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SYNTHESIS OF 4-ETHYNYL CHALCONES AS POTENT ANTIBACTERIAL AGENTS

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ABSTRACT

Synthesis of some new biologically active chalcone derivatives **3a-j** was achieved using the classical Claisen-Schmidt reaction utilizing 4-thynylbenzaldehyde and various substituted acetophenones. The structural determination of the newly synthesized chalcone derivatives was made on the basis of the spectroscopic techniques *viz.*, ^{1}H NMR, mass and IR data. These compounds were evaluated for antibacterial screening against Gram positive (*Staphylococcus aureus*, *Streptococcus pyogenes*) and Gram negative pathogens (*Escherichia coli*, *Pseudomonas aeruginosa*) with reference to the standard drug Ciprofloxacin (250µg mL^{-1}). It is observed that chalcones **3b**, **3g**, **3h** and **3j** with R = 4-OMe, 3-OH, 3-CN and 3,4,5-OMe exhibited good antibacterial activity (zone of inhibition; 22-26 mm) while the chalcones **3e** and **3f** with R = H and 3-NO_2 showed moderate antibacterial activity (zone of inhibition: 16-21 mm) and the remaining chalcones in the series such as **3a**, **3c**, **3d** and **3i** with R = 4-Br, 3-Br, 3-Br, 4-F and 4-CH_3 displayed weak antibacterial activity (zone of inhibition: < 16 mm) against tested Gram negative and Gram positive pathogens.

KEYWORDS: Acetophenones, Antibacterial activity, Chalcones, 4-ethynylbenzaldehyde, Synthesis.

1. INTRODUCTION

Chalcones, 1,3-diaryl-2-propen-1-ones, are abundant in edible plants. They are biosynthetic precursors of biologically active flavanoids and isoflavonoids and exhibit broad spectrum of biological activities such as antimicrobial, anticancer, antimalarial, anti-HIV, antipolio,

antitubercular, antidiabetic, antioxidant and anti inflammatory activities.[1-9] Some lead compounds with various pharmacological properties and non toxic at reasonable plasma concentration have been developed based on the chalcone skeleton.[10] Chalcones are good intermediates for the synthesis of various heterocyclic compounds such as isoxazolines, pyrazoles, pyrimidines, pyrans, oxirans, pyridines,[11] oxazoles,[12] and benzothiazepines.[13] For these reasons, chalcones became objects of continued interest in both academia and industry. Synthetic manipulations of chalcones or their isolation from natural products are being investigated worldwide for the development of more potent and efficient drugs for the treatment of several dreadful diseases such as cancer, diabetes, tuberculosis, malaria etc.

Acetylenic metabolites belong to a class of molecules containing triple bond(s). They are found in plants, fungi, microorganisms and marine invertebrates. In the last three decades, biologically active polyacetylenes having unusual structural features have been reported from plants, cyanobacteria, algae, invertebrates and other sources. Many of the naturally occurring aquatic acetylenes display important biological activities such as antitumor, antibacterial, antimicrobial, antifungal, phototoxic, HIV inhibitory and immunosuppressive properties.[14] Acetylenic drugs are frequently more active, less toxic and more easily absorbed into the body than their olefinic and saturated analogs.[15] The acetylenic moiety functions as a key pharmacophoric unit in acetylenic antibiotics[16] and its presence in anticancer[14] and antitubercular[17] agents is noteworthy. Acetylenic chalcones were reported to possess antimalarial and antitubercular activities.[16] In addition, acetylenic compounds play an important role as building blocks in many synthetic transformations and in new materials. In view of the biological importance of the chalcones and acetylene compounds, a set of 4-ethynylchalcones (**3a-j**) have been synthesized and evaluated for their antibacterial activity.

2. MATERIALS AND METHODS

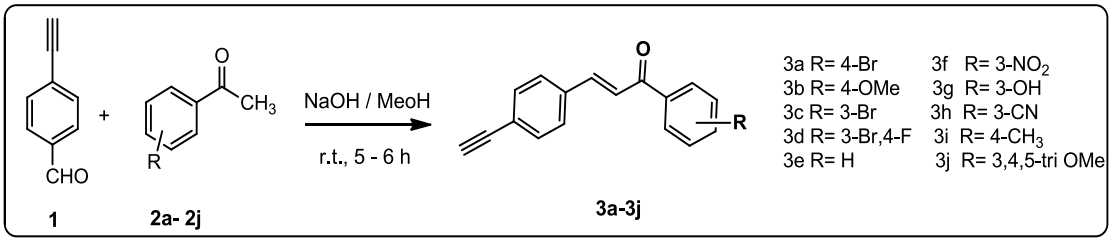
Chemicals and solvents were purchased from Sigma-Aldrich and Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E. Merck AL silica gel 60 F254 plates and visualized under UV light. IR spectra were recorded as KBr pellets with Perkin-Elmer Spectrum GX FTIR instrument and only diagnostic and/or intense peaks were reported. ^{1}H NMR spectra were recorded in $CDCl_3$ with Varian Mercury plus 400 MHz instrument, Broker Biospin Gmbh 300 MHz, 400MHz or 500MHz instruments. Signals due to the residual protonated solvent (^{1}H NMR) served as the internal standard. All the chemical shifts were reported in δ (ppm) using TMS as internal standard. The ^{1}H NMR

chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity was indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (*J*) correspond to the order of multiplicity assignment. Mass spectra were recorded with a PE Sciex model API 3000 instrument. All the reactions were carried out under nitrogen atmosphere.

2.1. EXPERIMENTAL

General experimental procedure for the synthesis of 4-ethynyl chalcone derivatives 3a-j

4-Ethynyl chalcone derivatives were synthesized from 4-ethynylbenzaldehyde as illustrated in **scheme 1**. 4-ethynylbenzaldehyde **1** was prepared in accordance to the literature procedure reported by us recently.[20] To a stirred solution of NaOH (0.16g, 4 mmol) in methanol at room temperature was added corresponding acetophenones **2a-j** (1 mmol) and stirred at the same temperature for 15 min. To the above homogenous reaction mixture was added aldehyde **1** (0.13g, 1 mmol) and stirred for 5-6 h. The reaction mixture was diluted with water and the precipitated solids were filtered and dried at the pump to obtain the corresponding chalcones **3a-j**. Note: In case of the chalcone derivative **3g** (R = 3-hydroxy), 3N HCl was used to neutralize the reaction mixture to isolate compound 3g. Yields of the chalcone derivatives differed from 70- 85%.



Scheme 1: Synthesis of 4-ethynyl chalcones.

Spectral characteristics of (*E*)-1-(4-bromophenyl)-3-(4-ethynylphenyl) prop-2-en-1-one (3a)

Yellow solid; Yield: 85%; M.p: 95-97^{o}C; IR (KBr): ν_{max} (cm^{-1}) 3295 (s, ≡C-H), 1655 (s, C=O), 1606 (s, C=C); 1H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 15.7 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 15.7 Hz, 1H), 3.22 (s, 1H); ESI MS: *m/z* 311 $(M+H)^+$.

Spectral characteristics of (*E*)-3-(4-ethynylphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (3b)

Pale yellow solid; Yield: 80%; M.p: 114-115^{o}C; IR (KBr): ν_{max}(cm^{-1}) 3302(w), 3263 (s, ≡C-H), 3070(w), 3027 (w, Ar-H), 2839(w, OCH_3), 1654 (s, C=O), 1595 (s, C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 15.7 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 15.7 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 3H), 3.20 (s, 1H ; ESI MS: *m/z* 262.8 $(M+H)^{+}$.

Spectral characteristics of (*E*)-1-(3-bromophenyl)-3-(4-ethynylphenyl) prop-2-en-1-one (3c)

Yellow solid; Yield: 78%; M.p: 79-80^{o}C; IR (KBr): ν_{max}(cm^{-1}) 3295 (s, ≡C-H), 1658 (s, C=O), 1604 (s, C=C); 1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 8.16 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 15.7 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.71 – 7.56 (m, 3H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 3.39 (s, 1H); ESI MS: *m/z* 311 $(M+H)^{+}$, 313 $(M+2+H)^{+}$.

Spectral characteristics of (*E*)-1-(3-bromo-4-fluorophenyl)-3-(4-ethynylphenyl) prop-2-en-1-one (3d)

Yellow orange solid; Yield: 80%; M.p: 117-118^{o}C; IR (KBr): ν_{max}(cm^{-1}) 3289(w), 3252 (s, ≡C-H), 3048 (w, Ar-H), 2101 (w, C≡C), 1657 (s, C=O), 1605 (s, C=C); 1H NMR (300 MHz, CDCl3+DMSO-*d6*): δ 8.28 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.12 – 7.95 (m, 1H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 15.6 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.29 (t, *J* = 8.3 Hz, 1H), 3.34 (s, 1H); ESI MS: *m/z* 329 $(M+H)^{+}$.

Spectral characteristics of (*E*)-3-(4-ethynylphenyl)-1-phenylprop-2-en-1-one (3e)

Pale yellow solid; Yield: 84%; M.p: 120-121^{o}C; IR (KBr): ν_{max}(cm^{-1}) 3291(w), 3260 (s, ≡C-H), 2105 (w, C≡C), 1659 (s, C=O), 1603 (s, C=C); ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.76 (d, *J* = 15.7 Hz, 1H), 7.70 – 7.39 (m, 8H), 3.39 (s, 1H); ESI MS: *m/z* 233 $(M+H)^{+}$.

Spectral characteristics of (*E*)-3-(4-ethynylphenyl)-1-(3-nitrophenyl)prop-2-en-1-one (3f)

Dark yellow solid; Yield: 76%; M.p: 104-105^{o}C; IR (KBr): ν_{max}(cm^{-1}) 3287 (w), 3234 (s, ≡C-H), 3082(w), 3031(w, Ar-H), 2102 (w, C≡C), 1659 (s, C=O), 1595 (s, C=C), 1530 (vs,

NO_2), 1348 (vs, NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (t, *J* = 1.7 Hz, 1H), 8.46 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 15.6 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.50 (m, 3H), 3.24 (s, 1H); ESI MS: *m/z* 277.9 $(M+H)^+$.

Spectral characteristics of (*E*)-3-(4-ethynylphenyl)-1-(3-hydroxyphenyl) prop-2-en-1-one (3g)

Yellow solid; Yield: 78%; M.p: 130-131^{o}C; IR (KBr): $\nu_{max}(cm^{-1})$ 3347 (br s, OH), 3250 (s, ≡C-H), 3066(w), 3036 (w, Ar-H), 2104 (w, C≡C), 1652 (s, C=O), 1572 (s, C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 15.7 Hz, 1H), 7.66 – 7.56 (m, 3H), 7.56 – 7.46 (m, 4H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.09 (dd, *J* = 7.9, 2.4 Hz, 1H), 5.16 (s, 1H), 3.21 (s, 1H); ESI MS: *m/z* 248.9 $(M+H)^+$ and 246.9 $(M-H)^+$.

Spectral characteristics of (*E*)-3-(3-(4-ethynylphenyl)acryloyl)benzonitrile (3h)

Pale yellow solid; Yield: 74%; M.p: 119-120^{o}C; IR (KBr): $\nu_{max}(cm^{-1})$ 3297(w), 3248 (s, ≡C-H), 3077 (w, Ar-H), 2231 (m, C≡N), 2103 (w, C≡C), 1664 (s, C=O), 1605 (s, C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 15.6 Hz, 1H), 7.70 – 7.60 (m, 3H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 15.6 Hz, 1H), 3.24 (s, 1H); ESI MS: *m/z* 257.8 $(M+H)^+$.

Spectral characteristics of (*E*)-3-(4-ethynylphenyl)-1-(*p*-tolyl) prop-2-en-1-one (3i)

Pale yellow solid; Yield: 74%; M.p: 108-109^{o}C; IR (KBr): $\nu_{max}(cm^{-1})$ 3298(w), 3250 (s, ≡C-H), 3072 (w, Ar-H), 2970 (w, CH_3), 2102 (w, C≡C), 1660 (s, C=O), 1603 (s, C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 2H), 7.78 (d, *J* = 15.5 Hz, 1H), 7.70-7.44 (m, 4H), 7.43-7.05 (m, 3H), 3.21 (s, 1H), 2.45 (s, 3H); ESI MS: *m/z* 246.9 $(M+H)^+$.

Spectral characteristics of (*E*)-3-(4-ethynylphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (3j)

Pale yellow solid; Yield: 80%; M.p: 123-124^{o}C; IR (KBr): $\nu_{max}(cm^{-1})$ 3293 (s, ≡ C-H), 3076 (w), 3031 (w, Ar-H), 2836 (w, OCH_3), 1656 (s, C=O), 1601 (s, C=C); 1H NMR (400 MHz, CDCl3): δ 7.79 (d, *J* = 15.7 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 15.7 Hz, 1H), 7.28 (s, 2H), 3.96 (s, 6H), 3.95 (s, 3H), 3.22 (s, 1H); ESI MS: *m/z* 322.8 $(M+H)^+$.

2.2. Antibacterial Bioassay

The synthesized chalcone derivatives **3a-j** were tested against Gram negative strains of (*i) Escherichia coli* (MTCC 443) and *(ii) Pseudomonas aeruginosa* (MTCC 424) and Gram positive strains of (i*ii*) *Staphylococcus aureus* (MTCC 96) and (*iv) Streptococcus pyogenes* (MTCC 442) using agar well diffusion method according to the literature protocol.[18,19] The compounds were dissolved in dimethylsulphoxide at 250µg mL^{-1} concentration and Ciprofloxacin was used as the reference antibacterial drug. Antibacterial activity of the compounds was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control. All the samples were taken in triplicate.

3. RESULTS AND DISCUSSION

3.1. Chemistry

Synthesis of chalcone derivatives **3a-j** was achieved using the classical Claisen-Schmidt reaction. Reactions of the acetophenones **2a-j** with 4-ethynylbenzaldehyde **1** in the presence of sodium hydroxide in methanol at room temperature resulted in the formation of corresponding chalcone derivatives **3a-j** in 70-85% yield. The structures of newly synthesized chalcone derivatives **3a-j** were established by spectroscopic techniques like ^{1}H NMR, mass and IR spectral data.

As an example, the ^{1}H NMR spectral details of (*E*)-1-(4-bromophenyl)-3-(4-ethynylphenyl) prop-2-en-1-one (**3a**) is exemplified here: The characteristic olefin protons resonating at 7.78 ppm and 7.47 ppm as doublets with J = 15.7 Hz indicate the existence of chalcone in '*E*' isomeric form. The protons resonating at 7.89 ppm and 7.65 ppm as doublets each with two proton integration are assigned to the 4-Bromo phenyl ring while the protons resonating at 7.60 ppm and 7.54 ppm as doublets each with two proton integration are assigned to the 4-ethynyl phenyl ring. The characteristic acetylenic proton resonated at 3.22 pm as singlet. Similarly, the ^{1}H NMR spectra of the remaining chalcone derivatives are in agreement with the desired structures.

The mass spectra of the compounds showed (M+1) peaks and are in agreement with their molecular formulae. The IR spectra of the compounds **3a-j** represented the characteristic peaks (distinct stretching peaks given in the experimental section) that comply with the desired functional group in the structure. The stretching frequencies at 3302-3234 cm^{-1} and 2105-2101 cm^{-1} corresponds to ≡**C-H** and -**C**≡**C**- groups respectively. The characteristic α, β

unsaturated carbonyl stretching bands appeared in the regions 1606-1572 cm^{-1} (**-C=C-** of enone moiety) and 1664-1654 cm^{-1} (**–C=O**, conjugated with C=C and benzene ring).

3.2. Biology

The newly synthesized compounds **3a-j** were evaluated for *in-vitro* antimicrobial activity against four bacterial strains, *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa*.

Antibacterial activity of chalcone derivatives 3a-j (agar diffusion assay)

The results of the antibacterial activity data are compiled in table -1. From the table 1, it is observed that chalcones **3b**, **3g**, **3h** and **3j** with R = 4-OMe, 3-OH, 3-CN and 3,4,5-OMe exhibit good antibacterial activity (zone of inhibition; 22-26 mm) against the tested Gram negative strains (*viz., E.coli and P.aeruginosa*), while the chalcones **3e** and **3f** with R = H and 3-NO_2 show moderate antibacterial activity (zone of inhibition: 16-21 mm) and the remaining chalcones in the series such as **3a**, **3c**, **3d** and **3i** with R = 4-Br, 3-Br, 3-Br, 4-F and 4-CH_3 display weak antibacterial activity (zone of inhibition: < 16 mm). Similar observations are also seen even in the case of Gram positive pathogens (*S.aureus* and *S.pyogenes*). In general, a further structural modification of the main scaffold by varying "R" may evolve a potential antibacterial drug.

Table-1: Antibacterial Activity of Compounds 3a-j

(Concentration Used 250 µg mL^{-1} of DMSO)

Compound No.	**R**	***Gram negative***		***Gram positive***	
		E.coli MTCC 443	***P.aeruginosa MTCC 424***	***S.aureus MTCC 96***	***S.pyogenes MTCC 442***
		Zones of Inhibition of compounds 3a –j in mm [b]			
3a	4-Br	**12**	**11**	**9-w**	**8**
3b	4-OMe	**23**	**22**	**18-g**	**16**
3c	3-Br	**15**	**14**	**6**	**6**
3d	3-Br,4-F	**13**	**12**	**7**	**7**
3e	H	**16**	**17**	**10-m**	**10**
3f	3-NO_2	**20**	**20**	**13**	**11**
3g	3-OH	**26**	**26**	**21**	**20**
3h	3-CN	**22**	**23**	**16**	**18**
3i	4-CH_3	**12**	**14**	**8**	**9**
3j	3,4,5-OMe	**25**	**26**	**19**	**17**
[a]Standard Drug	-	28	27	22	22

[a] *Ciprofloxacin (250 µg mL^{-1} of DMSO);* [b] *Zone of inhibition – (i) Gram negative bacteria: good activity: 22-26 mm; moderate activity: 16-21 mm; weak activity: < 16 mm; (ii) Gram*

positive bacteria: good activity: 16-21 mm; moderate activity: 10-15 mm; weak activity: < 10 mm;

4. CONCLUSION

In conclusion, we have prepared some novel chalcone derivatives **3a-j** and screened for antibacterial activity. Among the newly synthesized chalcone derivatives, chalcones **3b**, **3g**, **3h** and **3j** with R = 4-OMe, 3-OH, 3-CN and 3,4,5-OMe exhibited good antibacterial activity (zone of inhibition; 22-26 mm) with reference to the standard drug Ciprofloxacin.

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6. CONFLICT OF INTEREST

"The author(s) declare(s) that there is no conflict of interest regarding publication of this article".

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