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Synthesis, Characterization and Antibacterial Evaluation of Chalcones Carrying Aryl Furan Moiety

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ABSTRACT

In the present work, series of target compounds 3-(5-(2-chloro-4-nitrophenyl)furan-2-yl)-1-(1-(substitued phenyl)-5-methyl-1H-1,2,3-triazol-4-yl)prop-2-en-1-one (3a-3g) were prepared by Claisen Scmidt Condensation of (5-(2-chloro-4-nitrophenyl)furan-2-carbaldehyde)) with substituted triazole ketones in the presence of ethanolic potassium hydroxide solution. Synthesised compounds have been characterized by elemental analysis and spectral analysis i.e. using IR, Mass and NMR Spectroscopy, Further the synthesized compounds were screened for antibacterial activity. All the synthesized compounds exhibited quite promising activity against gram positive and gram negative bacterial strains.

Keywords: Aryl furan-2-carbaldehyde; Triazole ketone; Chalcones; Antibacterial activity

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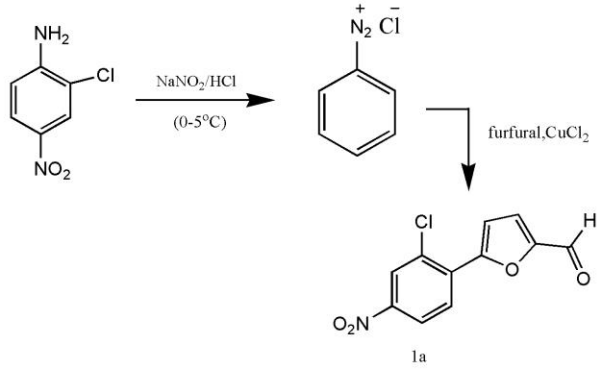
INTRODUCTION

In recent years, it has been observed that microbial infections are most common because of their hasty growth and increased resisting power against available antibiotics [1]. These infections may lead to death also [2]. This crucial point aims at designing better effective, less toxic and potent wide range of antimicrobial drugs [3]. Nitrogen containing heterocycles plays a very important role in modern medicinal chemistry because of their bio-active nature [4]. These are used in industry as corrosion inhibitor [5], photostabilizer and are also used in agrochemical industries as pesticides [6], fungicides [7], herbicides [8], and nematicides [9]. These factors made triazole moiety as a choice of antimicrobial drugs.

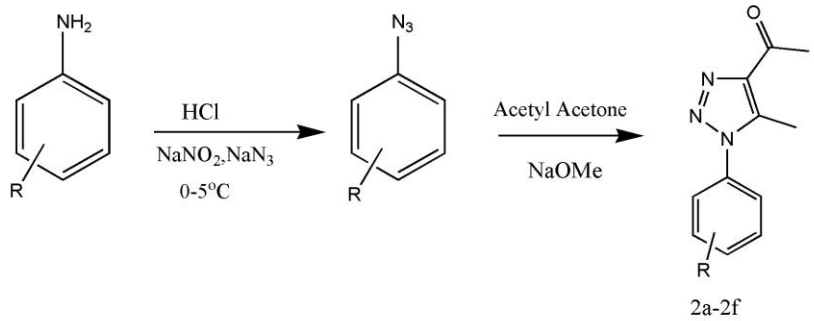
Substituted furan-2-carbaldehydes having carbonyl group act as a reactive centre for various condensation reactions. Fusion of one or more biologically active scaffolds results in a new pharmocophore with diverse pharmacological properties [10, 11]. Selection of Pharmacophore depends upon the factors like therapeutic values, synthetic ability and ease. Both scaffolds having high therapeutic values results in the moieties with enlarged potency [12]. Due to the presence of α-β unsaturated core, chalcones serve as precursors for many scaffolds like isoxazolines [13]. Pyramidines [14], cyanopyramidines, pyrazolines [15] etc. Chalcone with this linkage also exhibits wide range of biological activities like antimutagenic [16] antitumor-promoting, antibacterial [17,18], antiviral, and anti-inflammatory [19] activities. They are also useful in material science fields such as non-linear optics (NLO) [20], optical limiting, electrochemical sensing, Langmuir films and photo-initiated polymerization. In continuation with the ongoing research for nitrogen heterocycles, in the present review chalcones are prepared by condensing furan 2 carbaldehyde scaffolds with triazole ketones and their antibacterial activity has been evaluated.

MATERIALS AND METHODS

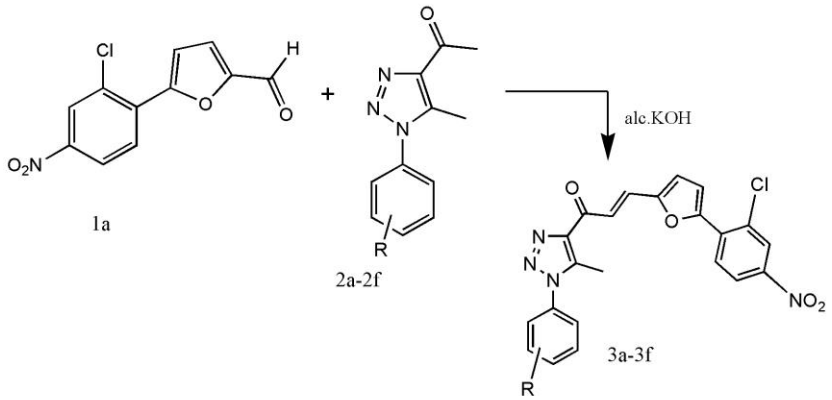
Reagents and solvents were purchased from Sigma-Aldrich, Spectrochem and are used after distillation/recrystallization. 1H NMR spectra were recorded on Bruker Avance II NMR spectrometer operating at 400 MHz and all the chemical shift values were reported in parts per million (ppm) in relative to TMS. Proton signals are indicated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Coupling constant (J) values were expressed in Hertz (Hz). LCMS (SHIMADZU LCMS-8030)-70 eV mass spectrometer was used to record mass. IR spectra of the compounds were recorded using a Schimadzu FT-IR 157 spectrophotometer. C H N analysis was performed with Vario-EI Elementar-III model analyzer. Melting points of the compounds were determined using open capillary method. Completion of reaction was monitored under UV lamp using silica coated plates and ethyl acetate: hexane (2:8) as mobile phase (Table 1).



Scheme 1.1-Synthesis of 5-(2-chloro-4-nitrophenyl)furan-2-carbaldehyde)-**1a**



Scheme 1.2-Synthesis of substituted triazole ketones **(2a-2f)**



Scheme 1.3-Synthesis of chalcone derivatives **(3a-3f)**

Table 1: Physical characteristics and elemental data of the compounds 3a-3g

Sample Code	-R	Yield (%)	Melting Point °C	Colour of the Compound	Molecular Formula/ Formula Weight	Elemental Analysis Calculated (Found)		
						C	H	N
3a	4-Cl	72	183-185	Dark Yellow	$C_{22}H_{14}Cl_2N_4O_4$	56.31	3.01	11.94
					469.27696	-56.35	-3.02	-11.95
3b	4-CH_3	71	190-192	Light Brown	$C_{23}H_{17}ClN_4O_4$	61.54	3.82)	12.48
					448.85848	-61.52	(3.85	-12.46
3c	4-NO_2	68	220-222	Brown	$C_{22}H_{14}ClN_5O_6$	55.07	2.94	14.6
					479.82946	-55.1	-2.98	-14.62
3d	3-NO_2	69	170-175	Dark brown	$C_{22}H_{14}ClN_5O_6$	55.07	2.94	14.6
					479.82946	-55.1	-2.97	-14.62
3e	2,3 dichloro	72	178-181	Yellow	$C_{22}H_{13}Cl_3N_4O_4$	52.46	2.6	11.12
					503.72202	-52.46	-2.58	-11.15
3f	4-Br	67	182-184	Brown	$C_{22}H_{14}BrClN_4O_4$	51.43	2.75	10.91
					513.72796	-51.46	-2.78	-10.95
3g	3-Cl	68	164-168	Brown	$C_{22}H_{14}Cl_2N_4O_4$	56.31	3.01	11.94
					469.27696	-56.34	-3.02	-11.94

Synthesis of Substituted Furan 2-Carbaldehyde (5-(2-Chloro-4-Nitrophenyl) Furan-2-Carbaldehyde))-1a

2chloro 4–nitro aniline (8 g) was heated in a mixture of HCl and water (1:1) with stirring. It was cooled in an ice bath at 0-5°C and to this a solution of Sodium nitrite (0.07 mol) was added drop wise. The reaction mixture was left aside for one hour for the completion of diazotization, it is then filtered, and filterate was collected. To the filterate, furfural (0.05 mol) was added, followed by solution of copper chloride (2 g in 10 ml) drop wise and continued stirring for 4 h, left for overnight at room temperature. Precipitate thus obtained was filtered, dried and recrystallized from ethanol.

Synthesis of Substituted Triazole Ketones (2a-2g)

10 g of substituted aniline was dissolved in Conc HCl and water (1;1), it was cooled to 0-5°C and stirred. To this sodium nitrite (0.08 mol) and sodium azide (0.07 mol) were added drop wise, it is then allowed to run for 1 h and kept aside for the reaction completion. The above solution is then extracted with chloroform, followed by washing with salt water. The organic layer is then dried over anhydrous sodium sulphate and the resultant solution was kept for evaporation for the formation of azide. Azide (0.05 mol) thus formed was treated with methanolic solution of

sodium methoxide (0.05 mol) and acetyl acetone (0.05 mol). It is then stirred for overnight and precipitate thus obtained was quenched with ice, filtered, dried and recrystaliized from ethanol. Yield: 70%-75%.

Synthesis of Chalcone (3a-3g)

Substituted triazole ketone (3 mmol) in ethanol was treated with synthesized aryl furan 2- carbaldehyde (3 mmol) and 20% 10 ml KOH was added drop wise, the reaction mixture was stirred for overnight at room temperature. It was quenched in ice and precipitate thus formed was filtered, dried and recrystallized from ethanol. Yield: 67-72%.

3-(5-(2-Chloro-4-Nitrophenyl) Furan-2-yl)-1-(1-(4-Chlorophenyl)-5-Methyl-1H-1,2,3-Triazol-4-yl) Prop-2-en-1-One (3a)

IR (KBr,cm^{-1}) : 3036 (Ar C-H), 1660 (C=O), 1562(C=C), 1337(C-NO_2), 795 (C-Cl) ; 1HNMR ($CDCl_3$,400Hz): δ 2.69 (s,3H, triazole ring CH_3), δ 6.94 (d,1H,J=3.6Hz,furan-H), δ 7.44 (d,2H, J=8.4Hz Ar-H), δ 7.53 (d, 1H,J=3.2Hz,furan-H), δ 7.58 (d,2H, J=8.4Hz Ar-H), δ 7.71 (d,1H,J=15.6Hz chalcone proton), δ 8.05 (d,1H,J=15.6Hz chalcone proton), δ 8.22 (dd,2H, J=8.84Hz, 8.84Hz Ar-H), δ 8.36 (s,1H, Ar-H) ; **LC-MS**: m/z: 469(M+), 471 (M++2), 472 (M++3).

3-(5-(2-Chloro-4-Nitrophenyl) Furan-2-yl)-1-(5-Methyl-1-p-tolyl-1H-1,2,3-Triazol-4-yl)Prop-2-en-1-One (3b)

IR (KBr,cm^{-1}) : 3107 (Ar C-H), 1653(C=O), 1584(C=C), 1331(C-NO_2), 793 (C-Cl) ;1HNMR ($CDCl_3$,400Hz): δ 2.48 (s,3H, phenyl CH_3), δ 2.66 (s,3H,triazole ring CH3), δ 6.93 (d,1H,J=3.72Hz,furan-H), δ 7.35 (m,4H,Ar-H), δ 7.52 (d,1H,J=3.68Hz,furan-H), δ 7.69 (d,1H,J=15.76Hz chalcone proton), δ 8.06 (d,1H,J=15.76Hz,chalcone proton), δ 8.20 (dd,1H, J=2.16Hz and 2.16Hz,Ar-H), δ 8.32 (d,1H, J=8.8Hz, Ar-H), δ 8.34 (d,1H, J=2.12Hz,Ar-H) ; **LC-MS**: m/z: 449(M+), 451 (M++2), 452 (M++3).

3-(5-(2-Chloro-4-Nitrophenyl) Furan-2-yl)-1-(5-Methyl-1-(4-Nitrophenyl)-1H-1,2,3-Triazol-4-yl)Prop-2-en-1-One (3c)

IR (KBr,cm^{-1}) : 3092 (Ar C-H), 1663 (C=O), 1595 (C=C), 1339 (C-NO_2), 802 (C-Cl);1HNMR ($CDCl_3$,400Hz): δ 2.70 (s,3H,triazole ring CH3), δ 6.96 (d,1H,J=3.64Hz,furan-H), δ 7.45 (d,2H,J=8.42Hz), δ 7.54 (d,1H,J=3.64Hz,furan-H), δ 7.59 (d,2H,J=8.4Hz) , δ 7.73 (d,1H,J=15. 6Hz,chalcone proton), δ 8.08 (d,1H,J=15. 6Hz,chalcone proton), δ 8.22 (dd,2H, J= 8.84Hz, 8.84Hz,Ar-H), δ 8.36 (s,1H, Ar-H); **LC-MS**: m/z: 480(M+), 482 (M++2), 483 (M++3).

3-(5-(2-Chloro-4-Nitrophenyl) Furan-2-yl)-1-(5-Methyl-1-(3-Nitrophenyl)-1H-1,2,3-Triazol-4-yl)Prop-2-en-1-One (3d)

IR (KBr,cm^{-1}) : 3092 (Ar C-H), 1653 (C=O), 1580(C=C), 1337 (C-NO_2), 747 (C-Cl); 1HNMR ($CDCl_3$,400Hz): δ 2.68 (s,3H, triazole ring CH3), δ 6.94 (d,1H,J=3.6Hz,furan-H), δ 7.53 (t,2H,Ar-H), δ 7.55 (d,1H,J=3.6Hz,furan-H), δ 7.72 (d,2H,J=8.4Hz,Ar-H), δ 7.79 (d,1H,J=15.6Hz chalcone proton), δ 8.07 (d,1H,J=15.6Hz chalcone proton), δ 8.19 (d,2H, J=8.4Hz, Ar-H), δ 8.25 (s,1H, Ar-H) ; **LC-MS**: m/z: 480(M+), 482 (M++2), 483 (M++3).

3-(5-(2-Chloro-4-Nitrophenyl) Furan-2-yl)-1-(1-(2,3-Dichlorophenyl)-5-Methyl-1H-1,2,3-Triazol-4-yl)Prop-2-en-1-One (3e)

IR (KBr,cm^{-1}) : 3076(Ar C-H), 1659 (C=O), 1595 (C=C), 1337 (C-NO_2), 789 (C-Cl); 1HNMR ($CDCl_3$,400Hz): δ 2.56 (s,3H, triazole ring CH_3), δ 6.96 (d,1H,J=3.64Hz,furan-H), δ 7.39 (d,1H, J=7.04Hz,Ar-H), δ 7.46 (t,1H,Ar-H) 7.54 (d,1H,J=3.64Hz,furan-H), δ 7.73 (d,1H, J=15.6Hz chalcone proton), δ 8.07(d,1H,J=15.6Hz chalcone proton), δ 8.22 (m,3H,Ar-H) , δ 8.36 (d,1H, J=1.8Hz,Ar-H) ; **LC-MS**: m/z: 503(M+-1), 505 (M++1), 507 (M++3), 508(M++4).

1-(1-(4-Bromophenyl)-5-Methyl-1H-1,2,3-Triazol-4-yl)3-(5-(2-Chloro-4-Nitrophenyl)furan-2-yl)-Prop-2-en-1-One (3f)

IR(KBr,cm^{-1}) : 3073 (Ar C-H), 1657 (C=O), 1582 (C=C), 1375 (C-NO_2), 617 (C-Br),741 (C-Cl); 1HNMR ($CDCl_3$,400Hz): δ 2.69 (s,3H, triazole ring CH_3), δ 6.95 (d,1H,J=3.6Hz,furan-H), δ 7.44 (d,2H, J=8.44Hz Ar-H), δ 7.53 (d, 1H,J=3.2Hz,furan-H), δ 7.59 (d,2H, J=8.44Hz Ar-H), δ 7.72 (d,1H,J=15.6Hz chalcone proton), δ 8.07 (d,1H,J=15.6Hz chalcone proton), δ 8.22 (dd,2H, J=8.84Hz, 8.84Hz Ar-H), δ 8.34 (s,1H, Ar-H); **LC-MS**: m/z: 514(M+), 516 (M++2), 517 (M++3).

3-(5-(2-Chloro-4-Nitrophenyl) Furan-2-yl)-1-(1-(3-Chlorophenyl)-5-Methyl-1H-1,2,3-Triazol-4-yl)Prop-2-en-1-One (3g)

IR(KBr,cm^{-1}) :3073 (Ar C-H), 1659 (C=O), 1580 (C=C), 1373 (C-NO_2), 827 (C-Cl); 1HNMR ($CDCl_3$,400Hz): δ 2.68 (s,3H, triazole ring CH_3), δ 6.94 (d,1H,J=3.6Hz,furan-H), δ 7.52 (d,2H, J=8.4Hz,Ar-H), δ 7.53

(d,1H,J=3.6Hz,furan-H), δ 7.58 (s,1H,Ar-H), δ 7.71 (t,1H,Ar-H), δ 7.75 (d,1H,J=15.6Hz chalcone proton), δ 8.06 (d,1H,J=15.6Hz chalcone proton), δ 8.29 (d,2H, J=8.4Hz Ar-H), δ 8.36 (s,1H, Ar-H) ; **LC-MS**: m/z: 469(M+), 471 (M++1), 472(M++2).

RESULTS AND DISCUSSION

The synthetic pathway for the title compound was illustrated in Scheme 1.3, and are synthesized in a good yield by Claisen Schmidt condensation of 5-(2-chloro-4-nitrophenyl)furan-2-carbaldehyde and substituted triazole ketone in ethanolic medium using alcoholic potassium hydroxide as a base [21]. The key starting material aryl furfural was synthesized according to literature procedure [22] by taking 2 chloro nitro aniline as parent compound (Scheme 1.1). The intermediate triazole ketone was also prepared by taking different substituted aniline as a starting material followed by azide formation then to triazole ketone according to the literature procedure [23]. Structures of all the newly synthesized compound were established by elemental analysis (CHN), mass, IR and NMR spectroscopy and all these results of synthesized compounds are fully in agreement with the proposed structure.

The FT-IR Spectrum of chalcones showed sharp band at 3036-3107 cm-1 which corresponds to aromatic C-H stretching frequencies. The absorption band which appears at 1653-1663 cm-1 was due to α-β unsaturated carbonyl system. C=C absorption band appeared at 1562-1595 cm-1 and C-NO2 absorption band appeared at 1331-1332cm-1 , C-Cl band at 741-827 cm-1 , C-Br band at 617 cm-1. The 400 MHz 1HNMR spectrum of the all the compound showed a singlet at δ 2.56-2.70 integrating for three protons of CH3 group attached to triazole ring and the compound 3b showed singlet at δ 2.48 integrating for three protons of CH3 group of p-tolyl ring. The α-β unsaturated protons of chalcones appeared as two doublets at δ 7.73 and δ 8.04 each with coupling constant J=15.6 Hz. This shows that chalcone protons are trans in nature. Since the starting material has chloro group, all the synthesized compounds showed isotopic peaks in mass spectra. The mass spectrum of compound 3a and 3g showed isotopic peak at m/z 469 (M+), 471(M++2) and 473(M++3) consistent with their molecular formula $C_{22}H_{14}C_{l2}N_4O_4$. The compound 3c,3d showed isotopic peak at m/z 480 (M+), 482 (M++2), 483 (M++3) consistent with molecular formula $C_{22}H_{14}C_lN_5O_6$ and the disubstituted compound 3e showed isotopic peak at m/z 503(M+-1), 505 (M++1), 507 (M++3), 508(M++4) in the ratio 3:1 whereas 3f showed isotopic peak at m/z 514 (M+), 516 (M++2), 517 (M++3).

Antibacterial Studies

In order to carry out the possible biological studies, the synthesized compounds were screened for antibacterial activity against gram positive strains *Staphylococcus aureus*, bacillus subtilis and gram negative strains *Pseudomonas aeruginosa* , *Eschericia coli* by cup plate method [24].

Screening results of antibacterial studies reveals that all the tested compounds showed moderate to good activity when compared with standard drug ciproflaxin and among them compounds with chloro substituent (3a, 6g) found to be more effective to *Pseudomonas aeruginosa* and compounds with bromo group (3f) showed comparatively good activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* whereas meta nitro substituted compound (3d) showed significant activity against *Staphylococcus aureus* (Figure 1).

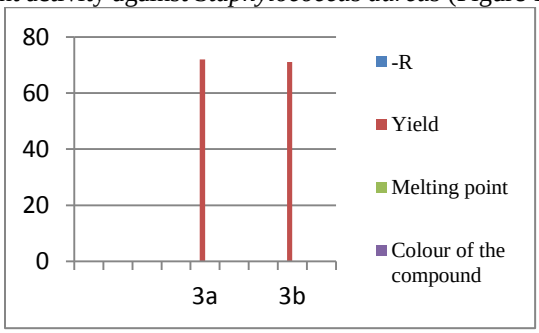


Figure 1: Antibacterial studies of aryl furan linked Chalcones (3a-3g)

CONCLUSION

In this study a novel series of chalcones carrying aryl furan moiety were synthesized by base catalyzed Claisen Schmidt condensation in a good yield and were characterized by elemental analysis, Mass, FT-IR and 1H NMR

spectral studies. These compounds were further evaluated for their antibacterial activity. Based on the studies, we pointed out that change in position of the substituent also varies the activity. All the compounds showed promising activity against the bacterial strains.

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