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Synthesis and antimicrobial evaluation of some novel 3,4-bis(substituted- phenyl)-7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5,7-dihydro-2H- pyrrolo[2,3-c:5,4-c']dipyrazole derivatives of 2,6-dichloro-4-trifluoro methyl aniline

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Abstract : Succinic anhydride was converted to 4-(2, 6-dichloro-4-(trifluoromethyl) Phenyl) amino)-4-oxobutanoic acid. It underwent cyclization in presence of acetyl chloride furnished 1-(2, 6-dichloro-4-trifluoromethyl-1-phenyl)-pyrrodine-2, 5-Dione. This pyrroline-2, 5-dione on condensation with substituted aromatic aldehydes in presence of acetic acid afforded (3E, 4E)-3, 4-bis (substituted benzylidene)-1-(2, 6-dichloro-4-(trifluoromethyl) phenyl) pyrrolidione-2, 5- Dione. These derivative underwent ring closer with hydrazine hydrate afforded 3, 4-bis (substituted phenyl)-7-(2, 6-dichloro-4-(trifluoromethyl) phenyl)-5, 7-dihydro-2H-pyrrole [2, 3-C: 5-4-C[1]] dipyrazole.All the synthesized compounds were analyzed by spectral and elemental analysis. Similarly these derivatives were screened for their microbial activity against S.aureus, E.coli, A. Alternaria and A.niger. Some of the derivatives showed potent activity against S.aureus and E.coli.
Keywords : Bis-chalcone, bis-pyrazole, anti-microbial activity.

Introduction:

Litrature survey shows that the 2, 6-dichloro-4-trifluoro methyl aniline is the compound particularly used to synthesize pesticides such as fipronil[1-3].Now a days the agrochemical research is at the peak of mountain. Researchers are much more attracted towards the project of pesticides synthesis. Here we have used this 2, 6-dichloro-4-trifluoro aniline for synthesis of some novel bis heterocyclic pyrazole via cyclic imide[4] 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2 and multifarious chalcones. Succinic anhydride was converted to 4-(2, 6-dichloro-4-(trifluoromethyl) Phenyl) amino)-4-oxobutanoic acid. It underwent cyclization in presence of acetyl chloride furnished 1-(2, 6-dichloro-4-trifluoromethyl-1-phenyl)-pyrrodine-2, 5-Dione. This pyrroline-2, 5-dione on condensation with substituted aromatic aldehydes in presence of acetic acid afforded (3E, 4E)-3, 4-bis (substituted benzylidene)-1-(2, 6-dichloro-4-(trifluoromethyl) phenyl) pyrrolidione-2, 5- Dione. These derivative underwent ring closer with hydrazine hydrate afforded 3, 4-bis (substituted phenyl)-7-(2, 6-dichloro-4-(trifluoromethyl) phenyl)-5, 7-dihydro-2H-pyrrole [2, 3-C: 5-4-C[1]] dipyrazole. All the synthesized compounds were analyzed by spectral and elemental analysis. Simillarly these derivatives were

screened for their microbial activity against S.aureus, E.coli, A. Alternaria and A.niger. Some of the derivatives showed potent activity against S.aureus and E.coli.

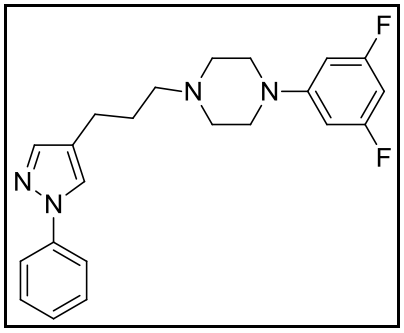
Chalcones and their derivatives are known for their biological activities such as anti-bacterial[5-6], anti-ulcer[7], anti-fungal[8], anti-malerial[9], anti-cancer[10] etc. They also act as precursor for many crucial heterocyclic compounds like bis heterocyclic pyrazole,isoxazole, flavones, pyrrozoline[11-12] etc.

Now a days heterocyclic compounds are core heart in the research and development field and it covers the wide area of research especially in pharmaceutical sciences, by considering this advantage we have successfully synthesized series of novel bis heterocyclic pyrazole derivatives of 2, 6-dichloro-4-trifluoro methyl aniline.

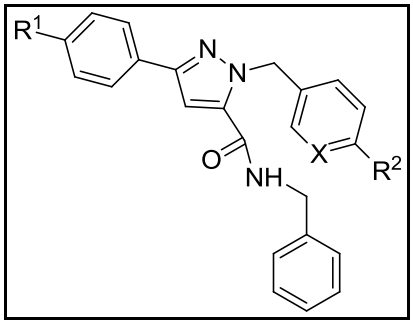
Pyrazole is a heterocyclic organic compound having formula $C_3 H_3 N_2 H$. It is 5 membered ring which is classified by 3 carbon atoms and adjacent two nitrogen atoms.

It is reported that large number of pyrazole and their derivatives show significant biological activities. In the medicinal field pyrazole and their derivatives are utilized for various biological and pharmaceutical activities such as anti-inflammatory[13], antifungal [14], anti- analgesic[15], anti-viral[16], anti-tubercular[17], anti-convulsant[18], anti-bacterial[19-20], anti-oxidant[21] etc.

Pyrazole moiety also plays valuable role in the field of cancer, Hitoshi et al synthesized Pyrimidinyl pyrazole derivatives as anti-tumor agent which is also acts as antiproliferative agent[22].



Ding et al too synthesized a series of novel 3 aryl-1—arylmethyl-1H- pyrazole-5-carboxamide derivatives which reduces A549 lung cancer cell growth[23].



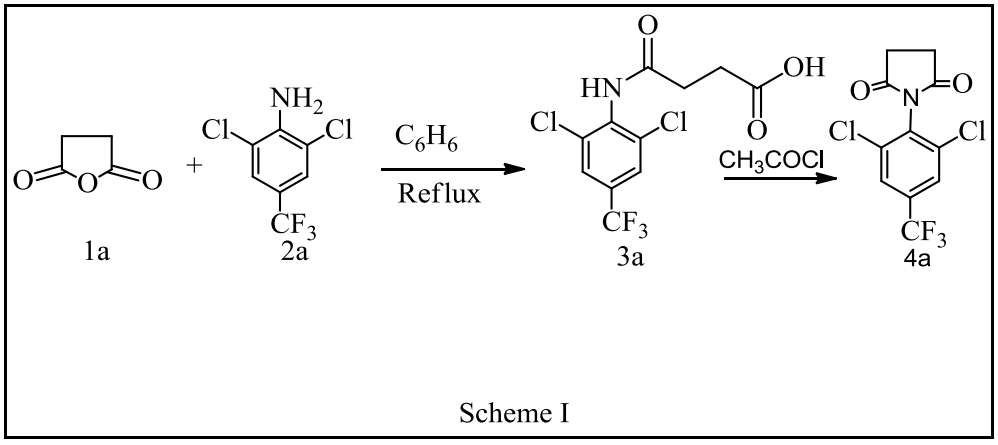
The researchers utilized pyrazole moiety for synthesizing cancer drug and still broad research is continue against cancer growth cell.[24-27]

Material and Methods:

All reagents and solvent utilized for synthesized compounds are of commercial grade, melting points are 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 as solvent and tetramethylsilane (TMS) used as internal reference (chemical shift in δ ppm) these all newly synthesized compounds were formed according to following scheme 1,2 and 4.

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

Succinic anhydride (0.01mol) was dissolved in 10mL benzene. Then 2, 6-dichloro-4-trifluoromethyl aniline (0.01mol) was added to it vigorously hence 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.



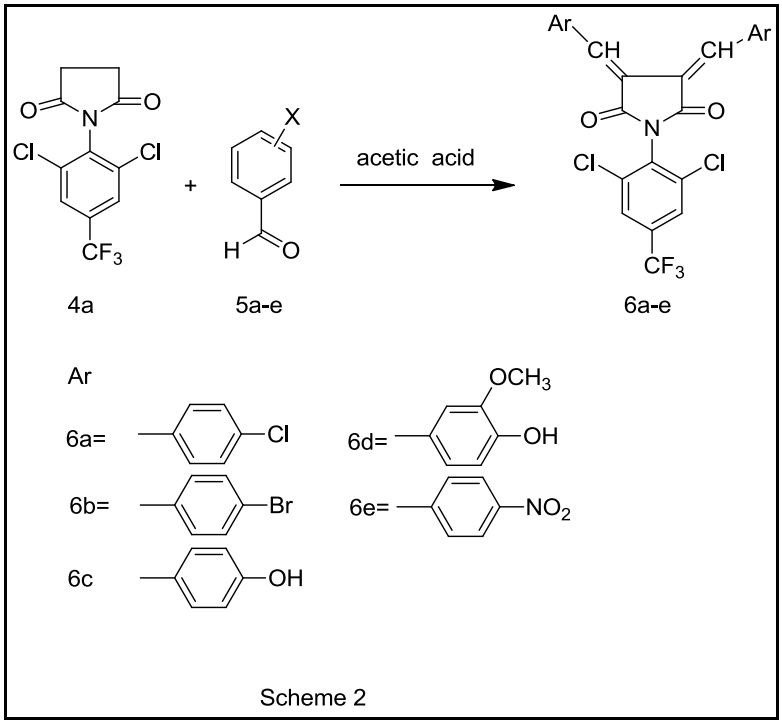
Scheme I

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.

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 derivatives of chalcones (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) then concentrated it on sand bath maintaining low flame. The colorless solid product was obtained (6a-e) and recrystallized from ethanol.



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: 552, Yield 91%, M.P. 161-163°C, C, H, N Elem. Anal: 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, 2C=CH-Ar), 7.7 (s, 2H, Ar-H), 7-6.8 (8H dd 2Ar-H).

ii)(3E,4E)-3,4-bis(4-bromobenzylidene)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)pyrrolidine-2,5-dione(6b): M.F: $C_{25}H_{12}\ Br_2Cl_2F_3\ NO_2$, 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 (dd, 8H, 2Ar-H).

iii) (3E, 4E)-3, 4-bis (2-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. 160-162°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), 6.9-8.08 (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-methoxybenzylidene) 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), 3300 cm^{-1} (C-H).

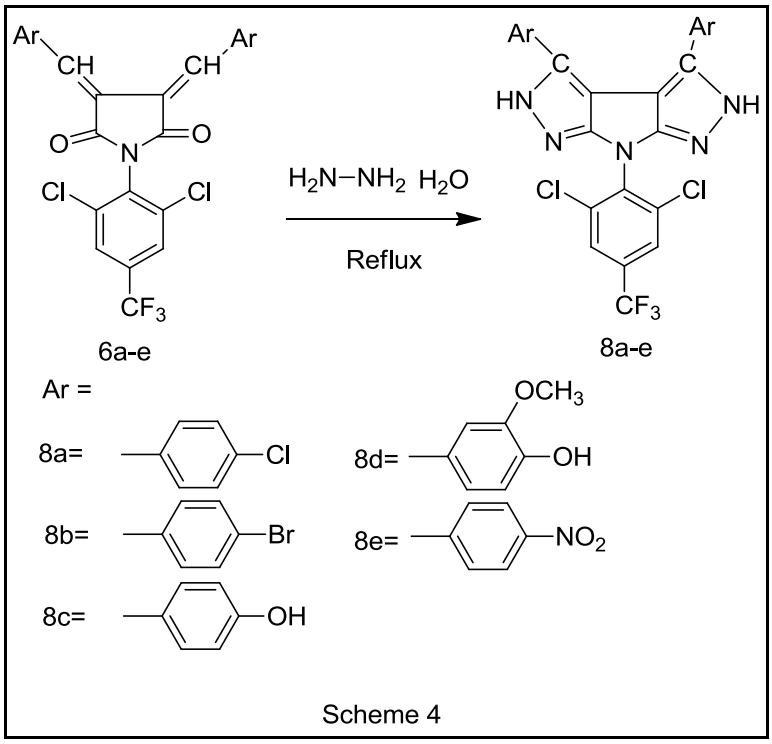
H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 8.006 (s, 2H, 2C=CH-Ar), 7.4 (s, 2H, Ar-H), 6.9-7.4(s, 6H, 2Ar-H), 9.7 (s 1H, Ar-O-H), 3.85 (s, 3H, O-CH_3).

v) (3E, 4E)-3, 4-bis (4-nitrobenzylidene)-1-(2, 6-dichloro-4-(trifluoromethyl) phenyl) pyrrolidine-2, 5-dione (6e): M.F: $C_{25}\ H_{12}\ Cl_2\ F_3\ N_3\ O_6$, M.W: 574, 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).

2.Synthesis derivatives of Pyrozole (4a-e): Dissolved chalcones derivatives (4a-e) (0.01 mol) in ethanol (8 ml) then add Hydrazine monohydrate (0.02 mol), reflux this mixture for next 16 hours with maintaining 80° to 90°C temperature on water bath .The precipitated coloured solid compounds were obtained, recrystallized from benzene.



Scheme 4

i)3,4-bis(4-chlorophenyl)-7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5,7-dihydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (8a): M.F: $C_{25}H_{12}Cl_4F_3N_5$, M.W: 581, Yield 80%, M.P. 171-173°C, C, H, N Elem. Anal. Calculated: C, 51.66; H, 2.08; N, 12.05. Obtained: C, 51.68; H, 2.03; N, 12.01.

IR (KBr) cm^{-1}: 3300-3400 cm^{-1} (N-H), 1520-1630 cm^{-1} (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1} (ArC=C).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 10.16 (s, 2H, N-H), 8.06 (s, 2H, Ar-H), 7.4-7.9 (dd, 8H, 2Ar-H).

ii)3,4-bis(4-bromophenyl)-7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5,7-dihydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (8b): M.F: $C_{25}H_{12}Br_2Cl_2F_3N_5$, M.W:670, Yield 78%, M.P. 161-163°C, C, H, N Elem. Anal. Calculated: C, 49.88; H, 1.80; N, 10.25. Obtained: C, 49.84; H, 1.79; N, 10.27.

IR (KBr) cm^{-1}: 3300-3400 cm^{-1} (N-H), 1520-1630 (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1}(ArC=C).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 10.16 (2H s, N-H), 8.1 (s, 2H, Ar-H), 7.5-7.8 (dd, 8H, 2Ar-H).

iii)2,2'-(7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5,7-dihydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole-3,4-diyl)diphenol (8c): M.F: $C_{25}H_{14}Cl_2F_3N_5O_2$, M.W: 543, Yield 80%, M.P. 233-235°C, C, H, N Elem. Anal. Calculated: C, 55.16; H, 2.59; N, 12.87. Obtained: C, 55.19; H, 2.69; N, 12.91.

IR (KBr) cm^{-1}: 3300-3400 cm^{-1} (N-H), 1520-1630 cm^{-1} (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1} (ArC=C).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 10.16 (2H s, N-H), 8.0 (2H s, Ar-H), 7.5-7.9 (dd, 8H, 2Ar-H) 9.8 (s, 1H, Ar-O-H).

iv)4,4'-(7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5,7-dihydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole-3,4-diyl)bis(2-methoxyphenol) (8d): M.F: $C_{27}H_{18}Cl_2F_3N_5O_4$, M.W: 604, Yield 79%, M.P. 121-123°C, C, H, N Elem. Anal. Calculated: C, 53.66; H, 3.00; N, 11.59. Obtained: C, 53.69; H, 3.09; N, 11.64.

IR (KBr) cm^{-1}: 3300-3400 cm^{-1} (N-H), 1520-1630 cm^{-1} (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1} (ArC=C).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 10.16 (2H s, N-H), 8.0 (2H s, Ar-H), 7.5-7.9 (s, 2H, dd, 4H, 2Ar-H), 9.8 (s, 1H, Ar-O-H), 3.8 (s, 3H, O-CH_3).

v)7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-3,4-bis(4-nitrophenyl)-5,7-dihydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (8e): M.F: $C_{25}H_{12}Cl_2F_3N_7O_4$, M.W: 562, Yield, 85%, M.P. 152-154°C, C, H, N Elem. Anal. Calculated: C, 49.85; H, 2.01; N, 16.28. Obtained: C, 49.89; H, 2.06; N, 16.23.

IR (KBr) cm^{-1}: 3300-3400 cm^{-1} (N-H), 1520-1630 cm^{-1} (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1} (ArC=C).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 10.16 (s, 2H, N-H), 7.8 (s, 2H, Ar-H), 8.0-8.2 (dd, 8H, 2Ar-H).

Antimicrobial Activity (8a-e)

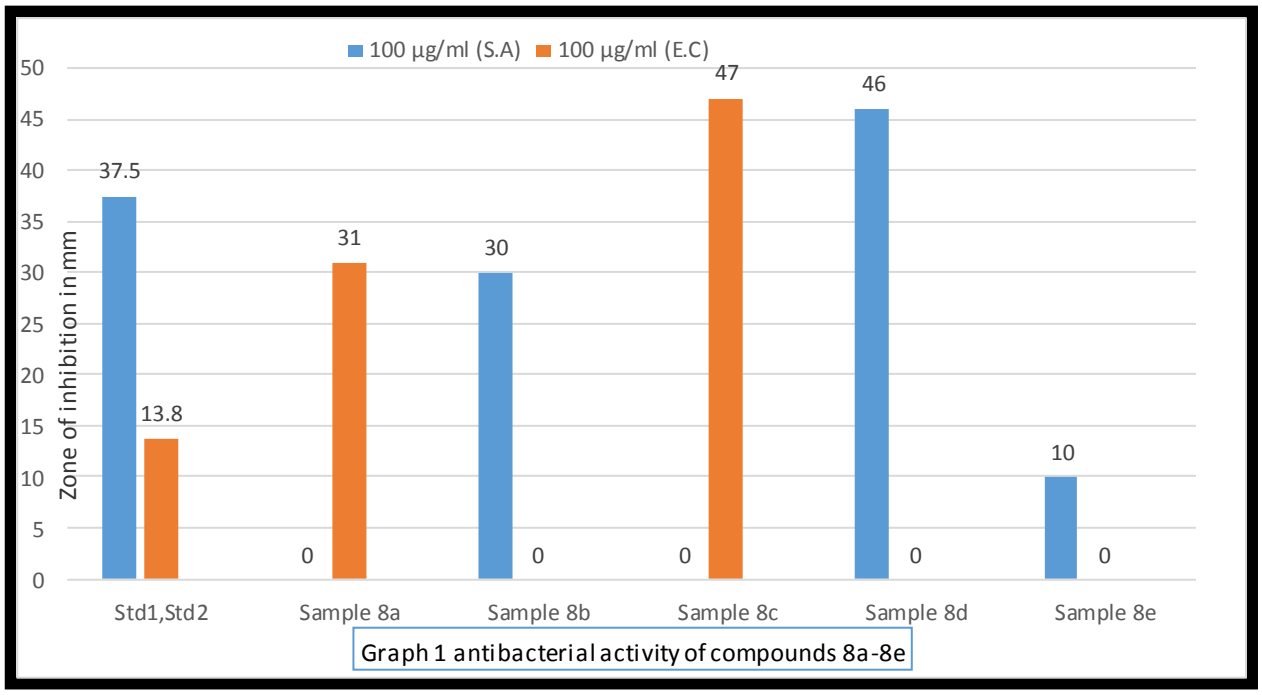
All the synthesized compounds (8a-e) were screened for their in vitro antimicrobial activity against bacteria and fungi such as *Staphylococcus aurreus*, *Escherichia coli*, *Alternaria altarnata*, and *Aspergilus niger* using paper disc diffusion method by aiding DMSO solvent.

Stock solution (100 microgram per ml) of each was compound 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 were results noted. The diameter of zone of inhibition were measured by Vernier Caliper in mm and tabulated in table I

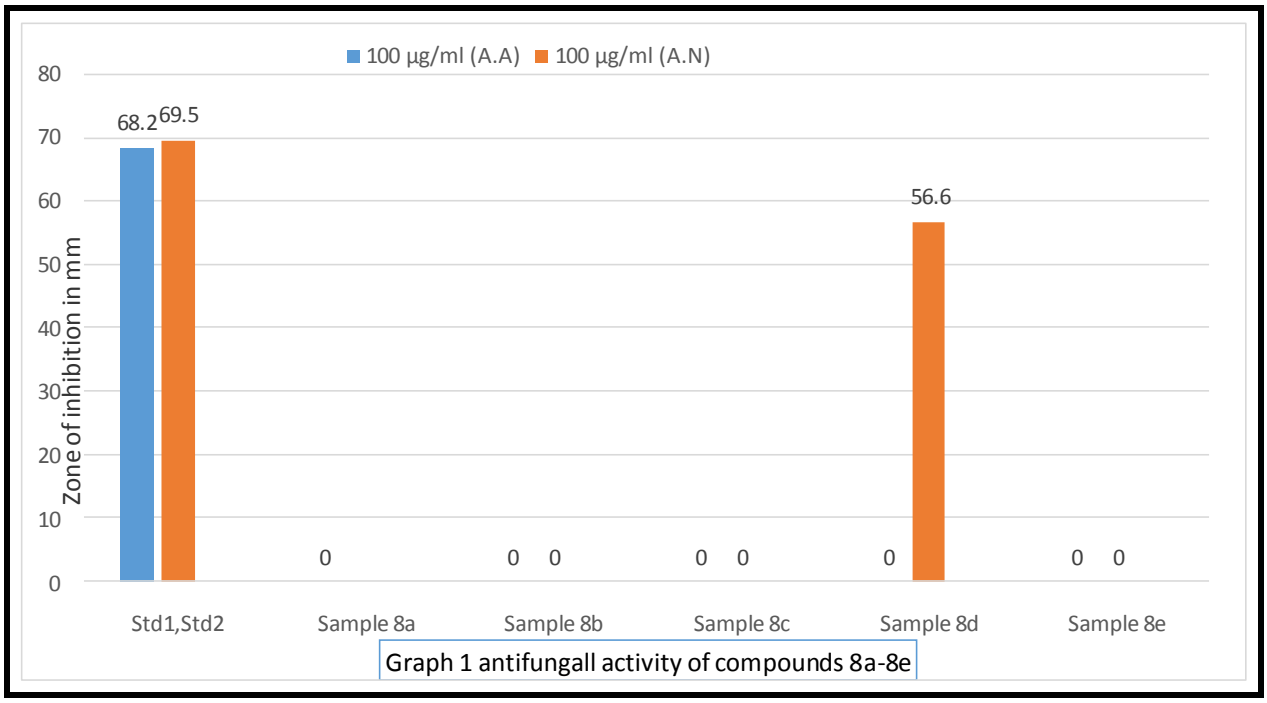
Table 1 Antimicrobial activity of compounds 8a-e

Sr.No.	Sample Code	*S. aureus*	*E. coli*	*A. altarnata*	*A.niger*
1	8a	-	31	-	-
2	8b	30	-	-	-
3	8c	-	47	-	-
4	8d	46	-	-	55.6
5	8e	10	-	-	
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

Result and Discussion

Starting imide 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (4a) was successfully synthesized and confirmed by H^1 NMR and FTIR spectroscopy. This imide and different benzaldehydes (5a-e) were used to synthesize multifarious chalcones (6a-e), these multifarious chalcones were cyclized by hydrazine monohydrate and furnished various pyrazoles. All these compounds analyzed by spectral analysis and elemental analysis technique.

Antibacterial activity :

All synthesized compounds were screened for their in vitro antimicrobial activity against one Gram positive bacterial strains and one fungal strain i.e. *Staphylococcus aureus*, *Alternaria altarnata* and one Gram negative bacterial strain and one fungal strain i.e. *Escherichia coli*, *Aspergilus niger* respectively. Some compounds were showed good activity and some showed moderate activity against these microorganism, Ciprofloxacin and terbinafine were used as standard drugs for bacteria and fungi respectively.

Conclusion:

All compounds have been successfully prepared and characterized by elemental analysis and spectroscopy techniques (H^1NMR and FTIR). Compounds 8a-e were screened for their in vitro antimicrobial activity, compound 8a and 8c showed potent activity against *Escherichia coli* and compounds 8b, 8d and 8e also showed good activity against *Staphylococcus aureus.*

In these compounds 8b, 8d and 8e, compound 8d exhibited good activity against *Aspergilus niger*.

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1. Tomlin CDS. "The Pesticide Manual. England Hampshire; 14th ed.; British Crop Protection Council., 2006; 462-464.
2. Aajoud A, Ravanel P, Tissut M. Fipronil metabolism and dissipation in a simplified aquatic ecosystem. J. Agric. Food. Chem, 2003; 51(12): 1347-1352.
3. Hainzl D, Casida JE. Fipronil insecticide: novel photochemical desulfinylation with retention of neurotoxicity. Proc. Natl. Acad. Sci, 1996; 93(23): 12764-12767.
4. Rajput SS, Sayyed RM. "Synthesis and formylation of cyclic imides using Vilsmeire-Haack reaction from 2, 6 dichloro-4-triflouromethyl aniline and their anti-microbial activity", WJPR., 2015; (4)12: 1689-1695.
5. Rajput SS, Sayyed RM."Synthesis, characterization and Biological Evaluation of 3,4-bis(substituted-Phenyl)-7-(2,6- dichloro-4-(trifluoromethyl)phenyl)-7H-pyrrolo[2,3-C:5,4- C'] diisoxazoles from 2, 6-dichloro-4-trifluoro methyl aniline. Int. J. Curnt. Tren. Pharm, Res., 2017, 5(1): 10-15.
6. Dhivare RS, Rajput SS. "Synthesis and antimicrobial evauation of some novel bis- heterocyclic chalcones from cyclic imides under microwave irradiation". Chemical Science Review and letter., 2015, 4(15): 937-944.
7. Jeffrey JA, Pamela EO, Jared LR, Jeffrey NJ, Peter DM, Linda MO, Pamela SW, and Beth LE. "Synth sis and biological evaluation of flavonoids and related compoundsgasprotective", Bioorganic & Medicinal Chemistry Letters., 1996; 6 (8): 995-998.
8. Lahtchev KL, Batovska DI,Parushev SP, Ubiyvovk VM,Sibirny AA. "Antifungal activity of chalcones: A mechanistic study using various yeast strains", European Journal of Medicinal Chemistry., 2008; 43(10): 2220-2228.
9. Ram VJ, Saxena A, Srivastava S and Chandra S. "Oxygenated chalcones and bischalcones as potential antimalarial agents. Bioorganic & Medicinal Chemistry Letters., 2000; 10(19): 2159-2161.
10. Mahapatra DK, Bharti SK, Asati V. "Anticancer Chalcones: Structral and molecular target perspectives", European journal of medical chemistry., 2015; 98(15): 69-114.
11. Kulkarni PS, Kondhare DD, Varala R, Zubaidha PK. "Cyclization of 2'-hydroxychalcones to flavones using ammonium iodide as an iodide as an iodine source-an eco-friendly approach", Journal of the sembian Chemical Society., 2013; 78(7): 909-916.
12. Detsi A, Majdalani M, Kontogiorgis CA, Hadjipavlou-Latina D. "Natural and synthetic 2-hydroxy -chalcones and aurones:Synthesis, characterization and evaluation of the antioxidant and soybean lipoxygenase inhibitory activity", Bioorganic & Medicinal Chemistry., 2009; 17(23): 8073–8085.

13. Ailwadi, S, Jyoti Y, Yadav M, Pathak D. Synthesis and characterization of some substituted pyrazoles as analgesics and anti-inflammatory agents", Der. Pharma. Chemica., 2011; 3(1): 215-222.
14. Priyadarsini, P, Ujwala B, venkata R, Madhava RV. "Synthesis and antimicrobial activity of some novel pyrazoles", Der Pharmacia letter., 2012; 4(4): 1123-1128.
15. Dias LR, Salvador RR. "Pyrazole Carbohydrazide Derivatives", Pharmaceuticals., 2012; 5(3): 317-324.
16. Osama I, El-Sabhagh, Baraka MM, Ibrahim SM. "Synthesis and antiviral activity of new pyrazole and thiazole derivatives", Eur J Med Chem., 2009; 44(9); 3746- 3753.
17. Kini SG, Bhat AR, Bryant B, Williamson JS, Dayan FE. Synthesis, antitubercular activity and docking study of novel cyclic azole substituted diphenyl ether derivatives. Eur J Med Chem., 2009; 44(2): 492-500.
18. Singh A, Rana AC. "Synthesis and anticonvulsant activity of 1-[(4, 5-dihydro-5-phenyl- 3-(phenylamino)pyrazol-1-yl)]ethanone derivatives". J. Chem. Pharm. Res., 2010; 2(1): 505-511.
19. Schmidt A, Dreger. "Recent Advances in the Chemistry of Pyrazoles.Properties,Biological activities, and synthesis", Curr.Org.Chem., 2011; 15 (9): 1423-1463.
20. Bekhit AA, Aziem TA. "Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents", Bioorg Medi Chem., 2004; 12(8): 1935–45.
21. Pasin JSM, Ferreria APO, Saraiva ALL, Ratzlaff, V, Andrighetto R., Machado P, Marchesam, S, Zanette, RA, Martins MAP. Antipyretic and antioxidant activities of 5- trifluoromethyl-4,5-dihydro-1H-pyrazoles in rats", Braz J Med Biol Res., 2010; 43(12): 1193-1202.
22. Ohki H, Hirotani K, Naito H, Ohsuki S, Minami M, Ejima A et al. "Synthesis and Mechanism of Action of Novel Pyrimidinyl Pyrazole Derivatives Possessing Antiproliferative Activity". Bioorg Med Chem Lett., 2002; 12(21): 3191–3193.
23. Ding XL, Zhang HY, Qi L, Zhao BX, Lian S, Lv HS et al." Synthesis of novel pyrazole carboxamide derivatives and discovery of modulators for apoptosis or autophagy in A549 lung cancer cells", Bioorg Med Chem Lett., 2009; 19(18): 5325–328.
24. Xia Y, Dong ZW, Zhao BX, Ge X, Meng N, Shin DS et al. "Synthesis and structure–activity relationships of novel 1-arylmethyl-3- aryl-1H-pyrazole-5-carbohydrazide derivatives as potential agents against A549 lung cancer", Bioorg Med Chem, 2008; 43(11): 2347-2353.
25. Farag AM, Ali KA, El-Debss TM, Mayhoub AS, Amr AGE, Abdel-Hafez NA et al. "Design, synthesis and structure activity relationship study of novel pyrazole-based heterocycles as potential antitumor agents", Eur J Med Chem., 2010; 45912): 5887- 5898.
26. Zheng LW, Li Y, Geb D, Zhao BX, Liu YR, Lv HS et al. "Synthesis of novel oxime containing pyrazole derivatives and discovery of regulators for apoptosis and autophagy in A549 lung cancer cells", Bioorg Med Chem Lett., 2010; 20(16): 4766–4770.
27. Quirante J, Ruiz D, Gonzalez A, López C, Cascante M, Cortés R et al. "Platinum(II) and palladium(II) complexes with (N,N) and (C,N,N)− ligands derived from pyrazole as anticancer and antimalarial agents: Synthesis, characterization and in vitro activities", J Inorg Biochem., 2011; 105(12): 1720–1728.

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