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SYNTHESIS AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF SOME NOVEL CHALCONES OF 2, 6-DICHLORO-4-TRIFLUORO METHYL ANILINE

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Abstracts: As part of our research program on going search for compounds with antimicrobial activity. A new series of chalcones were synthesized via reaction between 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-dione, 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-piperidine-2, 6 dione and substituted aromatic aldehydes in presence acetic acid. The synthesized chalcones were characterized by spectral analysis and all compounds were screened for their antimicrobial activities.

Keywords: Chalcone, Pyroliodine-2, 5-dione, Piperidine-2, 6 dione.

Introduction: In the era of 21st century the research and development is at the top of globe especially in the field of pharmaceuticals, Polymer and Agrochemicals. Now a days the researchers are working too hard for developing the drugs for deadly diseases such as AIDS, Cancer. In all these research heterocyclic chemistry plays vital role for synthesizing such a crucial drugs and the heterocyclic rings plays active part in these drugs.
Cyclic imides itself act as anti-microbial[1-3], anti-fungal[4], muscle relaxant[5], hypotensive[6] anti-depressant[7], anti-tubercular[8], nerve conduction blocking[9] etc.agents and some are act as building block material for other important heterocyclic compounds[10].
Chalcones are naturally occurring important biological active compounds which is also constituent of natural product[11], the name chalcones was given by Kostanecki and Tambhor. Chalcone having reactive α, β unsaturated keto group which is responsible for their antimicrobial activity. From few decades varieties of chalcones have been studied and still research is continue. It has known by literature survey that there are large number patent and research articles are co-related to chalcones which is indication of their versatility and values in research.

Chalcones having multitasking medicinal features such as it used as anti-bacterial[12-13], anti-fungal[14], anti-oxidant[15], anti-malerial[16], anti- inflammatory[17], anti-cancer[18], anti-ulcer[19], anti-tumor[20], vase relaxant agent[21] and tyrosine inhibitors[22].

Due to its wide range of medicinal and pharmacological potential the researcher developed the huge research platform for new generation and now a day's young researcher get attracted towards it.

Literature survey also shows that 2, 6 dichloro 4-fluromethyl aniline is selectively utilized for synthesis of pesticide such as fiprolin[23-24]. In present work we have used 2, 6 dichloro 4-fluromethyl aniline for synthesizing some novel chalcones derivatives via cyclic imide 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (4a) using various substituted benzaldehyde.

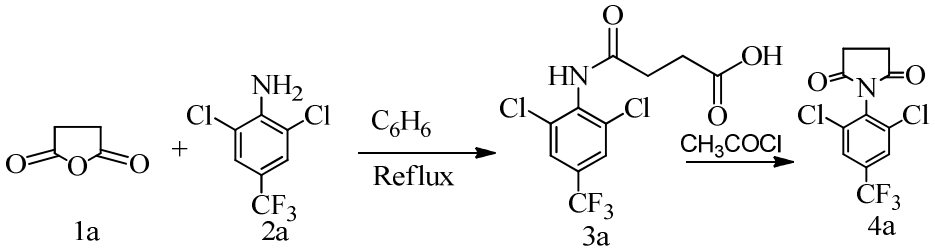
Material and Methods:

The chemicals are used for synthesized compound were chemically pure and branded. All melting points of synthesized compounds were taken in open capillary method and were found uncorrected. FTIR spectra are recorded on Perkin-Elmer spectrum. H^1NMR spectra are recorded on Bruker DRX 500 MHz NMR spectrometer with DMSO-d^6 solvent and TMS used as internal reference (chemical shift in δ ppm). The reaction was monitored by TLC which was accomplished by using pre-coated silica gel aluminum plates with mixture of hexane, ethyl acetate as solvent

1. Synthesis of 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione:

Succinic anhydride (0.01mol) was dissolved in benzene (10ml) then 2, 6-dichloro-4-trifluoromethyl aniline (0.01mol) was added to it vigorously. The 4-((2, 6-dichloro-4-(trifluoromethyl) phenyl) amino)-4-oxobutanoic acid was formed. This acid was cyclized by using (0.09) mole of fresh acetyl chloride at reflux conditions. The product (4a) was obtained and recrystallized from methanol (Scheme 1).

1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (4a): M.F: $C_{11}H_6Cl_2F_3N$, M.W: 312, Yield 90%, M.P.165-167°C, C, H, N Elem. Anal. Calculated: C, 38.34; H, 1.94; N, 4.49. Obtained: C, 38.24; H, 1.83; N, 4.34.

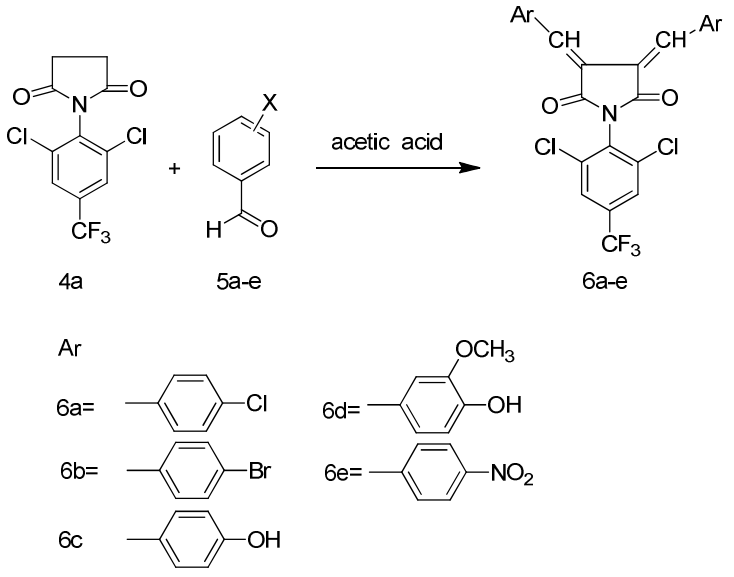


Scheme I

IR (KBr) cm^{-1}: 2900-3000 cm^{-1} (CH_2), 1650-1700 cm^{-1} (C=O), 1470-1500 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (C-N).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 2.5 (s, 4H), 7.7 (s, 2H, Ar-H).

2. Synthesis of chalcone derivatives (6a-e): Cyclic imide 1-(2,6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2,5-Dione (0.01 mol) and aromatic aldehyde (5a-e) (0.02 mol) was dissolved in glacial acetic acid (8 ml) and then concentrated on sand bath maintaining low flame. The colorless solid product was obtained (6a-e) and recrystallized from ethanol (Scheme 2).



Scheme 2

i) (3E,4E)-3,4-bis(4-chlorobenzylidene)-1-(2,6-dichloro-4- (trifluoromethyl) phenyl)pyrrolidine-2,5-dione (6a) : M.F: $C_{25}H_{12}Cl_4F_3NO_2$, M.W: 554, Yield 91%, M.P. 161-163°C, C, H, N Elem. Anal. Calculated: C, 53.89; H, 2.17; N, 2.51. Obtained: C, 53.59; H, 2.11; N, 2.57.

IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 3200-3550 cm^{-1} (Ar-OH).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 8.08 (s, 2H, C=CH-Ar), 7.70 (s, 2H, Ar-H), 7.68 (dd, 8H, 2Ar-H).

ii) (3E, 4E)-3, 4-bis (4-bromobenzylidene)-1-(2, 6-dichloro-4-(trifluoromethyl) phenyl) pyrrolidine-2, 5-dione (6b): M.F: $C_{25}H_{12}Br_2Cl_2F_3NO_2$, M.W: 646, Yield 90%, M.P. 191-193°C, C, H, N Elem. Anal. Calculated: C, 46.48; H, 1.87; N, 2.17.Obtained: C, 46.40; H, 1.83; N, 2.47.

IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 3200-3550 cm^{-1} (Ar-OH).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 8.01 (s, 2H, 2C=CH-Ar), 7.9 (s, 2H, Ar-H), 7.5-7.8 (8H dd 2Ar-H).

.

iii) (3E, 4E)-3, 4-bis (4-hydroxybenzylidene)-1-(2, 6-dichloro-4-(trifluoromethyl) phenyl) pyrrolidine-2, 5-dione (6c): M.F: $C_{25}H_{14}Cl_2F_3NO_4$, M.W: 520, Yield 92%, M.P. 120-122°C, C, H, N Elem. Anal. Calculated: C, 57.71; H, 2.71; N, 2.69. Obtained: C, 57.68; H, 2.69; N, 2.67.

IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 3200-3550 cm^{-1} (Ar-OH)

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 7.75 (s, 2H, 2C=CH-Ar), 7.77 (s, 2H, Ar-H), 6.9-8.008 (dd, 8H, 2Ar-H), 9.7 (s, 1H, Ar-O-H).

iv) 3E,4E)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-3,4-bis(4-hydroxy-3-methoxy benzylidene) pyrrolidine-2,5-dione(6d): M.F: $C_{27}H_{18}Cl_2F_3NO_6$, M.W: 580, Yield 94%, M.P. 91-93°C. C, H, N Elem. Anal. Calculated: C, 55.88; H, 3.13; N, 2.41. Obtained: C, 58.86; H, 3.10; N, 2.43.

IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 3200-3550 cm^{-1} (Ar-OH), 1000-1300 cm^{-1} (O-CH_3), 3300 cm^{-1} (C-H).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 8.008 (s, 2H, 2C=CH-Ar), 7.4 (s, 2H, Ar-H), 6.9-7.4(6H s 2Ar-H), 9.7 (s, 1H, Ar-O-H), 3.85 (s, 3H OCH_3).

v) (3E, 4E)-3, 4-bis (4-nitrobenzylidene)-1-(2, 6-dichloro-4-(trifluoromethyl) phenyl) pyrrolidine-2, 5-dione (6e): M.F: C_{25} $H_{12}Cl_2F_3$ N_3O_6, MF: 578, Yield 89%, M.P. 141-143°C, C, H, N Elem. Anal. Calculated: C, 51.92; H, 2.09; N, 7.27. Obtained: C, 51.90; H, 2.1; N, 7.30.

IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 1550-1600 cm^{-1} (N=O).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 7.99 (s, 2H, 2C=CH-Ar), 8.17(s, 2H, Ar-H), 8.1-8.4 (dd, 8H, 2Ar-H).

Preparation of media for microbial screening: All derivatives of chalcone 6a-e synthesized in our laboratory were screened for their in-vitro antimicrobial activity directed against Gram positive bacterial viz *Staphylococcus aureus* and Gram negative bacterial *E.coli* and two fungal cultures viz *Alternaria alternata* and *Aspergilus niger* using well diffusion method (Reference). Derivatives of chalcone 6a-e were dissolved in DMSO solvent. The antimicrobial activity of chalcone 6a-e was compared with ciprofloxacin and terbinafine.

Stock solution (100 microgram per ml) of each compound were prepared in DMSO solvent. Similarly stock solution of standard drug ciprofloxacin used for antibacterial activity and terbinafine used for antifungal activity had been prepared. Microbiological media used for bacteria is nutrient agar (Hi media) and potato dextrose agar (Hi-media) for fungi.

concentration 100µg/ml per well poured as per well diffusion method and incubated for 24 hours at 37ºC after incubation the results were obtained, where the compounds showed activity there was zone of inhibition occurred, similarly for fungi stock solution 100µg/ml per well poured as per well diffusion method and incubated for next seven days at 29ºC after seven days results were noted. The diameter of zone of inhibition measured by Vernier Caliper in mm and tabulated in below mentioned (table-1).

RESULTS AND DISCUSSION

We have synthesized cyclic imide 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (4a) as shown in scheme (I) and this cyclic imide were confirmed by spectral analysis (H^1 NMR, FTIR) and elemental analysis techniques. This imide and various benzaldehydes (5a-e) were used to synthesize multifarious chalcones (6a-e) as shown in scheme (II). All these synthesized chalcones (6a-e) were analyzed by FTIR, H^1NMR spectroscopy and elemental analysis.

Biological testing of the compounds: Sample 6a was active against Gram positive bacteria *Staphylococcus aureus* and did not inhibit the growth of Gram negative bacteria *E.coli*, it was equally active against *Alternaria alternata* however, it showed potent antifungal activity against *Aspergilus niger* (Table 1).

Sample 6b was more active against Gram positive bacteria *Staphylococcus aureus* but was ineffective against Gram negative bacteria *E.coli*, its exhibited antifungal activity against *Aspergilus niger* however, it showed potent antifungal activity against *Alternaria alternata*.

Sample 6c was effective only against *Alternaria alternata*. Rest of the cultures under test resisted the action of this compound.Sample 6d was effective against *E.coli* and *Alternaria alternata*. Sample 6e was effective against all cultures under test, however its exhibited potent activity against *Alternaria alternata*.

Antimicrobial activity of all preparations was comparable with standard antimicrobial agents. Antifungal activity of all samples and antibacterial (*against E.coli*) of sample 6d and 6e was superior over the activity of standard antimicrobial agents

Table 1 Antimicrobial activity of compounds 6a-e

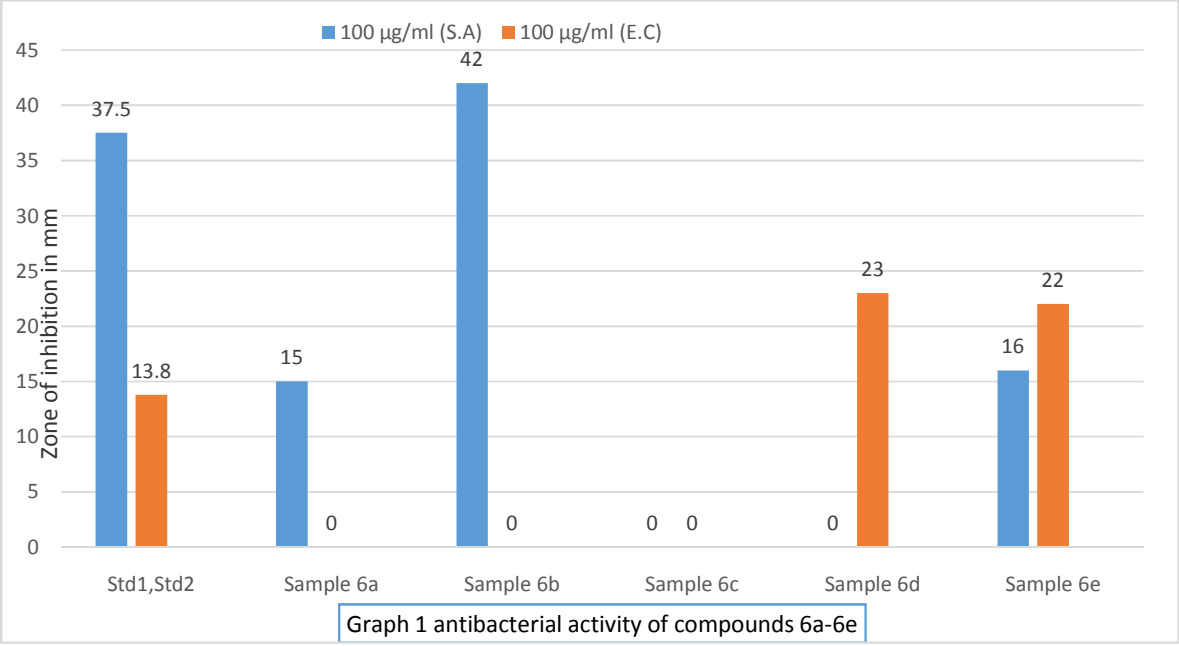
Sr.No.	Sample Code	*S. aureus*	*E. coli*	*A. altarnata*	*A.niger*
1	6a	15	-	14.3	56.6
2	6b	42	-	36.4	22.4
3	6c	-	-	12.3	-
4	6d	-	23	72.4	
5	6e	16	22	23.2	68.2
6	Ciprofloxacin	37.5	13.8	NA	NA
7	Terbinafine	NA	NA	68.2	69.5
8	DMSO (control)	-	-	-	-

Keyword: ' –' means no zone of inhibition, NA means not applicable

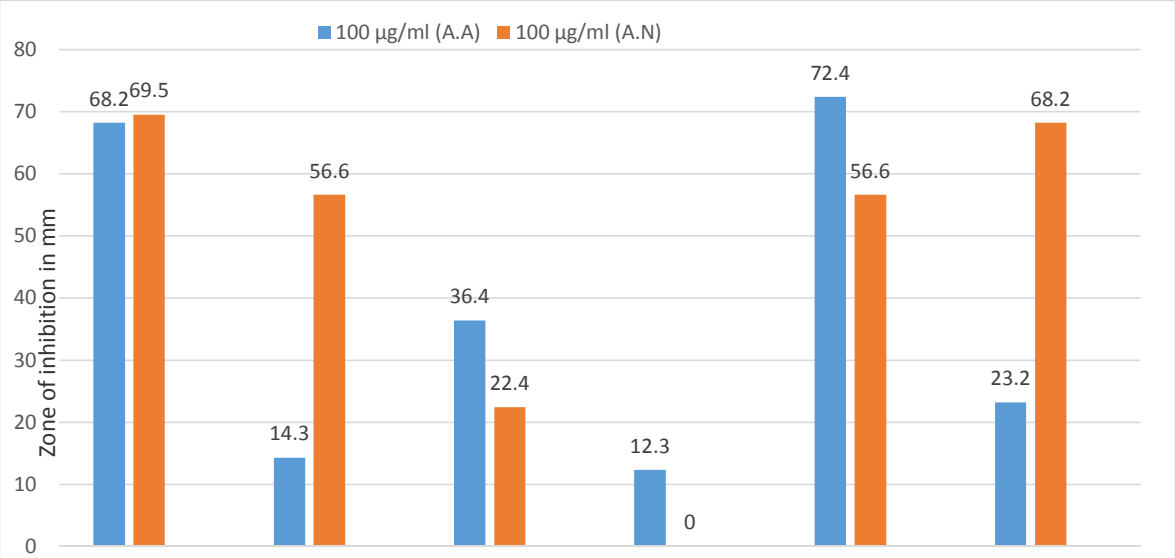
Graphical comparison of antimicrobial activity

Graph1.antibacterial activity comparison with standard drugs

Graph II Antifungal activity comparison with standard drug



Graph 1 antibacterial activity of compounds 6a-6e



Graph 1 antifungall activity of compounds 6a-6e

CONCLUSION:

Most of the chalcone derivatives were found to be active against *Staphylococcus aureus, Alternaria. alternata* and *Aspergillus niger*. Chalcone 6b and 6e showed potent activity against *Staphylococcus aureus*, *Alternaria alternata* respectively while 6d superior over the activity of standard antimicrobial agents.

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