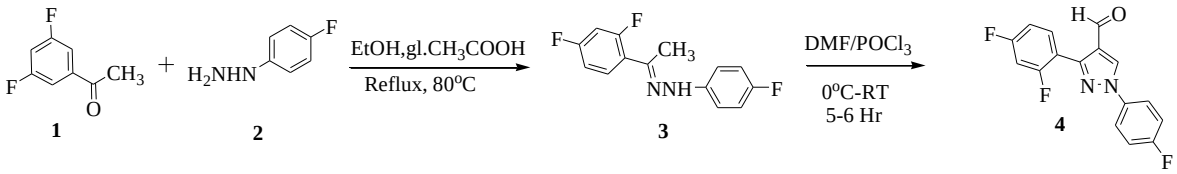
Executive Summary

Principal Investigator: - Dr. Sunil Sheshrao Bhagat

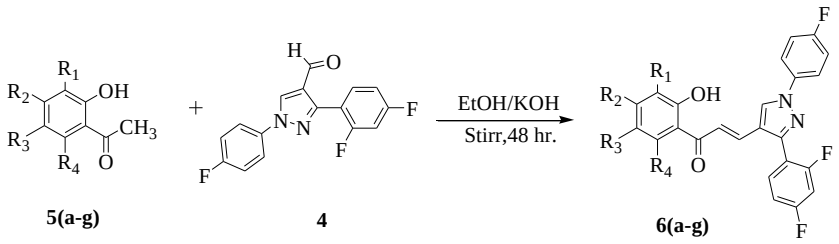
Title of Minor Research Project: - Synthesis, Characterization and Antimicrobial Screening of Some Fluorinated Heterocyclic Compounds.

UGC File No.:- 47-677/13 (WRO, PUNE) dated 19-03-2014



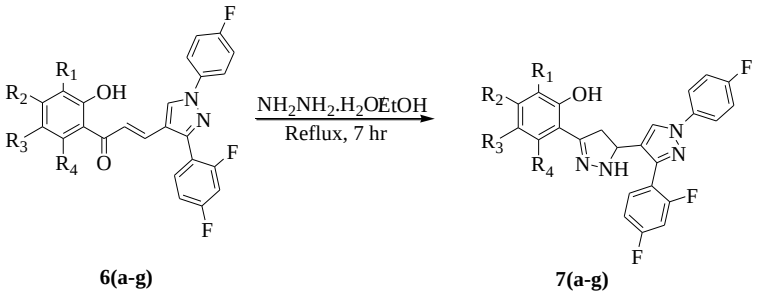
1 **2** **3** **4**

Scheme A



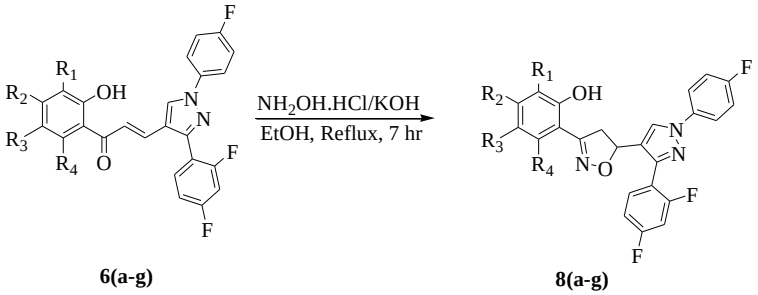
5(a-g) **4** **6(a-g)**

Scheme B



6(a-g) **7(a-g)**

Scheme C



6(a-g) **8(a-g)**

Scheme D

Table 1: Physical data of compounds 5(a-g)

Comp.	R_1	R_2	R_3	M.P./B.P. (ºC)
5a	H	H	H	210-212
5b	H	H	CH_3	60-62
5c	H	H	Cl	56-58
5d	Cl	H	Cl	94-96
5e	H	H	F	50-52
5f	H	CH_3	Cl	64-66
5g	H	H	Br	66-68

Table 2: Physical data of compounds 6(a-g)

Comp.	R_1	R_2	R_3	M.P. (ºC)	Yield (%)
6a	H	H	H	198-200	72
6b	H	H	CH_3	180-182	79
6c	H	H	Cl	170-172	75
6d	Cl	H	Cl	188-190	72
6e	H	H	F	192-194	76
6f	H	CH_3	Cl	230-232	80
6g	H	H	Br	184-186	78

Table 3: Physical data of compounds 7(a-g)

Comp.	R_1	R_2	R_3	M.P. (ºC)	Yield (%)
7a	H	H	H	96-98	69
7b	H	H	CH_3	120-122	73
7c	H	H	Cl	108-110	68
7d	Cl	H	Cl	126-128	80
7e	H	H	F	130-132	71
7f	H	CH_3	Cl	90-92	67
7g	H	H	Br	110-112	81

Table 4: Physical data of compounds 8(a-g)

Comp.	R_1	R_2	R_3	M.P. (ºC)	Yield (%)
8a	H	H	H	118-120	70
8b	H	H	CH_3	156-158	69
8c	H	H	Cl	110-112	72
8d	Cl	H	Cl	120-122	67
8e	H	H	F	134-136	65
8f	H	CH_3	Cl	90-92	70
8g	H	H	Br	160-162	72

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Synthesis of fluorinated pyrazolines as an anti-inflammatory agents containing pyrazole moiety

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Abstract : In the present work, seven novel 2-(5-(3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenol 2(a-g) were synthesized by cyclization between substituted chalcones and hydrazine hydrate in the presence of glacial acetic acid under reflux condition. The structures of the synthesized compounds were characterized on the basis of IR, ^{1}HNMR and Mass spectral data. All the synthesized compounds are screened for their anti-inflammatory activity by paw oedema method. Diclofenac employed as a reference standard. From the results it is concluded that, compounds 2b-2f exhibited moderate anti-inflammatory activity.
Keywords : Pyrazolines,antimicrobial activity,ulcerogenic activity.

Introduction

Nitrogen-linked heterocyclic compounds received considerable attention in recent times because of their medicinal and pesticidal importance. It is well known that the study of pyrazole derivatives is significant in pesticide chemistry, and some of the pyrazole derivatives were widely used because of theiranti-inflammatory[1], antitumor[2], antimicrobial[3], analgesic[4], antagonist[5], antidepressant andanticonvulsant[6], hypoglycemic[7], antioxidant[8],antidepressant properties[9], immunosuppressive[10],ulcerogenic and lipid peroxidation activities[11]. In addition, many biological compounds contain a fluoro moiety, which indicates that this moiety may be important for biological activity[12].

Experimental

A General procedure for the synthesis of4-chloro-2-(5-(3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)-5-ethylphenol(2c):

Compound 1**c** (0.01mol) was dissolved in 15ml ethanol. To this reaction mixture, 0.02 mol of hydrazine hydrate was added. Contents were heated under mild reflux for 4 hr and then to the reaction mixture 4-5 drops of glacial acetic acid was added and heating was continued further for 3hr and then cooled to room temperature. Cold water (50ml) was slowly added to the flask and separated product was filtered, washed with cold water for several times and crystallized from ethanol. The compounds **2(a-g)**were prepared by following the general procedure. Physical data are recorded in **Table 1**. Their structures have been confirmed by IR, ^{1}HNMR and Mass spectra.

IR (2c) (cm^{-1}): 964(C-Cl), 1062(Ar-F), 1266(C-O), 1514(Ar C=C), 1595(C=N),

3084(O-H), 3341(N-H).

^{1}H NMR (2c)(DMSO)δ ppm: 3.0637-3.1254 (dd, 1H, -CH_2-,*J*=8.48Hz & 8.28 Hz),3.4480-3.5147 (dd, 1H, -CH_2-,*J*=10.48Hz & 10.72 Hz), 4.8287-4.8740 (t,1H,-CH-,*J*=9Hz &9.12Hz), 6.0463(s, 1H, Pyrazoline N-H), 6.5917-6.9933 (m, 3H, Ar-H), 7.0147-7.2131 (m, 4H, Ar-H), 7.3221-7.6842(m, 3H, Ar-H), 8.0925 (s, 1H,Pyrazole-H), 10.9231 (s, 1H, Ar-OH).

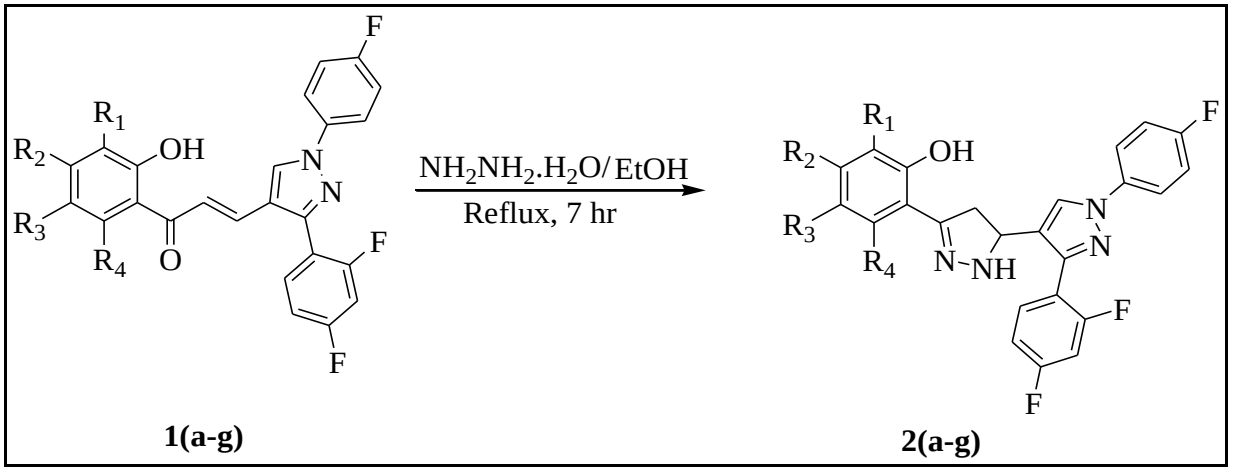
ES-MS (2c) (m/z):469.43(M+1), 471.43(M+3).

IR (2f) (cm^{-1}): 964(C-Cl), 1063(Ar-F), 1267(C-O), 1514(Ar C=C), 1595(C=N),

3084(O-H), 3128(N-H).

^{1}H NMR (2f) (DMSO)δ ppm: 2.3160 (s, 3H, CH_3), 3.047-3.1096 (dd, 1H, -CH_2-,*J*=8.28Hz & 8.44 Hz),3.4240-3.4955 (dd, 1H, -CH_2-,*J*=12.24Hz & 10.16 Hz), 4.8040-4.8497 (t,1H,-CH-,*J*=9.44Hz & 8.84Hz), 6.0132(s, 1H, Pyrazoline N-H), 6.7853 (s, 1H, Ar-H), 6.8816-6.9554(m, 1H, Ar-H), 6.9764-6.9818(m, 1H, Ar-H),7.1076-7.1235 (m, 1H, Ar-H), 7.1445-7.1659(m, 1H, Ar-H) ,7.2041-7.2111(m, 1H, Ar-H), 7.5421-7.5652(m, 1H, Ar-H), 7.6459-7.6574(m, 1H, Ar-H), 7.6681-7.6794(m, 1H, Ar-H), 7.9449 (s, 1H,Pyrazole-H), 10.8053 (s, 1H, Ar-OH).

ES-MS (2f) (m/z): 481.21(M-1), 483.19(M+2).



Scheme1- Synthesis of various substituted 2-(5-(3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenol

Table 1: Physical data of compounds (2a-g)

Comp.	R_1	R_2	R_3	M.P. (^{o}C)	Yield (%)
2a	H	H	H	96-98	69
2b	H	H	CH_3	120-122	73
2c	H	H	Cl	108-110	68
2d	Cl	H	Cl	126-128	80
2e	H	H	F	130-132	71
2f	H	CH_3	Cl	90-92	67
2g	H	H	Br	110-112	81

Results and Discussion

Antimicrobial activity:

Compounds **2(a-g)** were screened for their in vitro antimicrobial activity against *Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus (ATCC 25923)* using Gentamycin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluated against *Candida sp.* using Nystatin as standard drug. All the tests were evaluated at 100 µg/ml concentration.

The culture media was Muller Hinton agar. The zone of inhibition was measured in mm after 24 hr of incubation at 37^{o}C.Microbial data for corresponding compounds is summarized in **Table 2.**

Table 2: Antimicrobial Analysis Data

Sr. No.	**Comp. No.**	***Escherichia coli (ATCC 25922)***	***Pseudomonas aeruginosa (ATCC 27853)***	***Staphylococcus aureus (ATCC 25923)***	***Candida sp.***
1	2a	No Zone	No Zone	No Zone	No Zone
2	2b	No Zone	No Zone	No Zone	No Zone
3	2c	No Zone	No Zone	No Zone	No Zone
4	2d	No Zone	No Zone	No Zone	No Zone
5	2e	No Zone	No Zone	No Zone	No Zone
6	2f	No Zone	No Zone	No Zone	No Zone
7	2g	No Zone	No Zone	No Zone	No Zone
8	Gentamycin	28 mm	23 mm	32 mm	--
9	Nystatin	--	--	--	23 mm

Anti-Inflammatory Activity:

Compounds **2(b-f)** were screened for their anti-inflammatory activity. All analysis was performed using graph pad prism for Windows. All statistical analysis is expressed as mean ± standard error of the mean (SEM). Data were analyzed by one way ANOVA, where applicable $p<0.05$ was considered statistically significant, compared with vehicle followed by Dunnett's test.

Table 3.Effect of different Compounds 2b-2fon paw oedema induced by carrageenan in rat

	Treatment	**Mean Difference in Paw volume (ml)**	**Percentage Inhibition (%)**
Control	**0.1 ml of 1% (w/v)**	**1.6±0.02**	**----**
Diclofenac	30	1.5±0.02	93.75
2b	10	1.0±0.01	62.50
	20	1.1±0.03*	68.75
2c	10	0.9±0.01	56.25
	20	1.1±0.01*	68.75
2d	10	1.1±0.01*	68.75
	20	1.2±0.01**	75.00
2e	10	1.0±0.01	62.50
	20	1.2±0.02*	68.75
2f	10	1.0±0.01	62.50
	20	1.2±0.02**	75.00

Each data suggests Mean ± SEM (n=6). One-way ANOVA using Dunnett's test is applied for statistical analysis, Treatment groups compared with Control group.

Significant at* $p < 0.01$, compared to control group.

Conclusion

The novel synthesized compounds were tested againstGram positive and Gram negative bacterial strains. As well asthey were tested against Candida species. The other compounds have shown no activity compared to standard drug.The synthesized compounds were screened for their anti-inflammatory activity bypaw oedema method. Diclofenacemployed as a reference standard. From the results it is concludedthat, compounds 2b-2f exhibited moderate anti-inflammatoryactivity.

Acknowledgements

The authors are thankful to UGC, WRO, Pune for financial support and Principal Dr. B. B. Sonwane for providing laboratory facilities.The authors are grateful to Director, SAIF/CIL, Panjab University, Chandigarh for providing spectral data. The authors are thankful to Uday Khedkar, Director, BAC-TEST Laboratory, Nashik for antimicrobial analysis. The authors are grateful to Prabhat Jain, Director, Scan Research Laboratory, Bhopal for anti-inflammatory activity.

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Synthesis, Characterization and Antimicrobial Activity of Novel Chalcones from Fluorinated Formyl Pyrazole

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ABSTRACT

Various substituted 2-hydroxy acetophenones (1) on condensation with 3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (2) yields the title compounds Chalcones (E)-3-(3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-ones (3). Spectral techniques like IR, ^{1}H NMR and Mass spectral data confirms the structures of novel synthesized compounds. Antimicrobial screening of newly prepared compounds was carried out.

Keywords: Chalcones, antimicrobial activity, 3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde

INTRODUCTION

Pyrazole and derivatives are key substructures in a large variety of compounds with important biological activities and pharmacological properties [1-3]. Synthesis of chalcones is carried out by Claisen-Schmidt condensation of aldehyde and ketone in presence of base or acid which on subsequent dehydration yield chalcones. A variety of important biological compounds possess central core of chalcones. Three carbon α,β-unsaturated highly electrophilic carbonyl system in chalcone has assumed more importance because of its versatile nature in the preparation of many heterocyclic compounds. Chalcone have been reported to possess various biological activities like anti-inflammatory, antiulcerative, analgesic, antiviral, antifungal, antimalarial, antibacterial and anticancer activities [4-11]. Chalcone considered being a very good synthon for the preparation of various heterocycles like isoxazole, pyrimidine, pyrazole, thiazine, diazepine, oxazine, pyridine [12,13]. Hence, preparation of chalcones has attracted much interest particularly in organic chemistry.

Synthesis of chalcones can be carried out by several methods as reported in literature. The most widely adopted method is Claisen-Schmidt base catalyzed reaction of an aldehyde and a methyl ketone using Potassium Hydroxide (KOH) [14], Lithium Hydroxide ($LiOH{\cdot}H_2O$) [15] and Sodium Hydroxide (NaOH) [16] and Barium Hydroxide ($Ba(OH)_2$) [17]. In the present communication we report the reaction of 3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-*1H*-pyrazole-4-carbaldehyde with differently substituted 2-hydroxy acetophenones to afford novel chalcones [18-24].

MATERIALS AND METHODS

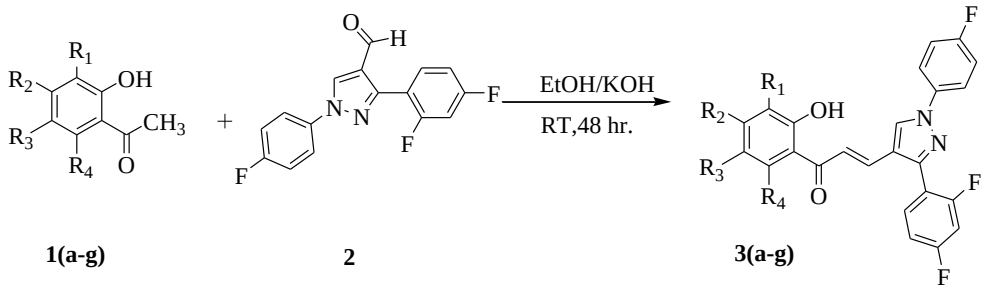
All the chemicals were obtained from Sigma Aldrich and SD Fine chemicals. Melting points were determined in open capillaries and are uncorrected. Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded on Bruker Avance II 400 MHz NMR Spectrophotometer in Deuterated Dimethyl Sulfoxide (DMSO-d_6) using Tetramethylsilane (TMS) as an internal standard. The Infra-Red (IR) spectra were recorded as potassium bromide disk using Fourier Transform Infrared (FTIR) Spectrophotometer Model RZX (Perkin Elmer). Mass spectra were recorded on Macromass spectrophotometer (Waters) by Electro-Spray method (ES). The purity of the compounds was checked by Thin Layer Chromatography (TLC) silica gel coated plates obtained from Merck as stationary phase and solvent mixture ethyl acetate/hexane (20:80) as mobile phase.

Procedure for the synthesis of (*E*)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl) prop-2-en-1-one (3f)

A mixture of 1 (0.01 mol) and 2 (0.01 mol) was dissolved in 40 ml ethanol and contents were cooled to 0°C in ice bath. To this reaction mixture, 2 g KOH pellets were added maintaining temperature below 5°C. The stirring of reaction mixture was continued for 48 h at room temperature. Then reaction mixture was poured on to crushed ice and contents were acidified with 2 M HCl. Resulting yellow solid obtained was separated by filtration and washed with cold water several times. Product was recrystallized from ethanol. This typical experimental procedure was followed to prepare other analogs of this series. The melting point and percentage yield of the compounds 3(a-g) were recorded in Table 1 (Scheme 1).

IR (3c) (cm^{-1}): 1067(C-Cl), 1230 (C-O), 1537 (C=C), 1585 (C=N), 1649 (C=O), 3139 (O-H). ^{1}H-NMR (3c) (DMSO-d_6) δ ppm: 6.9824-7.0045 (d, 1H, Ar-H, *J*=8.84 Hz), 7.1954-7.2624 (dd, 1H, Ar-H), 7.2938 7.3798 (m, 3H, Ar-H), 7.5034-7.5249 (d, 1H, Ar-H, *J*=8.6 Hz), 7.6216-7.6495 (d, 1H, CH=C-, *J*=11.16Hz), 7.6671-7.6874 (d, 1H, Ar- H, *J*=8.12 Hz), 7.8158-7.8538 (d, 1H, CH=C-, *J*=15.2 Hz), 7.9515-8.0784 (m, 3H, Ar-H), 9.4032 (s, 1H, pyrazole-H), 12.5869 (s, 1H, Ar–OH). ES-MS (3c) (m/z): 455.38 (M+1), 457.40 (M+3).

IR (3f) (cm^{-1}): 1059 (C-Cl), 1228 (C-O), 1536 (C=C), 1587 (C=N), 1651(C=O), 3143(O-H). ^{1}H-NMR (3f) (DMSO-d_6) δ ppm: 2.3618 (s, 3H, -CH_3), 7.0169 (s, 1H, Ar-H), 7.2683-7.3160 (m, 1H, Ar-H), 7.3784-7.4838 (m, 3H, Ar-H), 7.5039-7.5749 (m, 1H, Ar-H), 7.6628-7.7218 (dd, 1H, Ar-H, *J*=6.64 Hz & J=8.48 Hz), 7.8205-7.8589 (d, 1H, CH=C-, *J*=15.36 Hz), 7.9454-7.9570 (d, 1H, Ar-H, *J*=4.64 Hz), 7.9680-7.9797 (d, 1H, Ar-H, *J*=4.68 Hz), 8.0834 (s, 1H, Ar-H), 9.4339 (s, 1H, pyrazole-H), 12.5092 (s, 1H, Ar–OH). ES-MS (3f) (m/z): 469.25 (M+1), 471.25 (M+3).



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

Scheme 1: Melting point and percentage yield

Table 1: Melting point and percentage yield of the compounds 3(a-g)

Compound	R_1	R_2	R_3	R_4	Melting point (°C)	Yield (%)
3a	H	H	H	H	160-162	65
3b	H	H	CH_3	H	224-226	67
3c	H	H	Cl	H	170-172	72
3d	Cl	H	Cl	H	234-236	80
3e	H	H	Br	H	212-214	78
3f	H	CH_3	Cl	H	230-232	74
3g	H	H	F	H	208-210	69

RESULTS AND DISCUSSION

The chalcones were synthesized successfully in good yields. The novel compounds were identified by physical techniques on the basis IR, ^{1}H-NMR, Mass spectral data. All compounds were screened for antimicrobial activity using disc diffusion method.

Antimicrobial activity

Compounds 3(a-g) and 2 were screened for their *in vitro* antimicrobial activity against *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923) using gentamycin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluated against *Candida sp.* using nystatin as standard drug. All the tests were evaluated at 100 µg/ml dose levels. The culture media was Muller Hinton agar. The zone of inhibition was measured in mm after 24 h of incubation at 37^{o}C. Microbial data for corresponding compounds is summarized in Table 2.

Table 2: Antimicrobial analysis data

S. No.	Compound number	*Escherichia coli* (ATCC 25922)	*Pseudomonas aeruginosa* (ATCC 27853)	*Staphylococcus aureus* (ATCC 25923)	*Candida sp.*
1	2	No zone	No zone	08 mm	No zone
2	3a	No zone	No zone	No zone	No zone
3	3b	No zone	No zone	No zone	No zone
4	3c	No zone	No zone	No zone	No zone
5	3d	No zone	No zone	No zone	No zone
6	3e	No zone	No zone	No zone	No zone
7	3f	No zone	No zone	No zone	No zone
8	3g	No zone	No zone	No zone	No zone
9	Gentamycin	28 mm	23 mm	32 mm	-
10	Nystatin	-	-	-	23 mm

CONCLUSION

The synthesized compounds were tested against *Candida sp.* and Gram-positive as well as Gram-negative bacterial strains. Among them, the compound 2 exhibited good activity only against *S. aureus* (ATCC 25923) bacteria. The other chalcone compounds 3(a-g) containing fluorine have shown no activity compared to standard drug.

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