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Synthesis and biological activities of novel heterocyclic chalcone derivatives by two different methods using anhydrous potassium carbonate as an efficient catalyst

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ABSTRACT

*A series of twenty heterocyclic chalcones **3(a-t)** were synthesized by using conventional and microwave irradiation methods in the presence of anhydrous potassium carbonate as an safe, inexpensive and efficient basic catalyst. Synthesized compounds were evaluated for their in vitro antimicrobial activity against variety of microbial strains and it was characterized by IR, NMR (^{1}H & ^{13}C) and mass spectral analysis. The biological screening results indicated that some of the compounds showed significant antibacterial and antifungal activities. Compound **3s** was displayed excellent antimicrobial activity against various microbial strains. The newly synthesized high potent compound **3s** was subjected to Thermogravimetric analysis (TGA), Differential scanning calorimetric (DSC) and single crystal XRD.*

Keywords: Chalcones, Anhydrous potassium carbonate, Microwave irradiation and antimicrobial activities.

INTRODUCTION

Heterocyclic chalcones exhibit a broad spectrum of biological activities [1]. These are the main precursors in the biosynthesis of flavonoids [2] abundant in edible plants. Chemically they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system. They have been reported to show various pharmacological activities like anticancer [3,4], antimalarial [5], anti-inflammatory [6], anti-tubercular [7], cytotoxic [8], gastroprotective [9], modulation of nitric oxide production [10] and so on. These compounds are important synthons for the preparation of five and six membered ring systems [11] as well as intermediate in the synthesis of many pharmaceutically important compounds [12]. Having such a varied pharmacological activity and synthetic utility, chalcones have attracted chemists to develop newer strategies for their synthesis and screening them for their *in vitro* microbial activity.

By far the most popular way of synthesis for chalcone is the Claisen-Schmidt condensation of an appropriate acetophenone with benzaldehyde in presence of aqueous bases like NaOH [13-15], KOH [16], $Ba(OH)_2$ [17,18] etc. Other base catalysts such as magnesium *t*-butoxide [19], potassium carbonate [20], alumina [21], MgO [22], calcinated hydrotalcites [23,24], natural phosphate/$NaNO_3$ [25,26], KF/natural phosphate [27] and piperidine [28] have also been used for their synthesis. Similarly, using acid catalysts such as HCl, BF_3, B_2O_3, PTSA, $SOCl_2$/ EtOH [29], $AlCl_3$ [30], BF_3-Et_2O [31], $TiCl_4$ [32], zeolites [33], $RuCl_3$ [34], Bronsted acidic ionic liquids [35] and H_2SO_4

in AcOH [36], but many of them suffer from the drawbacks of lower yields and harsh, environmentally detrimental reaction conditions. In continuation of our interest in the synthesis of different flavonoid derivatives using conventional and microwave irradiation techniques, it was our effort to develop an efficient method for synthesis of flavanones by using an inexpensive, safe, simple and common reagent. Alkali metal carbonates are weak bases and they are nontoxic in nature. Therefore, we endeavored to utilize anhydrous K_2CO_3 for the synthesis of flavanones particularly because there are several recent applications of this base in the synthesis of flavonoids [37]. Initially, laboratory experiments were performed using K_2CO_3 in various solvents DMF, ethanol, *tert*-butanol and 1,4-dioxane. It was observed that the optimum conversion and yield of the flavonoid derivatives were almost same in all the solvents except 1,4-dioxane within comparable time spans. We have opted environmentally benign, non toxic and low boiling ethanol for all the cases studied. Structures of all the new compounds **3(a-t)** were unambiguously confirmed by IR, ^{1}H NMR, ^{13}C NMR and MS.

MATERIALS AND METHODS

Melting points were determined using a Büchi apparatus. IR spectra were recorded for KBr disc on a Mattson 5000 FTIR spectrometer. All of the commercial chemicals and solvents were of reagent grade and were used without further purification. ^{1}H and ^{13} NMR spectra were measured on a Bruker WP 300 / 400 in DMSO-d_6 as solvent, using TMS as internal standard, chemical shifts are expressed as δ/ppm and *J* values are given in Hz. Mass spectrometric data were determined using an Agilent 6890 series instrument. TGA analysis was done by SHIMADZU Thermal Analyzer (DTG-60). The progress of the reaction was monitored by TLC using aluminum silica gel plates 60 F_{245}. Products were purified by flash column chromatography using silica gel (60-120 mesh).

Table 1: Physicochemical data of synthesized chalcone derivatives 3(a-t)

Compound	Ar	Molecular formula	M. P. (^{o}C)
3a	2-OCH_3-pyridine-3-yl	$C_{15}H_{15}NO_3$	116-119
3b	2-Cl, 3-CF_3-phenyl	$C_{16}H_{12}ClF_3O_2$	99-102
3c	3-F, 2-CH_3-phenyl	$C_{16}H_{15}FO_2$	133-135
3d	2-Br, 5-Cl-phenyl	$C_{15}H_{12}BrClO_2$	112-114
3e	4-(benzyloxy)phenyl	$C_{22}H_{20}O_3$	116-119
3f	naphthalen-2-yl	$C_{19}H_{16}O_2$	111-113
3g	biphenyl-2-yl	$C_{21}H_{18}O_2$	119-121
3h	3,5-Br_2,2-OH,4-OCH_3-phenyl	$C_{16}H_{14}Br_2O_4$	112-114
3i	4-(methylsulfonyl)phenyl	$C_{16}H_{16}O_4S$	89-91
3j	2-(benzyloxy)phenyl	$C_{22}H_{20}O_3$	102-105
3k	2-(4-fluorophenoxy)phenyl	$C_{21}H_{17}FO_3$	99-101
3l	2,5-difluoro-phenyl	$C_{15}H_{12}F_2O_2$	102-104
3m	2-Cl,5-NO_2-phenyl	$C_{15}H_{12}ClNO_4$	125-128
3n	4-(benzyloxy)-3-methoxyphenyl	$C_{23}H_{22}O_4$	110-112
3o	3,5-bis(trifluoromethyl)phenyl	$C_{17}H_{12}F_6O_2$	107-109
3p	2-F, 4-CF_3-phenyl	$C_{16}H_{12}F_4O_2$	102-104
3q	4-(1*H*-imidazol-1-yl)phenyl	$C_{18}H_{16}N_2O_2$	112-114
3r	5-methylfuran-2-yl	$C_{14}H_{14}O_3$	80-82
3s	3-methylthiophen-2-yl	$C_{14}H_{14}O_2S$	87-89
3t	6-(trifluoromethyl)pyridin-3-yl	$C_{15}H_{12}F_3NO_2$	118-121

General procedure for the synthesis of 3-acetyl-2,5-dimethylfuran (2):

To a solution of acetylacetone in toluene (2g, 0.02 moles) were added propargyl bromide (0.02 moles), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.04 moles) and a catalytic amount of CuI (0.002 moles). The resulting mixture was heated to 90 ^{o}C under nitrogen atmosphere for 5 hrs. Solvents were removed and the residue was subjected to the column chromatography using silica gel eluting with a 95/5 ratio of n-hexane and ethyl acetate mixture to obtain a title compound **(2)**, which was confirmed by IR, ^{1}H & ^{13}C NMR and mass. ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.21 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.42 (s, 3H, -$COCH_3$), 6.09 (s, 1H, furyl-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 189.42, 159.14, 152.70, 124.40, 106.24, 34.65, 14.64, 13.42. IR (KBr, ν cm^{-1}): 1664 (C=O). MS (ESI) m/z: 139.2 $(M+H)^+$.

General procedure for the synthesis of chalcones 3(a-t) using conventional heating method:

A solution of 3-acetyl-2,5-dimethylfuran (1mmol) and the various substituted aromatic aldehyde (1mmol) in dry ethanol (25 ml) was refluxed with added anhydrous K_2CO_3 (1.5 g), monitoring the progress of reaction by TLC and

LCMS. The reaction was stopped at the appropriate point (3-6 h), the reaction mixture was worked up and subjected to column chromatography over silica gel (60-120 mesh) using 10-15% ethyl acetate in hexane as eluent.

General procedure for the synthesis of chalcones 3(a-t) under the microwave irradiation:
A mixture of 3-acetyl-2,5-dimethylfuran (1mmol), various substituted aromatic aldehyde (1mmol) and anhydrous K_2CO_3 (1.5 g) in the presence of minimal quantity of dry ethanol, was subjected to microwave irradiation at 100 ^oC (for 6 min, entries **3a**, **3(c-h)** and **3(j-t)** or 100 ^oC (for 30 min , entry **3b** and **3i**), monitoring the progress of reaction by TLC and mass. The reaction mixture was worked up and subjected to column chromatography over silica gel (60-120 mesh) using 10-15% ethyl acetate in hexane as eluent. Physicochemical data and comparative study of the title compounds are presented in **Table 1** and **2**.

Table 2: Anhyd. K_2CO_3 catalyzed synthesis of flavanones

Compound	Conventional method		MW irradiation method	
	Time	%Yield	Time	%Yield
3a	4 h	42	6 min	47
3b	3 h	58	30 min	61
3c	3 h	57	6 min	59
3d	3 h	62	6 min	66
3e	3 h	24	6 min	29
3f	6 h	49	6 min	54
3g	3 h	28	6 min	39
3h	6 h	54	6 min	59
3i	3 h	46	30 min	50
3j	3 h	42	6 min	44
3k	3 h	44	6 min	58
3l	3 h	58	6 min	69
3m	3 h	51	6 min	57
3n	3 h	59	6 min	73
3o	4 h	64	6 min	72
3p	3 h	62	6 min	65
3q	3 h	24	6 min	28
3r	3 h	45	6 min	49
3s	3 h	62	6 min	55
3t	3 h	51	6 min	53

Spectral Data

3-(2-Methoxypyridin-3-yl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3a)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.98 (s, 3H, -OCH_3), 6.70 (s, 1H, furyl-H), 7.08-7.11 (m, 1H, Ar-H), 7.56 (d, 1H, *J*=15.80 Hz, -CO-CH), 7.74 (d, 1H, *J*=15.80 Hz, =CH-Ar), 8.23-8.28 (m, 2H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.67, 159.20, 155.27, 146.21, 136.51, 134.45, 131.10, 128.80, 128.31, 126.31, 126.10, 123.23, 56.70, 14.67, 13.72. IR (KBr, ν cm^{-1}): 1657 (C=O), 1619 (C=C of Ar), 1562 (CH=CH), 1021 (C-O). MS (ESI) m/z: 258.28 $(M+H)^+$.

3-(2-Chloro-3-(trifluoromethyl)phenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3b)
^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 2.26 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 6.78 (s, 1H, furyl-H), 7.59 (d, 1H, *J*=15.60 Hz, -CO-CH), 7.62-7.65 (m, 1H, Ar-H), 7.90-7.92 (m, 1H, Ar-H), 7.95 (d, 1H, *J*=15.60 Hz, =CH-Ar), 8.37 (d, 1H, *J*=7.72 Hz, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.97, 159.21, 157.27, 145.28, 136.81, 134.50, 132.10, 129.81, 128.34, 126.39, 125.10, 124.27, 123.28, 106.70, 14.60, 13.79. IR (KBr, ν cm^{-1}): 1648 (C=O), 1612 (C=C of Ar), 1558 (CH=CH), 1018 (C-O). MS (ESI) m/z: 329.1 $(M+H)^+$.

1-(2,5-dimethylfuran-3-yl)-3-(3-fluoro-2-methylphenyl)prop-2-en-1-one (3c)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.26 (s, 3H, CH_3), 2.30 (s, 3H, Ar-CH3), 2.55 (s, 3H, CH_3), 6.77 (s, 1H, furyl-H), 7.20-7.24 (m, 1H, Ar-H), 7.26-7.32 (m, 1H, Ar-H), 7.41 (d, 1H, *J*=15.5 Hz, -CO-CH), 7.73-7.75 (m, 1H, Ar-H), 7.82 (d, 1H, *J*=15.5 Hz, =CH-Ar). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.15, 161.21, 158.91, 152.31, 146.12, 138.12, 127.33, 125.23, 122.44, 121.95, 121.44, 115.12, 104.24, 14.47, 13.54, 13.28. IR (KBr, ν cm^{-1}): 1662 (C=O), 1617 (C=C of Ar), 1561 (CH=CH), 1069 (C-O). MS (ESI) m/z: 258.9 $(M+H)^+$.

3-(2-Bromo-5-chlorophenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3d)
^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 2.20 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.86 (s, 1H, furyl-H), 7.38-7.42 (m, 1H, Ar-H), 7.59 (d, 1H, *J*=15.54 Hz, -CO-CH), 7.70-7.73 (m, 1H, Ar-H), 7.77 (d, 1H, *J*=15.54 Hz, =CH-Ar), 8.21-8.22 (m, 1H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.07, 159.24, 157.70, 146.28, 135.80, 135.50, 133.10, 129.27, 128.30, 126.56, 125.28, 124.70, 122.26, 14.61, 13.70. IR (KBr, ν cm^{-1}): 1656 (C=O), 16072 (C=C of Ar), 1558 (CH=CH), 1023 (C-O). ESI MS (ESI) m/z: 340.8 $(M+H)^+$.

3-(4-(Benzyloxy)phenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3e)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 5.17 (s, 2H, -CH_2Ph), 6.76 (s, 1H, furyl-H), 7.07-7.09 (m, 2H, Ar-H), 7.35 (d, 1H, *J*=15.60 Hz, -CO-CH), 7.38-7.47 (m, 5H, Ar-H), 7.58 (d, 1H, *J*=15.60 Hz, =CH-Ar), 7.77-7.79 (m, 2H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.04, 159.24, 157.20, 146.21, 145.18, 136.80, 136.50, 133.28, 132.10, 129.80, 128.36, 128.10, 126.49, 125.16, 125.09, 124.22, 124.10, 123.18, 109.70, 68.07, 14.61, 13.70. IR (KBr, ν cm^{-1}): 1658 (C=O), 1616 (C=C of Ar), 1556 (CH=CH), 1010 (C-O). MS (ESI) m/z: 333.2 $(M+H)^+$.

1-(2,5-dimethylfuran-3-yl)-3-(naphthalen-2-yl)prop-2-en-1-one (3f)
^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 2.20 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 6.82 (s, 1H, furyl-H), 7.53-7.56 (m, 2H, Ar-H), 7.59 (d, 1H, *J*=15.60 Hz, -CO-CH), 7.76 (d, 1H, *J*=15.60 Hz, =CH-Ar), 7.93-7.96 (m, 3H, Ar-H), 8.02-8.05 (m, 1H, Ar-H), 8.26 (s, 1H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.16, 159.28, 157.76, 146.18, 135.86, 135.50, 134.10, 133.20, 129.24, 128.30, 126.56, 125.28, 125.18, 124.70, 123.10, 122.26, 108.16, 14.62, 13.74. IR (KBr, ν cm^{-1}): 1656 (C=O), 1609 (C=C of Ar), 1558 (CH=CH), 1023 (C-O). MS (ESI) m/z: 276.9 $(M+H)^+$.

3-(biphenyl-2yl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3g)
^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 2.25 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.73 (s, 1H, furyl-H), 7.31-7.33 (m, 2H, Ar-H), 7.41 (d, 1H, *J*=15.50 Hz, -CO-CH), 7.42 (m, 6H, Ar-H), 7.56 (d, 1H, *J*=15.50 Hz, =CH-Ar), 8.09-8.11 (m, 1H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.22, 158.20, 151.27, 145.10, 136.57, 135.37, 135.12, 133.45, 131.10, 129.80, 128.31, 127.40, 127.15, 126.31, 126.10, 125.81, 125.34, 124.89, 122.70, 14.62, 13.70. IR (KBr, ν cm^{-1}): 1667 (C=O), 1617 (C=C of Ar), 1570 (CH=CH), 1040 (C-O). MS (ESI) m/z: 303.3 $(M+H)^+$.

3-(3,5-dibromo-2-hydroxy-4-methoxyphenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3h)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.23 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.66 (s, 3H, -OCH_3), 6.50 (s, 1H, furyl-H), 7.34 (s, 1H, Ar-H), 7.53 (d, 1H, *J*=15.8 Hz, -CO-CH), 7.67 (d, 1H, *J*=15.8 Hz, =CH-Ar). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 186.16, 169.59, 155.97, 155.46, 149.54, 143.06, 132.50, 123.61, 121.17, 117.65, 112.89, 106.80, 92.85, 59.76, 14.41, 13.42. IR (KBr, ν m^{-1}): 1646 (C=O), 1616 (C=C of Ar), 1499 (CH=CH), 1021 (C-O). MS (ESI) m/z: 430 $(M+H)^+$.

1-(2,5-dimethylfuran-3-yl)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-one (3i)
^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 2.26 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.24 (s, 3H, -SO_2CH_3), 6.80 (s, 1H, furyl-H), 7.65 (s, 2H, Ar-H), 7.93 (d, 1H, *J*=15.42 Hz, -CO-CH), 7.96 -8.06 (m, 2H, Ar-H), 8.1 (d, 1H, *J*=15.42 Hz, =CH-Ar). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 184.64, 157.64, 149.86, 141.60, 139.97, 139.51, 129.31, 128.20, 128.46, 127.52, 127.40, 122.20, 106.20, 43.34, 14.11, 12.94. IR (KBr, ν cm^{-1}): 1660 (C=O), 1618 (C=C of Ar), 1561 (CH=CH), 1085 (C-O). MS (ESI) m/z: 304.9 $(M+H)^+$.

3-(2-(benzyloxy)phenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3j)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.23 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 5.21 (s, 2H, -CH_2Ph), 6.34 (s, 1H, furyl-H), 7.02-7.05 (m, 1H, Ar-H), 7.23 (d, 1H, *J*=15.50 Hz, -CO-CH), 7.40-7.49 (m, 6H, Ar-H), 7.53 (d, 1H, *J*=15.60 Hz, =CH-Ar), 7.82-7.88 (m, 2H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.16, 159.28, 157.76, 146.18, 135.86, 135.50, 134.10, 133.20, 132.18, 129.24, 128.30, 128.10, 126.56, 125.28, 125.18, 124.70, 123.16, 122.20, 108.16, 68.09, 14.61, 13.68. IR (KBr, ν cm^{-1}): 1659 (C=O), 1607 (C=C of Ar), 1555 (CH=CH), 1020 (C-O). MS (ESI) m/z: 333.3 $(M+H)^+$.

3-(2-(4-fluorophenoxy)phenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3k)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.26 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 6.71 (s, 1H, furyl-H), 6.92 (d, 1H, *J*=8.2 Hz, Ar-H), 7.05-7.08 (m, 2H, Ar-H), 7.23-7.27 (m, 3H, Ar-H), 7.45 (t, 1H, *J*=7.6 Hz, Ar-H), 7.54 (d, 1H, *J*=15.8 Hz, -CO-CH), 7.86 (d, 1H, *J*=15.8 Hz, =CH-Ar), 8.1 (d, 1H, *J*=7.72 Hz, Ar-H). ^{13}C NMR (75.46 MHz,

DMSO-d_6, δ, ppm) 185.25, 160.28, 157.71, 156.00, 153.27, 150.25, 135.93, 132.63, 129.08, 126.19, 125.97, 124.61, 122.64, 120.44, 119.38, 117.04, 106.55, 14.51, 13.38. IR (KBr, ν cm^{-1}): 1657 (C=O), 1615 (C=C of Ar), 1501(CH=CH), 1040 (C-O). MS (ESI) m/z: 337 $(M+H)^+$.

3-(2,5-difluorophenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3l)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 6.80 (s, 1H, furyl-H), 7.33-7.37 (m, 2H, Ar-H), 7.59 (d, 1H, *J*=15.90 Hz, -CO-CH), 7.64 (d, 1H, *J*=15.90 Hz, =CH-Ar), 7.97-8.01 (m, 1H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.68, 160.44, 159.13, 157.26, 155.85, 150.32, 132.55, 128.08, 124.09, 122.50, 119.20, 118.03, 106.58, 14.53, 13.36. IR (KBr, ν cm^{-1}): 1661 (C=O), 1621 (C=C of Ar), 1562 (CH=CH), 1010 (C-O). MS (ESI) m/z: 263 $(M+H)^+$.

3-(2-chloro-5-nitrophenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3m)
^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 6.92 (s, 1H, furyl-H), 7.78 (d, 1H, *J*=15.60 Hz, -CO-CH), 7.81-7.84 (m, 1H, Ar-H), 7.89 (d, 1H, *J*=15.96 Hz, =CH-Ar), 8.22-8.25 (m, 1H, Ar-H), 8.90 (m, 1H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 184.18, 158.44, 152.73, 146.21, 145.20, 137.32, 135.40, 131.90, 130.03, 129.70, 126.10, 123.54, 106.73, 14.49, 13.37. IR (KBr, ν cm^{-1}): 1660 (C=O), 1618 (C=C of Ar), 1518 (CH=CH), 1010 (C-O). MS (ESI) m/z: 306.1 $(M+H)^+$.

3-(4-(benzyloxy)-3-methoxyphenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3n)
^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 2.26 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.83 (s, 3H, -OCH_3), 5.13 (s, 2H, -CH_2Ph), 6.77 (s, 1H, furyl-H), 7.06-7.09 (m, 1H, Ar-H), 7.23-7.43 (m, 7H, Ar-H), 7.48 (d, 1H, *J*=15.60 Hz, -CO-CH), 7.55 (d, 1H, *J*=15.60 Hz, =CH-Ar). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.31, 157.26, 153.63, 150.51, 149.75, 142.96, 137.22, 136.77, 130.21, 128.96, 128.32, 128.12, 126.34, 123.80, 122.72, 119.7, 113.61, 110.20, 106.75, 70.28, 56.20, 14.14, 13.41. IR (KBr, ν cm^{-1}): 1677 (C=O), 1616 (C=C of Ar), 1501 (CH=CH), 1019 (C-O). MS (ESI) m/z: 363.1 $(M+H)^+$.

3-(3,5-bis(trifluoromethyl)phenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3o)
^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.89 (s, 1H, furyl-H), 7.73 (d, 1H, *J*=15.82 Hz, -CO-CH), 7.83 (d, 1H, *J*=15.82 Hz, =CH-Ar), 8.09 (s, 1H, Ar-H), 8.57 (s, 2H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 184.12, 162.30, 158.02, 152.70, 145.27, 135.87, 131.76, 126.43, 125.10, 122.34, 121.40, 104.76, 14.52, 13.65. IR (KBr, ν cm^{-1}): 1666 (C=O), 1619 (C=C of Ar), 1563 (CH=CH), 1010 (C-O). MS (ESI) m/z: 364.1 $(M+H)^+$.

3-(2-fluoro-4-(trifluoromethyl)phenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3p)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.79 (s, 1H, furyl-H), 7.67 (d, 1H, *J*=15.80 Hz, -CO-CH), 7.68-7.69 (m, 2H, Ar-H), 7.81 (d, 1H, *J*=15.80 Hz, =CH-Ar), 8.26-8.30 (m, 1H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 184.78, 159.12, 158.32, 150.46, 132.19, 130.73, 130.69, 129.41, 126.82, 122.47, 122.15, 114.28, 113.94, 106.53, 14.58, 13.36. IR (KBr, ν cm^{-1}): 1662 (C=O), 1617 (C=C of Ar), 1509 (CH=CH), 1065 (C-O). MS (ESI) m/z: 313 $(M+H)^+$.

3-(4-(*1H*-imidazol-1-yl)phenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3q)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.83 (s, 1H, furyl-H), 7.14 (s, 1H, imidazol-H), 7.55 (d, 1H, *J*=15.68 Hz, -CO-CH), 7.66 (d, 1H, *J*=15.68 Hz, =CH-Ar), 7.76 (d, 2H, *J*=8.52 Hz, Ar-H), 7.87 (s, 1H, imidazol-H), 7.99 (d, 2H, *J*=8.52 Hz, Ar-H), 8.4 (s, 1H, -NCHN-). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.26, 157.64, 150.17, 141.44, 138.51, 136.06, 133.47, 132.2, 130.77, 130.59, 129.6, 125.04, 122.70, 120.63, 118.22, 106.72, 14.54, 13.41 IR (KBr, ν cm^{-1}): 1654 (C=O), 1611 (C=C of Ar), 1517 (CH=CH), 1059 (C-O). MS (ESI) m/z: 293.2 $(M+H)^+$.

3-(5-methylfuran-2-yl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3r)
^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 2.23 (s, 3H, CH_3), 2.34 (s, 3H, furyl-CH_3), 2.51 (s, 3H, CH_3), 6.29-6.30 (m, 1H, furyl-H), 6.59 (s, 1H, furyl-H), 6.91-6.93 (m, 1H, furyl-H), 7.00 (d, 1H, *J*=15.40 Hz, -CO-CH), 7.35 (d, 1H, *J*=15.40 Hz, =CH-Ar). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 184.26, 158.26, 154.54, 152.70, 149.80, 131.51, 127.46, 125.32, 112.14, 109.52, 104.71, 14.42, 14.21, 13.52. IR (KBr, ν cm^{-1}): 1653 (C=O), 1609 (C=C of Ar), 1559 (CH=CH), 1012 (C-O). MS (ESI) m/z: 231.1 $(M+H)^+$.

1-(2,5-dimethylfuran-3-yl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one (3s)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.26 (s, 3H, CH_3), 2.34 (s, 3H, thiophen-CH_3), 2.54 (s, 3H, CH_3), 6.65 (s, 1H, furyl-H), 7.00 (d, 1H, *J*=15.20 Hz, -CO-CH), 7.01-7.02 (m, 1H, thiophen-H), 7.64-7.65 (m, 1H, thiophen-H), 7.79 (d, 1H, *J*=15.20 Hz, =CH-Ar). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 184.57, 159.02, 152.89, 138.20, 134.20, 131.97, 130.40, 127.40, 126.30, 125.34, 106.7, 14.49, 14.35, 13.34. IR (KBr, ν cm^{-1}): 1651 (C=O), 1616 (C=C of Ar), 1574 (CH=CH), 1006 (C-O). MS (ESI) m/z: 247 $(M+H)^+$.

3-(6-(trifluoromethyl)pyridin-3-yl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (3t)
^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 6.82 (s, 1H, furyl-H), 7.66-7.99 (q, 2H, Ar-H), 7.98 (d, 1H, *J*=15.26 Hz, -CO-CH), 8.55 (d, 1H, *J*=15.26 Hz, =CH-Ar), 9.16 (s, 1H, Ar-H). ^{13}C NMR (75.46 MHz, DMSO-d_6, δ, ppm) 185.17, 159.20, 157.72, 152.7, 149.3, 146.20, 135.16, 135.50, 134.18, 133.21, 132.18, 129.26, 108.09, 14.68, 13.70. IR (KBr, ν cm^{-1}): 1669 (C=O), 1621 (C=C of Ar), 1565 (CH=CH), 1012 (C-O). MS (ESI) m/z: 262.2 $(M+H)^+$.

Table 3: MIC (µg/mL) of active compounds 3(a-t) against various bacterial and fungal strains

Compound	*K. Pneumonia* [ATCC-13883]	*S. Aureus* [ATCC-25923]	*E. coli* [ATCC-9637]	*R. Arrhizus* [ATCC-11145]	*C. Albicans* [ATCC-28366]	*A. Niger* [ATCC-26036]
3a	43.2	21.7	12.5	61.8	76	>100
3b	28.02	58.1	33	>100	46	92
3c	34.1	29	0	17.2	12.5	9.9
3d	74	0	>100	15.6	>100	78.4
3e	>100	26	65	32.1	>100	61.4
3f	0	45.8	29.7	>100	88.5	94
3g	12.5	32.2	0	>100	0	16.2
3h	18.2	2.9	32.7	8.6	17.1	23.6
3i	3.2	27.6	>100	0	46	0
3j	52.08	0	>100	31.2	0	>100
3k	26.04	16.5	>100	46	41.7	>100
3l	>100	22.9	45	>100	0	>100
3m	17.1	9.6	74	>100	35	>100
3n	>100	33	50	16.9	74.2	0
3o	28.4	31.6	>100	22.5	>100	16.3
3p	45.87	30.5	19.1	32.7	>100	71.2
3q	21.2	6.3	32.1	78.2	37.8	40.5
3r	29.3	4.1	37.19	0	82.6	>100
3s	12.5	8.4	14.2	3.9	10.5	44.5
3t	18.7	7.5	47.5	9.8	31.2	71.5
Ciprofloxacin	1.2	1.71	0.86	-	-	-
Fluconazole	-	-	-	1.9	2.7	1.9

Antimicrobial activity
The antimicrobial activity of newly synthesized compounds **3(a-t)** were determined by well plate method in nutrient agar for antibacterial activity and Sabouraud dextrose agar for antifungal activity [38]. In this work, *Escherichia coli* [ATCC-9637], *Staphylococcus aureus* [ATCC-25923] and *Klebsiella pneumonia* [ATCC-13883] were used to investigate the antibacterial activities. Similarly, *Candida albicans* [ATCC-28366], *Rhizopus arrhizus* [ATCC-11145] and *Aspegillus niger* [ATCC-26036] were used to investigate the antifungal activities against their reference standard. Minimum inhibitory concentration (MIC) of all compounds was determined, which is defined as the lowest concentration of inhibitor at which bacterial growth was not visually apparent. The initial optical density (OD) of the medium was measured by spectrophotometer at 600 nm. Different concentrations of compounds (5, 10, 25 and 50 µg/ml) were tested for the inhibition of growth of these microbes in separate tubes. The activity of compounds was determined in comparison to standard antibiotic disc of Ciprofloxacin (10µg) and Fluconazole (10µg) respectively. Investigation on antimicrobial screening data **Table 3** showed some of the compounds were active against various microbial organisms.

Single crystal growth and characterization for Compound (3s):
The solubility studies in different solvents showed that the compound is insoluble in water and highly soluble in methanol and ethanol. Based on various experimental results, ethanol was used as solvent system to grow single crystals of title compound **(3s)**. A known volume of solvent was taken in a clear glass 5ml vial with plastic screw cap, which was immersed in a constant temperature bath. The mixture was heated to obtain clear solution. Vial was

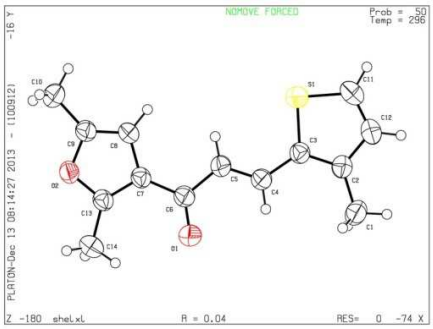
tightly capped and allowed to cool to room temperature. After cooling tiny particles of the original crystals are seen at the bottom of the vial and kept for another two days at room temperature.

The molecular structure of (**3s)** was depicted in **Figure 1**. A good quality single crystal of dimension 0.35x0.30x0.25 mm was used for data collection using Bruker kappa Apex II diffractometer. The data was collected at room temperature using Mo K alpha radiation at a generator setting of 50 KV and 30 mA. Cell refinement was done using APEX2/SAINT. Data reduction was done using SAINT/ XPREP. Multi-scan absorption correction method was followed with reference to SADABS. The structure was solved using SIR92 in Wingx suite and refinements were done with SHELXL-97 [39] in the WinGx package suite (Version 1.80.05) [40]. The crystallographic details are provided in **Table 4**. The compound crystallized in the monoclinic, space group C2/c. The compound exist in *E* configurations with respect to their C_4=C_5 double bonds with bond distances of 1.323 (3) Å.

Table 4: Crystal data and structure refinement for the compound (3s)

Empirical formula	C_{14} H_{14} O_2 S
Formula weight	246.31
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 24.8531(13) A alpha = 90 deg
	b = 7.5673(4) A beta = 130.787(6) deg
	c = 17.9810(10) A gamma = 90 deg
Volume	2560.4(2) A^3
Z, Calculated density	8, 1.278 Mg/m^3
Absorption coefficient	0.240 mm^-1
F(000)	1040
Crystal size	0.35 x 0.30 x 0.25 mm
Theta range for data collection	2.16 to 28.21 deg
Limiting indices	-32<=h<=32, -8<=k<=10, -23<=l<=23
Reflections collected / unique	9514 / 3087 [R(int) = 0.0267]
Completeness to theta = 28.21	98.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9425 and 0.9208
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3087 / 0 / 157
Goodness-of-fit on F^2	1.015
Final R indices [I>2sigma(I)]	R1 = 0.0430, wR2 = 0.1090
R indices (all data)	R1 = 0.0752, wR2 = 0.1274
Largest diff. peak and hole	0.209 and -0.212 e.A^-3

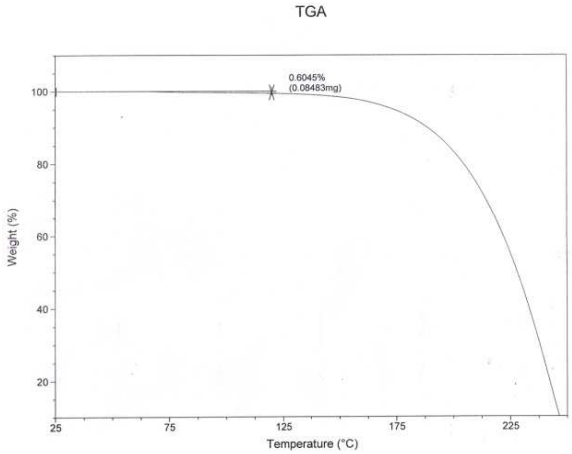
Figure 1: Molecular structures of compound (3s) with atom numbering schemes



Thermogravimetric analysis

The thermal property of 1-(2,5-dimethylfuran-3-yl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one **(3s)** was studied in the powder form by recording the TGA response curve in the temperature range 25 ^oC to 230 ^oC, at a rate of 10 ^oC /min, in air using SHIMADZU Thermal Analyzer (DTG-60). The TGA plot shown in **Figure 2** shows good thermal stability for the compound up to 120 ^oC.

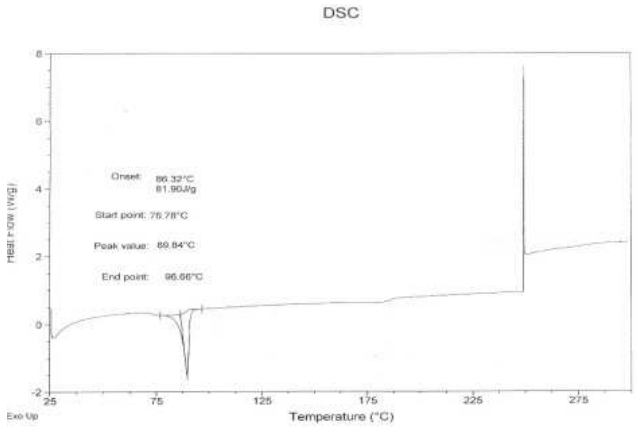
Figure 2: TGA curve of 1-(2,5-dimethylfuran-3-yl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one



DSC analysis

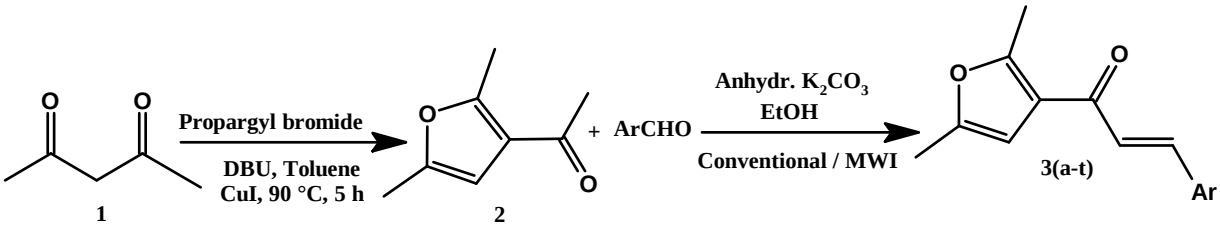
The DSC curve indicates that there is no phase transition before melting. The endothermic peak at 76.78 °C in compound **(3s)** shown in **Figure 3** exactly correlates to its melting point (76 °C-97 °C). The sharpness of endothermic peak indicates relative purity and crystalline compound. The heat of fusion (ΔHfus) or enthalpy of fusion of organic compound was found to be 81.90 J/g and molar heat of fusion as 0.0819 KJ/mole, this show exact phase transition from solid state to liquid state.

Figure 3: DSC spectrum of 1-(2,5-dimethylfuran-3-yl)-3-(3-methylthiophen-2-yl)prop-2-en-1-one



RESULTS AND DISCUSSION

The novel heterocyclic chalcone derivatives were synthesized by classical as well as microwave irradiation method using anhydrous potassium carbonate condition. Microwave irradiation method was reduced the time of reaction completion and improves yield of products (6-30 sec. and 29-73%) than classical method (3-6 hr and 24-64%). All the synthesized compounds were characterized by IR, ^{1}H & ^{13}C NMR and Mass spectral analysis. Based on biological results, compound-**3s** was subjected to single crystal XRD, Thermogravimetric analysis and Differential scanning calorimetry. The spectral data confirms the presence of −C═O, −C═C− and aromatic ring by (IR at 1666-1640, 1595-1510 and 856 cm^{-1} respectively. ^{1}H NMR chemical shifts in the range of (7.76 to 8.0) ppm also confirms the presence of aromatic rings. The C_{α}-C_{β} double bond in the enone moiety of chalcones can potentially adopt either a *Z* or an *E* configuration. The ^{1}H NMR spectrum of each compounds exhibited CH=CH protons around 7.41-8.55 ppm, with $J > 15$, would suggest that the compounds were an (*E*) configuration.



Scheme 1: Synthesis of various heterocyclic chalcone derivatives Ar-Various substituted aromatic compounds

Antimicrobial activity

The results of antimicrobial activity of newly synthesized compounds **3(a-t)** reveal that out of twenty compounds, eight compounds were found to have good antibacterial activity and five compounds showed good antifungal activity. Compound **3s** showed significant antibacterial activity against all three bacterial strains such as *Klebsiella pneumonia*, *Staphylococcus aureus* and *Escherichia coli* with MIC range between 8.4-14.2. Compound **3h** displayed excellent antibacterial activity with MIC 2.9 *against Staphylococcus aureus*. Compounds **3k**, **3m**, **3q, 3t** and **3r** were exhibited significant activity against *Staphylococcus aureus* with MIC range between 4.1-16.5. Compound **3i** also showed potential activity against *Klebsiella pneumonia* with MIC 3.2. The antifungal activity of compounds was determined in comparison to standard antifungal drug Fluconazole (10µg). Compound **3s** showed significant antifungal potent against *Rhizopus arrhizus* and *Candida albicans* with MIC 3.9 and 10.5 respectively. Compound **3c** displayed significant antifungal activity for all three fungal strains with MIC between 9.9-17.2. Compound **3h** also displayed good antifungal activity against *Rhizopus arrhizus* and *Candida albicans* with MIC 8.6 and 17.1 respectively. Compounds **3g** and **3o** were shown moderate activity against *Aspegillus niger* with MIC 16.2 and 16.3 respectively. The activity of DMSO has been tested for the above organisms and it was found to be inactive.

CONCLUSION

A series of heterocyclic derivatives **3(a-t)** were synthesized by conventional and microwave irradiation method with the use of anhydrous potassium carbonate as an efficient, inexpensive and safe basic catalyst. Microwave irradiation technique helped in reducing the reaction time, improving the yield and purity than conventional method. Thus, it is the time saving and efficient technique for the synthesis of chalcones. All the synthesized compounds were evaluated for in vitro antimicrobial activity against various pathogenic bacterial and fungal strains. Chalcone **3s** showed valuable inhibitory activity against most of the microorganism such as *Klebsiella pneumonia*, *Staphylococcus aureus*, *Escherichia coli*, *Rhizopus arrhizus* and *Candida albicans*. Introducing, methyl substituted thiophene derivative in 2,5-dimethylfuran ring was found to be the most active compound **(3s)** against all the microbial strains except *Aspegillus niger*. Compound **3s** was subjected to various analysis such as single crystal XRD, TGA and DSC. Crystal of compound **(3s)** was successfully grown and subjected to single crystal XRD studies indicated the monoclinic structure of the crystal. The crystal is thermally stable up to 120 ^{o}C. We would like to mention that we have developed simple and efficient methods for the synthesis of flavanones using anhydrous K_2CO_3 as an inexpensive and safe base catalyst.

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