-	-	9	-	-	9
3d	14	9	12	-	10	-
3e	9	-	8	-	12	-
3f	8.5	9	8	-	9	-
5a	11	9	-	-	12	-
5b	16	12	14	10	14	10
5c	9	-	10	-	-	10
5d	12	-	11	9	-	9
5e	5.5	9	13	9.5	9	12
5f	10	-	11	-	12	-
STD[a] (TC)[b]	18	18	16	16	-	-
STD[a] (FLZ)[c]					20	20

[a]STD - Standard, [b]TC - Tetracycline,[c]FLZ – Fluconazole

RESULTS AND DISCUSSION

The structure of all the synthesized compounds was confirmed by IR, 1H NMR and Mass spectra. Spectral analysis of the newly synthesized compounds **3 (a-f) & 5(a-f)** were in full agreement with the proposed structure. The IR spectrum of **3(a-f)** showed a characteristic absorption band around 1643-1658cm^{-1}that was assigned to (C=O) stretching. Absorption band around 608-682 cm^{-1} that was assigned to (C-S) stretching. Absorption band around 839-1258cm^{-1} that was assigned to (C-N) stretching. In the ^{1}H-NMR spectra of **3(a-f),** (C=H) of olefin group displayed a signal around δ 7.3δppm. The IR spectrum of **5(a-f)** showed a characteristic absorption band around 1249-1598 cm^{-1} that was assigned to (C=N) stretching. Absorption band around 839-1258 cm^{-1} that was assigned to (C-N) stretching. Absorption band around 608-682cm^{-1} that was assigned to (C-S) stretching. In the ^{1}H NMR spectra of **5(a-f),** (C-H$_2$) H$_B$ of methylene group displayed a signal around δ 3.1ppm. (C-H$_2$) H$_A$ of methylene group displayed a signal around δ 3.7ppm. (C-H) H$_C$ displayed a signal around δ 5.15ppm

Antibacterial activity

The antibacterial activity was screened at the concentration of 100ug/ml. The compounds **3a, 3d, 5b** showed significant activity against *Bacillus subtilis* and *E.coli* and **3b, 3e, 5a, 5c, 5d, 5f** showed moderate activity and **3c** was inactive against *Bacillus subtilis*. The compounds **5b, 5e**showed significant activity, **3b, 3d, 3f, 5a, 5e** showed moderate activity and **3c, 3e, 5c, 5d, 5f** were inactive against *S.aureus*. **3b, 3c, 3e, 3f, 5c, 5d, 5e, 5f** and **3a, 3b, 5b, 5d, 5e**showed moderate activity and **5a** and **3c, 3e, 3d, 3f, 5a, 5c, 5f** was inactive when tested against *E coli* and *P. aeroginosa*.

Antifungal activity

The antifungal activity of test compounds **(3a-3f)** and **(5a-f)** were evaluated by disc diffusion method taking drug at a concentration of 100ug/ml. The ZOI of test compound is compared to that of the standard drug, Fluconazole. The compounds **3a, 3b, 3d, 3e, 5a, 5b, 5f** and **3a, 3b, 5b, 5c, 5e**showed significant activity,**3f, 5e**and **3c, 5d** showed moderate activity, **3f, 5e 3d, 3e, 3f, 5a, 5f**were inactive when tested for antifungal activity against *C. albicans* and *S.cerevisiae*.

CONCLUSION

To conclude, the strategy adopted for the synthesis of substituted chalcones and pyrazolines utilizes easily available commercial compounds as starting materials. The reactions were completed in shorter times with high purity and the yields were found to be good. All the synthesized compounds were purified by column chromatography and characterized by spectral data (IR, 1H, Mass). The compounds were evaluated for antibacterial and antifungal activity by disc diffusion method. All compounds were found to have good anti-bacterial activity against both gram-positive and gram-negative bacteria and anti-fungal activities especially the compounds **3a & 5b.**

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