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Synthesis, characterization and biological screening of novel (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted)phenylprop-2-en-1-one

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ABSTRACT

Synthesis of various Chalcones of (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted)phenylprop-2-en-1-one 3(a-o) from 3,5 Bis (trifluoromethyl)acetophenone and substituted benzaldehydes in presence of KOH. The structures of the synthesized compounds were confirmed on the basis of spectral and elemental analysis. The synthesized compounds were screened for antimicrobial activity.

Keywords: Chalcones; 3,5 Bis (trifluoromethyl)acetophenone; substituted benzaldehydes, α,β-unsatutated keto compounds.

INTRODUCTION

Chalcones are well known intermediates for synthesizing various heterocyclic compounds.The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial[1], anti-inflammatory[2], analgesic[3], antiplatelet[4], antiulcerative[5], antimalarial[6], anticancer[7], antiviral[8], antileishmanial[9], antioxidant[10], antitubercular[11], antihyperglycemic[12], immunomodulatory[13], inhibition of chemical mediators release[14], inhibition of leukotriene B4[15], inhibition of tyrosinase[16] and inhibition of aldose reductase[17] activities. The presence of a reactive α,β-unsatutated keto function in chalcones is found to be responsible for their antimicrobial activity.

In the present communication we wish to report the reaction of halosubstituted acetophenone derivatives with different aromatic aldehyde derivatives to form chalcones (3a-o). The structures of the various synthesized compounds were assigned on the basis of IR, 1H-NMR spectral data and elemental analysis. These compounds were also screened for their antimicrobial activity.

MATERIALS AND METHODS

The solvents and reagents used in the synthetic work were of analytical grade obtained from Hi-media and were purified by distillation or crystallization where necessary and their boiling or melting points were compared with the available literature values. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded FTIR Unicorn Maltson 1000 spectrophotometer**.**1H-NMR spectra were recorded on Bruker Ac-80 (80

MHz) spectrometer (300MHz in DMSO-d6) using TMS as internal standard and chemical shifts are indicated in δ (ppm). The progress of the reaction was monitored on precoated silica gel 60 F 254 plates (Merck) using different solvent systems and visualizing the spots under ultraviolet light and iodine chamber. Elemental analyses for C, H and N were carried out using a Perkin -Elmer C, H, and N analyzer.

General method for the preparation of (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted)phenylprop-2-en-1-one[18,19]: A mixture of the 3,5 Bis (trifluoromethyl)acetophenone (0.01 M),substituted benzaldehydes (0.01 M) and potassium hydroxide (0.2 M) was refluxed in methanol (10 ml) for 25 hrs. After cooling, methanol (~10 ml) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted)phenylprop-2-en-1-one which were recrystallized from ethanol.

(3a). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one :
Yield: 77%; MS: *m/z* 374; mp 203ºC; Anal. Calcd. for $C_{18}H_{12}F_6O_2$: C, 57.76; H, 3.23; F, 30.46; O, 8.55; Found: C, 57.54; H, 3.02; F, 30.21; O, 8.23%; IR (cm-1): 3049 (C-H stretching of aromatic ring), 1651 (C=O stretching), 1622, 1564 and 1519 (C=C stretching of aromatic ring), 1640 (C=C stretching of vinyl) 1203 (C-O-C stretching of ether) 1078 (C-H in plane deformation of aromatic ring), 825 (C-H out of plane bending of 1,4-disubutituion), 1012 (C-F stretching); 1H NMR (DMSO-*d6*) δ ppm: 3.86 (s, 3H,-OCH_3), 6.85-6.91 (m, 2H,Aromatic), 7.52 (s, 2H,Aromatic), 7.25(s, 2H, Vicinal), 8.21-8.57(m, 3H,Aromatic Fluorinated ring).

Similarly remaining compounds were confirmed by elemental analysis and their Mass spectra.

(3b). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-p-tolylprop-2-en-1-one:
Yield: 58%; mp 201ºC; Anal. Calcd. for C18H12F6O: C, 60.34; H, 3.38; F, 31.82; O,4.47; Found: C, 60.11; H, 3.12; F, 11.82; O, 4.21%; MS: *m/z* 358.

(3c). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(4-chlorophenyl)prop-2-en-1-one :
Yield: 67%; mp 189ºC; Anal. Calcd. for C17H9ClF6O: C, 53.92; H, 2.40; Cl, 9.36; F, 30.10; O, 4.22; Found: C, 53.17; H, 2.15; Cl, 9.12; F, 30.01; O, 4.11%; MS: *m/z* 379.

(3d). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(4-fluorophenyl)prop-2-en-1-one:
Yield: 68%; mp 186ºC; Anal. Calcd. for C17H9F7O: C, 56.37; H, 2.50; F, 36.71; O,4.42; Found: C, 56.24; H, 2.14; F, 36.35; O, 4.12 %; MS: *m/z* 362.

(3e). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(4-bromophenyl)prop-2-en-1-One:
Yield: 74%; mp 221ºC; Anal. Calcd. for C17H9BrF6O: C, 48.25; H, 2.14; Br, 18.88; F, 26.94; O, 3.78; Found: C, 48.12; H, 2.00; Br, 18.54; F, 26.42; O, 3.21%; MS: *m/z* 423.

(3f). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one :
Yield: 56%; mp 204ºC; Anal. Calcd. for C19H14F6O3: C, 56.44; H, 3.49; F, 28.19; O, 11.87; Found: C, 56.16; H, 3.21; F, 28.01; O, 11.64%; MS: *m/z* 404.

(3g). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(3,4-dichlorophenyl)prop-2-en-1-one:
Yield: 76%; mp 224ºC; Anal. Calcd. for C17H8Cl2F6O: C, 49.42; H, 1.95; Cl, 17.16; F, 27.59; O, 3.87; Found: C, 49.12; H, 1.84; Cl, 17.01; F, 27.24; O, 3.56%; MS: *m/z* 413.

(3h). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(3-methoxyphenyl)prop-2-en-1-one:
Yield: 71%; mp 212ºC; Anal. Calcd. for C18H12F6O2: C, 57.76; H, 3.23; F, 30.46; O, 8.55; Found: C, 57.55; H, 3.05; F, 30.22; O, 8.21%; MS: *m/z* 374.

(3i). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(3-chlorophenyl)prop-2-en-1-one:
Yield: 80%; mp 195ºC; Anal. Calcd. for C17H9ClF6O: C, 53.92; H, 2.40; Cl, 9.36; F, 30.10; O, 4.22; Found: C, 53.13; H, 2.11; Cl, 9.11; F, 30.00; O, 4.09% MS: *m/z* 379.

(3j). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(3-bromophenyl)prop-2-en-1-one:
Yield: 77%; mp 182ºC; Anal. Calcd. for C17H9BrF6O: C, 48.25; H, 2.14; Br, 18.88; F, 26.94; O, 3.78; Found: C, 48.04; H, 2.01; Br, 18.34; F, 26.44; O, 3.12%; MS: *m/z* 423.

(3k). (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(2-chlorophenyl)prop-2-en-1-one:
Yield: 58%; mp 242ºC; Anal. Calcd. for C17H9ClF6O: C, 53.92; H, 2.40; Cl, 9.36;F, 30.10; O, 4.22; Found: C, 53.18; H, 2.11; Cl, 9.12; F, 30.04; O, 4.11% MS: *m/z* 379.

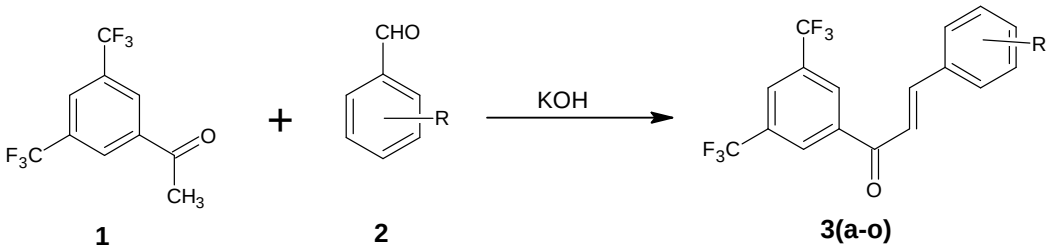
(3l) (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(2-fluorophenyl)prop-2-en-1-one :
Yield: 60%; mp 212ºC; Anal. Calcd. for C17H9F7O: C, 56.37; H, 2.50; F, 36.71; O,4.42; Found: C, 56.21; H, 2.34; F, 36.51; O, 4.12% MS: *m/z* 362.

(3m) (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(2,4-dimethylphenyl)prop-2-en-1-one :
Yield: 62%; mp 224ºC; Anal. Calcd. for C19H14F6O: C, 61.29; H, 3.79; F, 30.62; O,4.30; Found: C, 61.14; H, 3.54; F, 30.22; O, 4.12%; MS: *m/z* 372.

(3n) (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(2-methoxyphenyl)prop-2-en-1-one
Yield: 66%; mp 209ºC; Anal. Calcd. for C18H12F6O2: C, 57.76; H, 3.23; F, 30.46;O, 8.55; Found: C, 57.51; H, 3.04; F, 30.12; O, 8.21%; MS: m/z 374.

(3o) (E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(phenyl)prop-2-en-1-one:
Yield: 76%; mp 200ºC; Anal. Calcd. for C17H10F6O: C, 59.31; H, 2.93; F, 33.11; O,4.65; Found: C, 59.31; H, 2.93; F, 33.11; O, 4.65%; MS: m/z 344.

Reaction Scheme



1 **2** **3(a-o)**

Antimicrobial activity
The in vitro antibacterial activity was performed against Gram-positive bacteria including *Staphylococcus aureus* (**MTCC 96**), *Streptococcus pyogenes* (**MTCC 442**) and Gram negative bacteria including *Escherichia coli* (**MTCC 443**), *Pseudomonas aeruginosa* (**MTCC 424**). Yeast including *Candida albicans* (**MTCC 227**) and fungi *Aspergillus clavatus* (**MTCC 1323**) were used to test antifungal activity. Known antibiotics like **Amplicilline** and **Chloramphenicol** (the reference anti bacterial drugs) and **Fluconazole** (the reference antifungal drug) were used for comparison. The anmicrobial activities are summarized in Table 1.

From the result of antifungal data, compounds **3e, 3f, 3l, 3m** were active against C.albicans. while compounds **3b, 3c, 3h, 3j** were active against A.clavatus. Further in Antibacterial study shows compounds **3g, 3n** were moderately active against S.aures and compounds **3a** shows moderate activity against S.pyrogenes. In case of E.coli compounds **3b, 3g, 3h, 3i, 3j, 3k, 3l** shows moderate activity**.** Remaining compounds did not show any promising activity against tested bacteria and fungi.

RESULTS AND **DISCUSSION**

The different **(**E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted)phenylprop-2-en-1-one were synthesised by the condensation of 3,5 Bis (trifluoromethyl)acetophenone and substituted benzaldehydes in presence of KOH .The M.P. of the synthesised compounds was checked by the given literatures . The purity of compounds was analyzed by TLC. The structures of the synthesized compounds 3(a-o) were confirmed on the basis of spectral and elemental analysis. The IR spectrum of these compounds exhibited bands due to 3049 (C-H stretching of aromatic ring), 1651 (C=O stretching), 1622, 1564 and 1519 (C=C stretching of aromatic ring), 1640 (C=C stretching of vinyl) 1203 (C-O-C stretching of ether) 1078 (C-H in plane deformation of aromatic ring), 825 (C-H out of plane bending of 1,4-disubutituion), 1012 (C-F stretching).

.Further, in their 1H NMR (δ, ppm) spectrum, the appearance of signal at 6.85-6.91 (m, 2H, Aromatic), 7.52 (s, 2H, Aromatic), 7.25(s, 2H, Vicinal), 8.21-8.57(m, 3H, Aromatic Fluorinated ring) confirms the presence of two distinct substitution on aromatic ring along with Vicinal protons which confirms the E orientation.

Table -1: Antibacterial and Antifungal activity of novel Chalcones (3a-o)

Compound No.	Zone diameter of growth inhibition in mm					
	Antibacterial Activity				Antifungal Activity	
	Gram +ve		Gram –ve		*C. albicans*	*A clavatus*
	S. aureus	*S. pyrogenes*	*E. coli*	*P. aeruginosa*		
3a	+	++	+	+	++	++
3b	+	+	++	+	++	+++
3c	+	+	+	+	++	+++
3d	+	+	+	+	++	++
3e	+	+	+	+	+++	++
3f	+	+	+	+	+++	++
3g	++	+	++	+	++	++
3h	+	+	++	+	++	+++
3i	+	+	++	+	++	++
3j	+	+	++	+	++	+++
3k	+	+	++	+	++	++
3l	+	+	++	+	+++	+
3m	+	+	+	+	+++	+
3n	++	+	+	++	++	+
3o	+	+	+	+	+	+
Amplicilline	++	++	++	++	-	-
Chloramphenicol	+++	+++	++	++	-	-
Fluconazole	-	-	-	-	+++	+++

**Effectively was classified in to three zones on the bases of the diameter of zone of inhibition*

+++: Good ++: Moderate +: Poor - : Non effective

CONCLUSION

The newly synthesized compounds **(**E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted)phenylprop-2-en-1-one, compound 3e, 3f, 3l, 3m and 3b, 3c, 3h, 3j were found to be active against C.albicans and A.clavatus respectively as an antifungal compound. In the study of antibacterial study compounds 3g, 3n were moderately active against S.aures and compounds 3a shows moderate activity against S.pyrogenes. In case of E.coli compounds 3b, 3g, 3h, 3i, 3j, 3k, 3l shows moderate activity**.** It can be concluded that this class of compounds certainly holds great promise towards the pursuit to discover novel classes of antimicrobial agents.

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