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An Efficient, Solvent Free Synthesis of Some Chalcone Derivatives and Their Biological Evaluation

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A solvent free grinding approach was adopted for the synthesis of (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-one derivatives. The synthesized derivatives were characterized by elemental analysis, mass, IR and NMR spectrometry. The *in vitro* antimicrobial activity of the derivatives showed moderate to potent activities against the tested microbes. Molecular docking studies were performed to evaluate the anticancer activities.

Keywords: Chalcones, Solvent free reactions, Antimicrobial activity, Molecular docking.

INTRODUCTION

Green chemistry exhibits extensive attention in organic chemistry due to the evasion of solvents in chemical reactions or replacement of hazardous solvents with more benign solvents like water [1,2]. Use of solvents in organic reactions are toxic, expensive and considered to be harmful to environment as the disposal of such solvents is a serious threat to the nature. To overcome this problem, there is a need for eco-friendly alternatives like solvent free grinding reactions [3], microwave irradiation [4] and ultrasonic reactions [5].

Synthesis of chalcones and their derivatives are of great interest as they have been found to exhibit anticancer [6], antimalarial [7], antimicrobial [8], antiinflammatory [9] and antifibrogenic [10] activities. Chalcones act as an intermediate in the synthesis of variety of beneficial therapeutic agents. A conventional synthesis of chalcones needs solvents, long reaction time and expensive chemicals/catalyst. This prompted to synthesize some new chalcones using grindstone technique which is simple to operate, non-hazardous, convenient and more economical. In this paper, grinding technique was used to synthesize (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-one derivatives and they were characterized by various spectral techniques. Furthermore, the biological evaluation of the compounds was performed.

EXPERIMENTAL

Melting points were measured in open glass capillaries and were uncorrected. The FT-IR spectra were recorded in KBr pellets on AVATAR-330 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER Avance III 400 MHz spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on SCIEX-API 2000 spectrometer. Elemental analysis was carried out in VARIOMICRO V2.2.0 CNH analyzer.

Antimicrobial assay: The antimicrobial activities of the compounds were tested against bacterial strains *Staphylococcous aureus*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia, Pseudomonas aeruginosa*, *P. mirabilis* and a fungal strain *Candida albicans*. The antimicrobial evaluation by disc diffusion and serial dilution method were performed with reference to the literature [11].

Molecular docking: Molecular docking was performed with Maestro v. 9.3.5 of the Schrödinger software suite, 2011. The 3D crystallographic structure of protein (PDB ID: 4LRH) was retrieved from Protein Data Bank. The molecular docking studies were carried out by GLIDE.

Synthesis of (2*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-ones (3a-d): Equimolar mixture of 1-(2',4'-difluorobiphenyl-4-yl)ethanone (1 mmol), aryl aldehydes (1 mmol) and NaOH was ground together with a mortar and pestle, the viscosity rapidly increases to form a solid after 5 min of constant grinding. The pliable solid is now left to harden at room temperature for 30 min which results in the formation of sodium adduct as an amorphous powder. This was dissolved in cold distilled water, neutralized with dil. HCl and kept aside for overnight. The solid separated was filtered, dried and recrystallized from ethanol.

(2*E*)-1-(2',4'-Difluorobiphenyl-4-yl)-3-(4-chlorophenyl)-prop-2-en-1-one (3a): Pale yellow solid; Yield 89 %; m.p.: 158-160 °C; IR (KBr, ν_{max}, cm^{-1}): 1662 (C=O), 3088 (aromatic C-H), 2926 (aliphatic C-H), 1598 (C=C), 1093-1144 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.54 (d, 1H, H-2, *J* = 15.6 Hz), 7.80 (d, 1H, H-3, *J* = 15.6 Hz), 8.09 (d, 2H, H-2" and H-6"), 6.97 (m, 2H, H-3' and H-5'), 7.39-7.66 (m, 7H, Ar-H); ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 189.7 (C=O), 122.3 (C-2), 143.5 (C-3), 104.7 (C-3'), 111.9 (C-5'), 159.9 (C-4'), 162.8 (C-2'), 124.2-139.6 (Ar-C); mass (*m/z*): 355 $[M+1]^+$; Anal. calcd. ($C_{21}H_{13}OClF_2$): C 71.09 H 3.69 %. Found: C 70.26 H 3.51 %.

(2*E*)-1-(2',4'-Difluorobiphenyl-4-yl)-3-(4-bromophenyl)-prop-2-en-1-one (3b): Yellow solid; Yield 91 %; m.p.: 178-180 °C; IR (KBr, ν_{max}, cm^{-1}): 1662 (C=O), 3085 (aromatic C-H), 2930 (aliphatic C-H), 1598 (C=C), 1095-1143 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.56 (d, 1H, H-2, *J* = 15.6 Hz), 7.78 (d, 1H, H-3, *J* = 15.6 Hz), 8.09 (d, 2H, H-2" and H-6"), 6.97 (m, 2H, H-3' and H-5'), 7.46-7.67 (m, 7H, Ar-H); ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 189.7 (C=O), 122.4 (C-2), 143.6 (C-3), 104.7 (C-3'), 111.9 (C-5'), 159.9 (C-4'), 162.8 (C-2'), 124.1-139.6 (Ar-C); mass (*m/z*): 401 $[M+2]^+$; Anal. calcd. ($C_{21}H_{13}OBrF_2$): C 63.18 H 3.28 %. Found: C 61.96 H 3.64 %.

(2*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-(3-nitrophenyl)-prop-2-en-1-one (3c): Yellow solid; Yield 67 %; m.p.: 154-156 °C; IR (KBr, ν_{max}, cm^{-1}): 1666 (C=O), 3100 (aromatic C-H), 2923 (aliphatic C-H), 1613 (C=C), 1107-1143 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.66 (d, 1H, H-2, *J* = 14.4 Hz), 7.88 (d, 1H, H-3, *J* = 15.6 Hz), 8.28 (d, 2H, H-2" and H-6"), 6.99 (m, 2H, H-3' and H-5'), 7.47-8.55 (m, 7H, Ar-H); ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 189.1 (C=O), 122.4 (C-2), 148.8 (C-3), 104.7 (C-3'), 111.9 (C-5'), 159.9 (C-4'), 162.9 (C-2'), 124.1-141.8 (Ar-C); mass (*m/z*): 368 $[M+3]^+$; Anal. calcd. ($C_{21}H_{13}NO_3F_2$): C 69.04 H 3.59 %. Found: C 70.45 H 3.78 %.

(2E)-1-(2',4'-Difluorobiphenyl-4-yl)-3-(furan-2-yl)-prop-2-en-1-one (3d): Pale yellow solid; Yield 92 %; m.p.: 106-108 °C; IR (KBr, ν_{max}, cm^{-1}): 1662 (C=O), 3120 (aromatic C-H), 2926 (aliphatic C-H), 1596 (C=C), 1101-1144 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.54 (d, 1H, H-2, *J* = 13.2 Hz), 7.64 (d, 1H, H-3, *J* = 13.2 Hz), 8.11 (d, 2H, H-2" and H-6"), 6.97 (m, 2H, H-3' and H-5'), 6.54-7.65 (m, 7H, Ar-H); ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 189.2 (C=O), 119.2 (C-2), 145.0 (C-3), 104.7 (C-3'), 111.9 (C-5'), 159.9 (C-4'), 163.0 (C-2'), 112.8-151.7 (Ar-C; Anal. calcd. ($C_{19}H_{12}O_2F_2$): C 73.54 H 3.90 %. Found: C 74.23 H 3.68 %.

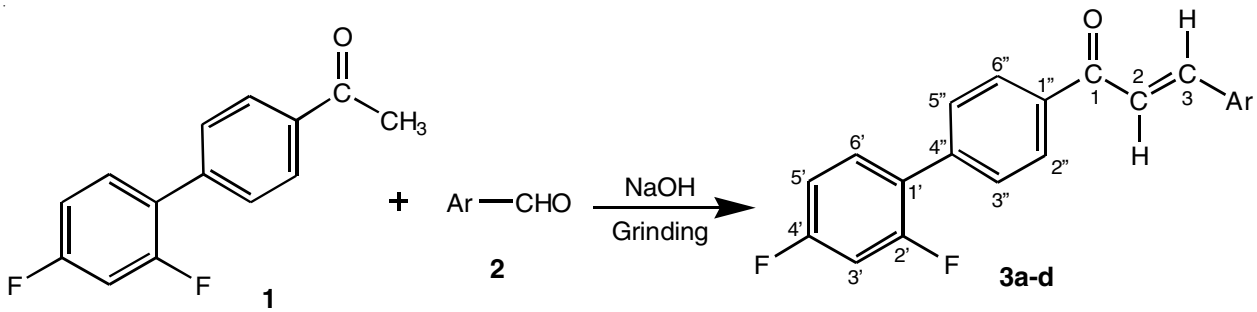
RESULTS AND DISCUSSION

Previously, some of the derivatives of (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-ones were prepared by the condensation of 1-(2',4'-difluorobiphenyl-4-yl)ethanone with various substituted aldehydes under conventional method [11]. The present work aims to study the effectiveness of the synthesis of some other derivatives by solvent free grinding technique. Remarkably, this solvent free Claisen-Schmit condensation proceeds in a clean and simple way with excellent yields (**Scheme-I**). The structures of the compounds were characterized by IR, NMR, mass and elemental analysis. The spectral discussions were made with the representative compound **3a**.

The IR spectra showed a strong absorption band at 1662 cm^{-1} for C=O and a band at 1598 cm^{-1} for C=C. The C-F stretching frequency appears at 1144-1093 cm^{-1}. The mass spectrum shows a molecular ion peak at *m/z* 355 $[M+1]^+$ peak. In ^{1}H NMR spectrum, the olefinic protons H-2 and H-3 appear as doublets at 7.54 ppm and 7.80 ppm which confirms the formation of chalcone. The measured coupling constant (*J* = 15.6 Hz) indicates that it was an (*E*)-isomer. The signals at 6.97 ppm and 8.09 ppm refer to the protons adjacent to fluorine substituted carbon atoms and protons *ortho* to carbonyl group, respectively. The aromatic protons appeared at 7.39-7.66 ppm. The signals observed at 189.7 ppm (C-1), 122.3 ppm (C-2) and 143.5 ppm (C-3) in ^{13}C NMR spectrum corroborate the structures determined by ^{1}H NMR spectrum.

Antimicrobial studies: *in vitro* Antimicrobial screening of the compounds **3a-d** against various microbes were given in Table-1. The investigations show that the furyl substituted compound (**3d**) exhibit higher activity on fungal strain *C. albicans*, better activity against Gram-positive bacteria *S. aureus*, *B. subtilis* and moderate activity against Gram-negative bacteria. The compounds with chlorine (**3a**) and bromine (**3b**) substitution are moderately active and the compound with nitro group (**3c**) is least active with reference to the positive control. The minimum inhibitory concentration (MIC) results also reveal that **3d** is the most active inhibitor against the tested microbial strains (Table-1).

Molecular docking studies were performed with the human folate receptor alpha in complex with folic acid (4LRH) to illustrate the cytotoxic activity of the compounds. The efficiency of the ligands was evaluated by G score and the results are furnished in Table-2. The results revealed that the ligands



Ar = **3a:** 4-ClC_6H_4; **3b:** 4-BrC_6H_4; **3c:** 3-$NO_2C_6H_4$; **3d:** 2-Furyl

Scheme-I

TABLE-1
ANTIMICROBIAL ACTIVITY OF COMPOUNDS **3a-d** BY DISC DIFFUSION AND TWO FOLD SERIAL DILUTION METHODS

Microbial strains	Disc diffusion method					Two fold serial dilution method				
	Mean zone of inhibition[a] (mm)[b]					Minimum inhibitory concentration (µg/mL)				
	Compounds				Ciprofloxacin/ Amphotericin-B	Compounds				Ciprofloxacin/ Amphotericin-B
	3a	**3b**	**3c**	**3d**		**3a**	**3b**	**3c**	**3d**	
S. aureus	12.4±0.38	11.6±0.42	07.4±0.27	13.2±0.52	25.1±0.42	50	25	50	25	3.125
B. subtilis	13.2±0.45	12.7±0.32	09.2±0.26	12.9±0.38	23.0±0.50	25	50	50	12.5	3.125
P. aeruginosa	08.2±0.48	07.2±0.26	06.9±0.44	10.7±0.17	25.1±0.17	50	25	100	50	6.25
E. coli	12.2±0.31	11.5±0.28	10.8±0.36	12.2±0.26	26.2±0.17	50	100	200	25	6.25
K. pneumonia	08.6±0.46	07.3±0.34	06.4±0.28	09.3±0.17	26.4±0.40	100	50	200	50	6.25
P. mirabilis	08.3±0.14	07.2±0.28	07.4±0.19	09.3±0.26	23.9±0.35	100	200	200	100	12.5
C. albicans	12.4±0.28	11.2±0.55	09.7±0.33	12.3±0.47	13.5±1.12	50	100	50	25	6.25

[a]Diameter of zone inhibition (mm); [b]Mean of three assays±standard deviation.

have enhanced binding affinity towards active pocket and possess excellent G score. It was observed that the ligands **3c** and **3d** exhibit hydrogen bonding interaction with metal residue ASH 81 and water residue, respectively (Fig. 1). In addition, the ligands **3a-d** showed π-π stacking interactions with the hydrophobic and polar residues as mentioned in Table-2. The investigation explores that furyl substituted compound **3d** have potent inhibitory activity with score of -10.6 and the other ligands also showed appreciable activities.

TABLE-2
DOCKING SCORE OF COMPOUNDS **3a-3d**

Compd.	G score	Interacting residues
3a	-10.2	TRP171, TYR60, TRP102, PHE62, HIE135, TRP140
3b	-10.5	TRP171, TRP102, PHE62, TYR60, TRP140
3c	-9.0	TRP171, HIE135, H_2O
3d	-10.6	TYR85, ASH81, TYR60, TRP140

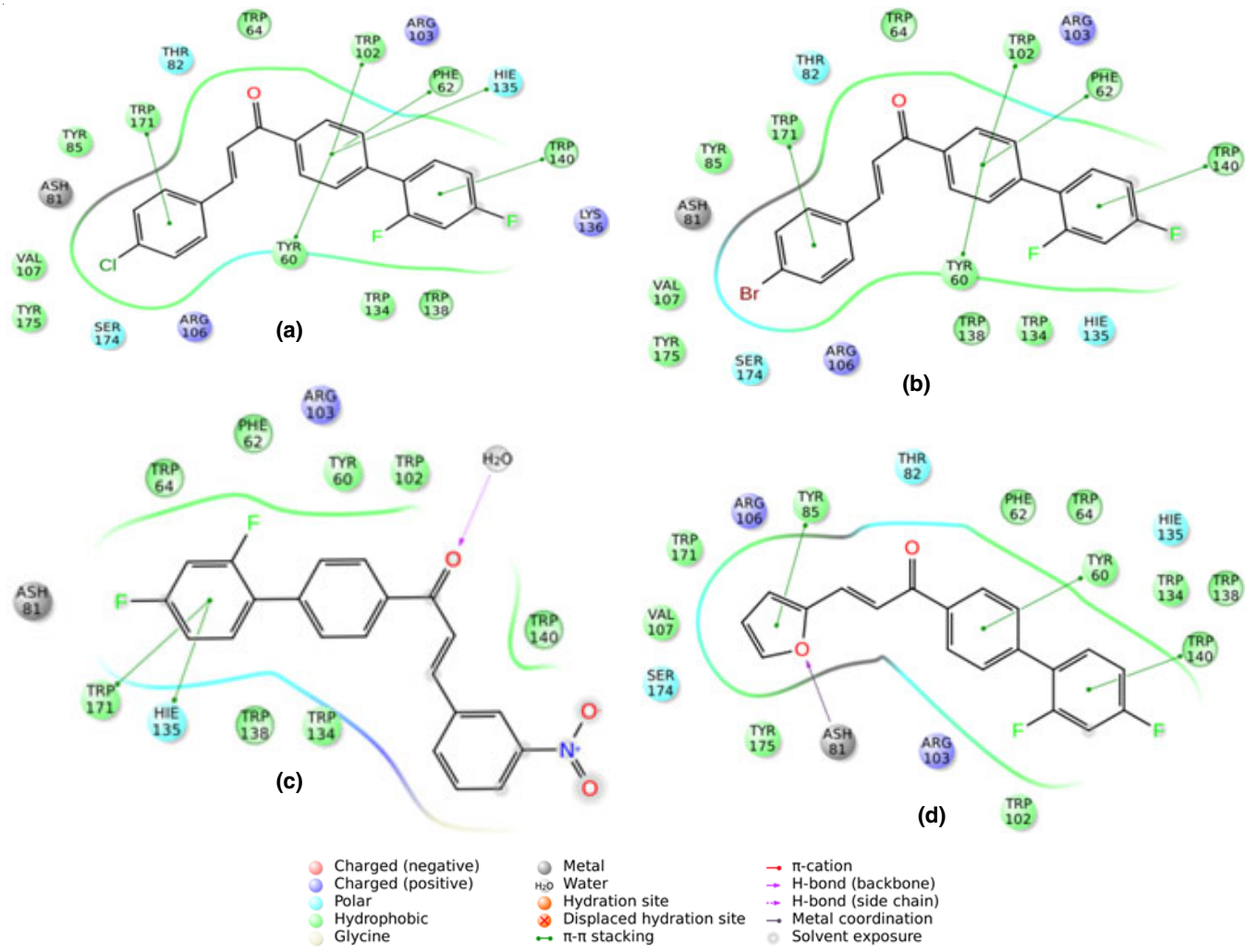


Fig. 1. Molecular docking of ligand **3a-d** with 4LRH protein

Conclusion

In conclusion, the (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-ones (**3a-d**) were effectively synthesized by feasible and simple method in good yields. The antimicrobial evaluation shows better inhibition against Gram-positive bacterial strains and fungal strain. Molecular docking studies demonstrate that the ligands **3d** and **3b** were efficient candidates to bind with the target protein. The present study found that the analogue **3d** exhibit superior inhibitory activity over the others and could serve as start point for novel drug discovery.

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