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ONE POT SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL CHALCONES AND PYRAZOLES FROM CYCLIC IMIDES UNDER MICROWAVE IRRADIATION

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ABSTRACT

In this research, an efficient one-pot synthesis of novel class of chalcones and pyrazoles has been developed via reaction of cyclic imides, p-chloro benzaldehyde/hydrazine hydrate in presence of catalyst neutral alumina. Chalcones and pyrazoles as heterocyclic-moieties privileged meditative arena and are prepared via carbon-heteroatom and carbon-carbon bond formation. The current methodology contribute a novel and efficient method for the synthesis of chalcones and pyrazoles with some advantages such as excellent yields, short reaction time, better recoverability and low catalyst lading. The compounds were abandoned for antimicrobial activities against bacterial strains gram positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* along with two fungal strains *Candida albicans* and *Aspergillus niger*. Some of the compounds displayed symbolic inhibitory activity against the bacterial and fungal strains.

KEYWORDS: Cyclic Imides, Chalcones, Pyrazoles, Antimicrobial, Anti bacterial, Anti fungal.

INTRODUCTION

The circumstances of life-alarming fungal infections have continued to upswing over the last two decades; especially within denizens of immune conciliate individuals.[1] Bacterial infections are engender by multi-drug rebellious gram-positive and gram-negative pathogens which disturbs millions of people in the subtropical region of the world and around twenty thousand deaths are occurs every year due to parasitic bacterial infections.[2] Various

antibiotics are broadly used for the treatment of infectious illness but with commonly increasing multi-drug resistant microbial strains there is a need of consistent development of novel antibacterial and antifungal agents. Steroids are one in million applications as diuretic, anti-inflammatory, contraceptive, anabolic, anti-androgenic, pro-gestational and anti-cancer agents.[3] Steroid plinth compounds turn out to be non-toxic, less vulnerable to multi-drug resistance (MDR) and highly bioavailable because of being capable of penetrating the cell wall.[4] Nitrogen containing hetero scaffolds like pyrazolines[5-7] malononitriles[8-11], glutarimides[12] , pyrimidines[13-16] succinimides[17,18] and Chalcones[19-21] are renowned for their disparate multitude of bioactivities. Conspicuously, they have been broadcast to seize pharmacological activities like antimalarial, anticancer, anti-tubercular, anti-inflammatory[22], cytotoxic, gastro protective[23] and antimicrobial activities.[24,25] Chalcone[26] configuration made up of three important components, viz. two phenyl rings and α, β-unsaturated carbonyl system joining them.

Bis-chalcones are synthesized by the condensation[27] of the substituted ketones and aldehyde groups.[28] The chalcones are also prepared by utilizing a number of synthetic routes like solid phase Claisen-Schemdit, mixed-aldol condensation, acid catalyst, coupling reaction[29] and microwave assisted synthesis.[30-34]

The pyrazoles[35] are prepared by hydrazine hydrate or aromatic hydrazine in presence of acetic acid[36] and sodium acetate.[37] They could be synthesized by grinding[38], conventional and microwave[39], tandem[40], chromine ring opening[41], solvent free[42] and regio-selective[43] methods and so on. The novel techniques of synthesis of pyrazole which includes eco-friendly solvent free, solid support, microwave[44], one pot multicomponent, and ultrasound synthetic methods are more useful than that of the traditional methods.[45]

EXPERIMENTAL

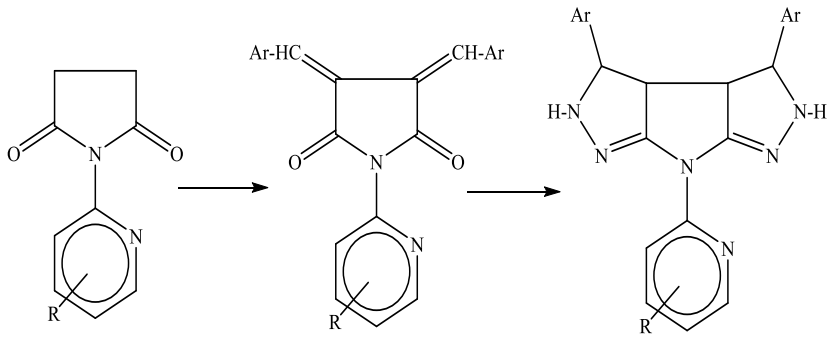
Material Methods

Melting points were recorded in open glass capillaries and were uncorrected. The chemical structures of the obtained compounds were confirmed by spectral analyses. IR spectra in KBr pallets were obtained on Simadzu and ATR Brucker alpha FT-IR spectrophotometer. ^{1}H NMR spectra were obtained on and 500.13 MHz by Brucker spectrophotometer. The chemical shifts were reported as parts per million (ppm) with $(CH_3)_4Si$ (TMS) as an internal standard. Signal multiplicities are represented by: s (singlet), d (doublet), t (triplet), m (multiplet). The purity of compound was checked by thin layer chromatography which was

performed by using pre-coated silica gel aluminium plates with mixture of diethyl ether and ethyl acetate 7:3 proportion. Anti-microbial and Anti-fungal activities were carried out by Agar diffusion assay (Disk diffusion method, Disk size 6 mm).[46, 47] All the compounds (3a-f and 5a-f) were synthesized from the corresponding Succinic and Glutaric Anhydride derivatives and commercially purchased *p*-chloro benzaldehyde, neutral alumina (Al_2O_3) and ethanol.

General Procedure of Synthesis of Chalcone (9a-c)

The bis-chalcones (9a-c) derivatives were synthesized by the mixture of 0.01 moles of N-phenyl succinimides and 0.02 mole of p-chloro benzaldehyde in 1 gm of neutral Al_2O_3 with the help of microwave irradiations. This mixture is maintained in microwave at 800W power for 4-6 minutes in solvent free condition. These bis-chalcones (9a-c) of N-phenyl succinimide were used for the preparation of novel pyrazole derivatives (12a-c) by microwave synthesis. The novel developed compounds were recrystallized from ethanol (Scheme – I).



Scheme - I

Physicochemical and analytical data for compounds 9a-c and 12a-c

3,4-bis((E)-4-chlorobenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione (9a)

Traffic Yellow solid, Yield (85.13%), M. P. 258 - 60ºC, M.F. $C_{24}H_{16}O_2N_2Cl_2$ M.W.435.30, Composition: C (66.22%) H (3.70%) Cl (16.29%) N (6.44%) O (7.35%); IR (KBr): 698,646,1691,1741,3006,888,833,813,2856,1154,1289,1579,1478,1380 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.62 (t,4H, Ar-H,J=7.5), 7.68 (t,4H,Ar-H,J=7.5), 7.75 (s, 2H, ethylene), 7.98 (d, 1H, pyridine), 7.52 (t, 1H, pyridine,J=7.5), 7.42 (d, 1H, pyridine), 2.16 (s, 3H, CH_3-pyridine).

3,4-bis((E)-4-chlorobenzylidene)-1-(4-methylpyridin-2-yl)pyrrolidine-2,5-dione (9b)

Dahlia Yellow solid, Yield (86.15%), M. P. 278 - 80ºC, M.F. $C_{24}H_{16}O_2N_2Cl_2$ M.W.435.30,

Composition: C (66.22%) H (3.70%) Cl (16.29%) N (6.44%) O (7.35%); IR (KBr): 708, 655,1690,1742,3006,861,837,2875,1165,1279,1587,1465,1374 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.62 (t,4H, Ar-H,J=7.5), 7.68 (t,4H,Ar-H,J=7.5), 7.75 (s, 2H, ethylene), 7.93 (d, 1H, pyridine), 7.40 (d, 1H, pyridine), 7.25 (t, 1H, pyridine), 2.22 (s, 3H, CH_3-pyridine).

3,4-bis((E)-4-chlorobenzylidene)-1-(6-methylpyridin-2-yl)pyrrolidine-2,5-dione (9c)

Broom Yellow solid, Yield (84.79%), M. P. 290 - 92ºC, M.F. $C_{24}H_{16}O_2N_2Cl_2$ M.W.435.30, Composition: C (66.22%) H (3.70%) Cl (16.29%) N (6.44%) O (7.35%); IR (KBr): 824,1593,1740,3022,997,2969,1090,1300,1593,1454,1372 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.62 (t,4H, Ar-H,J=7.5), 7.68 (t,4H,Ar-H,J=7.5), 7.75 (s, 2H, ethylene), 6.88 (t, 1H, pyridine, J=7.5), 7.63 (t, 1H, pyridine,J=7.5), 7.35 (t, 1H, pyridine,J=7.5), 2.46 (s, 3H, CH_3-pyridine).

3,4-bis(4-chlorophenyl)-7-(5-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (12a)

Traffic Yellow solid, Yield (81.84%), M. P. 296 - 98ºC, M.F. $C_{24}H_{20}N_6Cl_2$ M.W.463.36, Composition: C (62.21%) H (4.35%) Cl (15.30%) N (18.14%); IR (KBr): 622,707,1652,2997,2939,1211,1287,1483,1591,1371,1483 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.48 (t,8H, Ar-H,J=7.5), 2.28 (t,2H,methine,J=7.0), 3.8 (d,2H,methine,J=7.0), 9.97 (s, 2H, N-H), 7.90 (d, 1H, pyridine), 7.31 (t, 1H, pyridine,J=7.5), 6.54 (d, 1H, pyridine,J=7.5), 2.16 (s, 3H, CH_3-pyridine).

3,4-bis(4-chlorophenyl)-7-(4-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (12b)

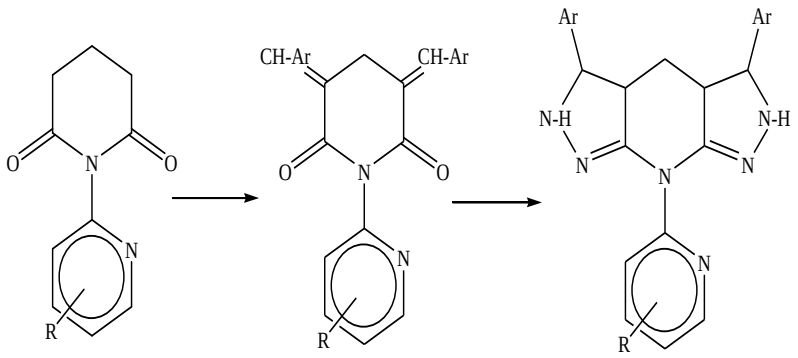
Melon Yellow solid, Yield (70.92%), M. P. 208 - 10ºC, M.F. $C_{24}H_{20}N_6Cl_2$ M.W.463.36, Composition: C (62.21%) H (4.35%) Cl (15.30%) N (18.14%); IR (KBr): 627,3154,708,1646,3026,818,2939,1210,1289,1486,1595,1437,1372 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.48 (t,8H, Ar-H,J=7.5), 2.28 (t,2H,methine,J=7.0), 3.8 (d,2H,methine,J=7.0), 9.97 (s, 2H, N-H), 7.85 (d, 1H, pyridine,J=7.5), 6.67 (t, 1H, pyridine,J=7.5), 6.52 (d, 1H, pyridine), 2.22 (s, 3H, CH_3-pyridine).

3,4-bis(4-chlorophenyl)-7-(6-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (12c)

Sulfur Yellow solid, Yield (84.32%), M. P. 304 - 06ºC, M.F. $C_{24}H_{20}N_6Cl_2$ M.W.463.36, Composition: C (62.21%) H (4.35%) Cl (15.30%) N (18.14%); IR (KBr): 819,3201,860,1623,3049,819,2940,1211,1312,1623,1592,1401,1485 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.48 (t,8H, Ar-H,J=7.5), 2.28 (t,2H,methine,J=7.0), 3.8 (d,2H,methine, J=7.0), 9.97 (s, 2H, N-H), 6.30 (t, 1H, pyridine, J=7.5), 7.42 (t, 1H, pyridine, J=7.5), 6.47 (d, 1H, pyridine, J=7.5), 2.46 (s, 3H, CH_3-pyridine).

General Procedure of Synthesis of Chalcone: 3,5-bis((E)-4-chlorobenzylidene)-1-(N-methylpyridin-2-yl)piperidine-2,6-dione (9d-f) and Pyrazole: 3,5-bis(4-chlorophenyl)-8-(N-methylpyridin-2-yl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (12d-f)

The bis-chalcones (9d-f) derivatives were synthesized by the mixture of 0.01 moles of N-phenyl glutarimides and 0.02 mole of p-chloro benzaldehyde in 1 gm of neutral Al_2O_3 with the help of microwave irradiations. This mixture is maintained in microwave at 800W power for 3-7 minutes in solvent free condition. These bis-chalcones (9d-f) of N-phenyl glutarimides were used for the preparation of novel pyrazole derivatives (12d-f) by microwave synthesis. The novel developed compounds were recrystallized from ethanol (Scheme – II).



Scheme - II

3,5-bis((E)-4-chlorobenzylidene)-1-(5-methylpyridin-2-yl)piperidine-2,6-dione (9d)

Ivory solid, Yield (84.74%), M. P. 264 - 66ºC, M.F. $C_{25}H_{18}O_2N_2Cl_2$ M.W.449.32, Composition: C (66.83%) H (4.04%) Cl (15.78%) N (6.23%) O (7.12%); IR (KBr): 661,1655,1732,3024,871,814,2960,2926,1088,1310,1570,1413,1372,1462 cm^{-1}. ^1H NMR

(500.13 MHz, DMSO-d^6, δ ppm): 7.62 (t,4H, Ar-H,J=7.5), 7.68 (t,4H,Ar-H,J=7.5), 7.21 (d, 2H, ethylene), 2.63 (t, 2H, methylene), 7.98 (d, 1H, pyridine), 7.52 (t, 1H, pyridine,J=7.5), 7.42 (d, 1H, pyridine), 2.16 (s, 3H, CH_3-pyridine).

3,5-bis((E)-4-chlorobenzylidene)-1-(4-methylpyridin-2-yl)piperidine-2,6-dione (9e)

Saffron Yellow solid, Yield (82.59%), M. P. 308 - 10ºC, M.F. $C_{25}H_{18}O_2N_2Cl_2$ M.W.449.32, Composition: C (66.83%) H (4.04%) Cl (15.78%) N (6.23%) O (7.12%); IR (KBr): 664,1679,1736,3026,879,815,2927,1088,1297,1572,1408,1371,1461 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.62 (t,4H, Ar-H,J=7.5), 7.68 (t,4H,Ar-H,J=7.5), 7.21 (d, 2H, ethylene), 2.63 (t, 2H, methylene), 7.93 (d, 1H, pyridine), 7.40 (t, 1H, pyridine), 7.25 (t, 1H, pyridine), 2.22 (s, 3H, CH_3-pyridine).

3,5-bis((E)-4-chlorobenzylidene)-1-(6-methylpyridin-2-yl)piperidine-2,6-dione (9f)

Saffron Yellow solid, Yield (82.26%), M. P. 288 - 90ºC, M.F. $C_{25}H_{18}O_2N_2Cl_2$ M.W.449.32, Composition: C (66.83%) H (4.04%) Cl (15.78%) N (6.23%) O (7.12%); IR (KBr): 667,1704,1740,3006,861,817,2967,2925,1088,1300,1571,1395,1371,1458 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.62 (t,4H, Ar-H,J=7.5), 7.68 (t,4H,Ar-H,J=7.5), 7.21 (d, 2H, ethylene), 2.63 (t, 2H, methylene), 6.88 (t, 1H, pyridine, J=7.5), 7.63 (t, 1H, pyridine,J=7.5), 7.35 (t, 1H, pyridine,J=7.5), 2.46 (s, 3H, CH_3-pyridine).

3,5-bis(4-chlorophenyl)-8-(5-methylpyridin-2-yl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (12d)

Cream solid, Yield (87.76%), M. P. 240 - 42ºC, M.F. $C_{25}H_{22}N_6Cl_2$ M.W.477.38, Composition: C (62.90%) H (4.64%) Cl (14.85%) N (17.60%); IR (KBr): 617,3107,708,1645,2999,817,2938,1207,1287,1485,1594,1445,1373,1483 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.48 (t,8H, Ar-H,J=7.5), 2.28 (t,2H,methine,J=7.0), 3.8 (d,2H,methine,J=7.0), 1.75 (m,2H,methylene), 9.97 (s, 2H, N-H), 7.90 (d, 1H, pyridine), 7.31 (t, 1H, pyridine,J=7.5), 6.54 (d, 1H, pyridine,J=7.5), 2.16 (s, 3H, CH_3-pyridine).

3,5-bis(4-chlorophenyl)-8-(4-methylpyridin-2-yl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (12e)

Pastel Orange solid, Yield (75.28%), M. P. 238 - 40ºC, M.F. $C_{25}H_{22}N_6Cl_2$ M.W.477.38, Composition: C (62.90%) H (4.64%) Cl (14.85%) N (17.60%); IR (KBr): 619,3197,709,1651,3044,817,2939,1209,1286,1594,1559,1444,1398,1484 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.48 (t,8H, Ar-H,J=7.5), 2.28 (t,2H,methine,J=7.0), 3.8

(d,2H,methine,J=7.0), 1.75 (m,2H,methylene), 9.97 (s, 2H, N-H), 7.85 (d, 1H, pyridine, J=7.5), 6.67 (t, 1H, pyridine, J=7.5), 6.52 (d, 1H, pyridine), 2.22 (s, 3H, CH_3-pyridine).

3,5-bis(4-chlorophenyl)-8-(6-methylpyridin-2-yl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (12f)

Zinc Yellow, Yield (76.34%), M. P. 318 - 20ºC, M.F. $C_{25}H_{22}N_6Cl_2$ M.W.477.38, Composition: C (62.90%) H (4.64%) Cl (14.85%) N (17.60%); IR (KBr): 621,3189,707,1659,2996,818,2941,1211,1288,1620,1589,1459,1371,1484 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.48 (t,8H, Ar-H,J=7.5), 2.28 (t,2H,methine,J=7.0), 3.8 (d,2H,methine,J=7.0), 1.75 (m,2H,methylene), 9.97 (s, 2H, N-H), 6.30 (t, 1H, pyridine, J=7.5), 7.42 (t, 1H, pyridine,J=7.5), 6.47 (d, 1H, pyridine,J=7.5), 2.46 (s, 3H, CH_3-pyridine).

RESULTS AND DISCUSSION

Chemistry

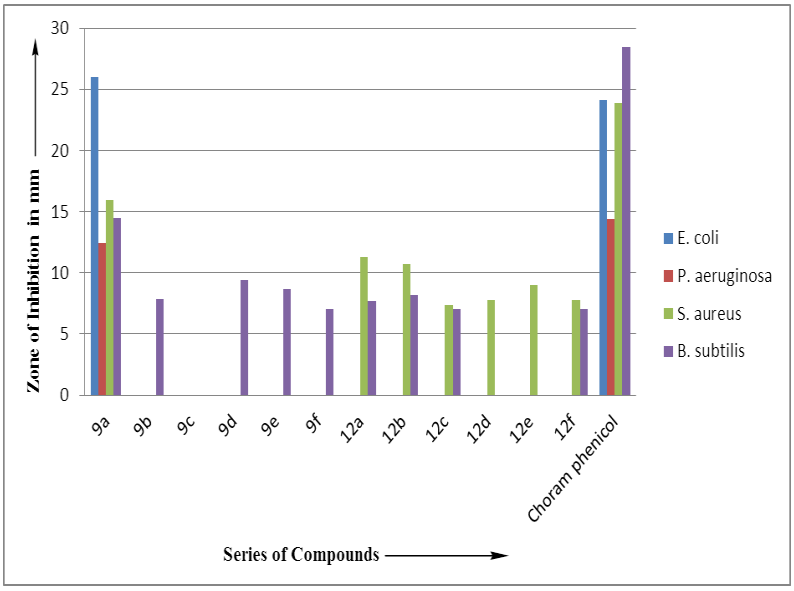
The series of bis-chalcones (9a-f) were synthesized by the reaction between N-phenyl succinimides/ N-phenyl succinimides and p-chloro benzaldehyde in presence of neutral Al2O3 with the help of microwave irradiations and reasonable yield is obtained. The formation of bis-chalcones was confirmed by IR, ^{13}CNMR and ^{1}H NMR and elemental analysis. The series pyrazole (12a-f) were prepared by the reaction of bis-chalcones (9a-f) and hydrazine hydrate in presence of neutral Al_2O_3 with the help of microwave irradiations and reasonable yield is obtained. The formation of pyrazoles was confirmed by IR, ^{13}C NMR and ^{1}H NMR and elemental analysis.

Antimicrobial Activities

All the synthesized bis-chalcones (9a-f) and pyrazole (12a-f) were screened for their antibacterial activity against gram positive bacteria *Staphylococcus aurous* (NCIM 2079), *Bacillus subtilis* (NCIM 2250) and gram negative bacteria *Escherichia coli* (NCIM 2109), *Pseudomonas aeruginosa* (NCIM 2036) using DMSO solvent. All these novel synthesized compounds were screened against Fungi (Yeast) *Candida albicans* (NCIM 3471) and *Aspergillus niger* (NCIM 545). The bacterial cultures were purchased from NCIM: National Collection of Industrial Microorganisms, National Chemical Laboratory (NCL), Pune, [India]. Some of the compound showed moderate to good activities against gram positive bacteria *S. aureus, B. subtilis* and synergetic activities against Fungi *C. albicans* and *A. niger* as shown in the Table –I and Graph –I;

Table-I: Antibacterial activities of bis chalcone (9a-f) and Pyrazole (12a-f)

Sr. No.	Sample	*E. coli*	*P. aeruginosa*	*S. aureus*	*B. subtilis*
		Mean±SD	***Mean ±SD***	***Mean ±SD***	***Mean ±SD***
1	**9a**	25.99±0.15	12.46±0.09	15.92±0.09	14.45±0.10
2	**9b**	- - -	- - -	- - -	7.90±0.07
3	**9c**	- - -	- - -	- - -	±
4	**9d**	- - -	- - -	- - -	9.40±0.04
5	**9e**	- - -	- - -	- - -	8.69±0.15
6	**9f**	- - -	- - -	- - -	7.05±0.05
7	**12a**	- - -	- - -	11.26±0.07	7.71±0.15
8	**12b**	- - -	- - -	10.72±0.18	8.17±0.05
9	**12c**	- - -	- - -	7.33±0.11	7.01±0.01
10	**12d**	- - -	- - -	7.79 ±0.16	- - -
11	**12e**	- - -	- - -	8.98±0.07	- - -
12	**12f**	- - -	- - -	7.80±0.07	7.04±0.06
	Choram phenicol	**24.09±0.10**	**14.39±0.07**	**23.92 ±0.17**	**28.43±0.29**

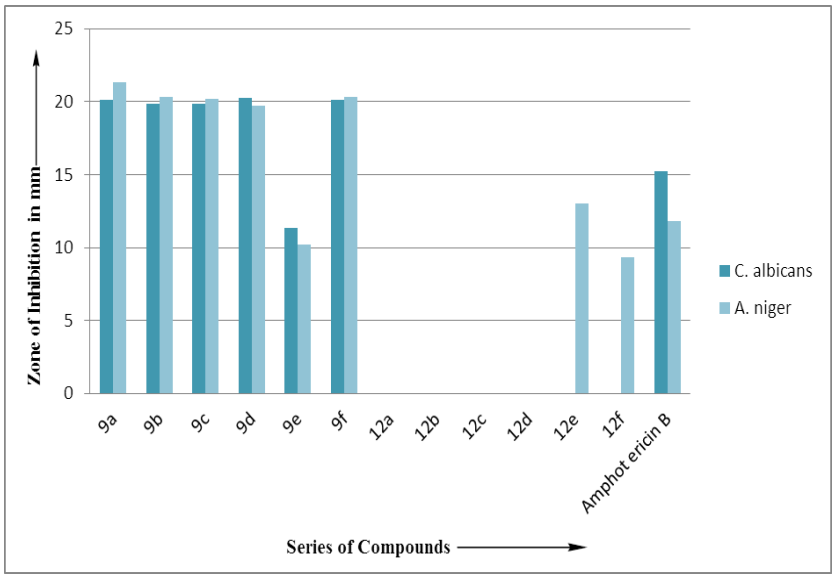


Graph-I: Antibacterial activities of bis chalcone (9a-f) and Pyrazole (12a-f).

Table-II: Antifungal activities of bis chalcone (9a-f) and Pyrazole (12a-f)

Sr. No.	Sample	*C. albicans*	*A. niger*
		Mean ±SD	***Mean ±SD***
1	**9a**	20.10±0.05	21.3±0.13
2	**9b**	19.83±0.16	20.3±0.12
3	**9c**	19.83±0.05	20.2±0.10
4	**9d**	20.27±0.27	19.7±0.17
5	**9e**	11.37±0.34	10.2±0.08
6	**9f**	20.14±0.01	20.3±0.07

7	**12a**	- - -	- - -
8	**12b**	- - -	- - -
9	**12c**	- - -	- - -
10	**12d**	- - -	- - -
11	**12e**	- - -	13±0.12
12	**12f**	- - -	9.34±0.10
	Amphot ericin B	**15.21±0.15**	**11.8±0.08**



Graph-II: Antifungal activities of Bis chalcone (9a-f) and Pyrazole (12a-f).

CONCLUSION

In this protocol, we have developed a novel and efficient way for the synthesis of chalcones and pyrazoles. The purview of the developed covenant is vast and kosher products could be retrieved without column chromatographic purification, which makes it a commercially viable process. A practical synthesis of these compounds has been achieved using our one pot microwave process as one of the important step. Currently, we are exploring the application of this newly developed protocol against gram positive bacteria *Staphylococcus aurous*, *Bacillus subtilis*; gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and Fungi (Yeast) *Candida albicans* and *Aspergillus niger.* Few of the compounds have shown moderate to good activities against gram positive bacteria *S. aureus, B. subtilis* and synergetic activities against Fungi *C. albicans* and *A. niger.*

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