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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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Abstract:
Chalcones are the most significant genre of organic compounds that are usually synthesized by condensation reactions such Claisen Schmidt condensation and Aldol condensation in presence of acid or base catalysis. These compounds have α, β-unsaturated carbonyl group along with unrivaled application in the arena of organic chemistry and are selectively classified for their wide spectrum biological significances such as antibacterial, antifungal, antiviral, anticancer, anti-HIV, antipyretic, and so forth.
In the present investigation, a new series of chalcones were synthesized via reaction between 1-(2, 6-dichloro-4- trifluoromethyl-phenyl)-piperidine-2, 6 dione and substituted aromatic aldehydes in the presence of acetic acid. The synthesized compounds were characterized by spectral analysis and were successfully screened for their antimicrobial properties..

Keywords: Chalcone, 2,6-dichloro-4-trifluoromethylaniline, substituted aromatic aldehydes, acetic acid.

1.0 Introduction:

Heterocycles have embodied the wide space in organic chemistry and are also determined as a vital part of the biological material such as DNA, RNA, riboflavin, biotin, vitamin E, hemoglobin, nicotinic acid, amino acids, hormones, etc. In these biological entities, heterocyclic compounds play a crucial role in cell metabolism as well as biochemical reactions and also provide an advantageous tool for alteration of solubility, polarity, lipophilicity, and hydrogen bonding opacity of biologically enhanced agents.

Heterocyclic compounds are the most complex and diversified group of organic molecules with synthetic, medicinal, and industrial applications. Furthermore, aromatic heterocycles are commonly used in the synthesis of significant dyes and polymeric materials. Researchers are constantly fascinated by the synthesis of heterocyclic compounds and their derivatives due to their wide range of applications in several fields[i-vii]. Among different kinds

of heterocyclic ring systems, nitrogen heterocyclic compounds are more abundant in nature as a part structural unit of important bioactive compounds. For the synthetic development of heterocycles, a variety of synthetic methods have been described in the literature.

Cyclic imides are also one of the most versatile clusters of heterocyclic compounds having a general structure -CO-N(R)-CO- while specifically succinimides, glutarimides, and their derivatives are the well-researched remarkable type of cyclic imides which are widely used in pharmaceutical, polymer and pesticides industries. Succinimides have been used as valuable reagents and intermediates in the synthesis of natural and synthetic compounds. By virtue of the milestone applications of succinimide and glutarimide derivatives in organic and medicinal chemistry, the development of new synthetic routes to these versatile compounds is an important endeavor. Because of a variation of industrial and pharmacological applications of imides, the study of their chemistry is extremely significant.

The chemistry of chalcones has sparked a flurry of research all across the world. The name "Chalcone" was given by Kostanecki and Tambor[viii]. Chalcones are also known as benzyl acetophenone or benzylidene acetophenone.

Chalcones are also used as the precursor of flavonoids and isoflavonoids, which are abundant constituents in edible plants. They consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system. Studies revealed that compounds with a chalcone-based structure have anti-inflammatory[ix], antibacterial[x], anti-fungal[xi], and anti-tumor activities[xii-xvii]. These activities are largely attributed due to the α,β-unsaturated ketone moiety. The introduction of various substituents into the two aryl rings is also a subject of interest because it leads to a useful structure-activity relationship.

More recently, there has been strong interest in the antimalarial activity of chalcones and bis-chalcones[xviii]. Because of the broad range of medical and pharmacological applications, researchers built a huge study platform for the next generation, and young researchers are now drawn to it.

According to a literature review, 2, 6 dichloro 4-flurомethyl aniline is selectively utilized for the production of pesticides such Fiprolin[xix-xx].

In this study, we have employed 2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (4a), and various substituted benzaldehydes to synthesize some new chalcones derivatives via cyclic imide 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (4a). In the present work we have used 2, 6 dichloro4- flurомethyl aniline for synthesizing some novel chalcone derivatives via cyclic imide 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-piperidine-2, 6-Dione (4a) using various substituted benzaldehyde.

2.0 Material and Methods:

All chemical reagents and solvents were utilized for the preparations of all novel compounds were unblended and pure. Melting points of all synthetically developed compounds were determined by the open capillary method and were found uncorrected. The reaction was monitored by TLC which was accomplished by using pre-coated silica gel aluminum plates with a mixture of hexane, ethyl acetate as solvent. FTIR spectra are recorded on Perkin-Elmer spectrum. H^1NMR and ^{13}C-NMR spectra are recorded on Bruker (Advance HD III) 500 MHz spectrometer with DMSO-d^6 solvent and TMS was used as internal reference (chemical shift in δ ppm). However, mass spectra were recorded on Bruker (Impact HD) mass spectrometer using dlc-ms 600mz method.

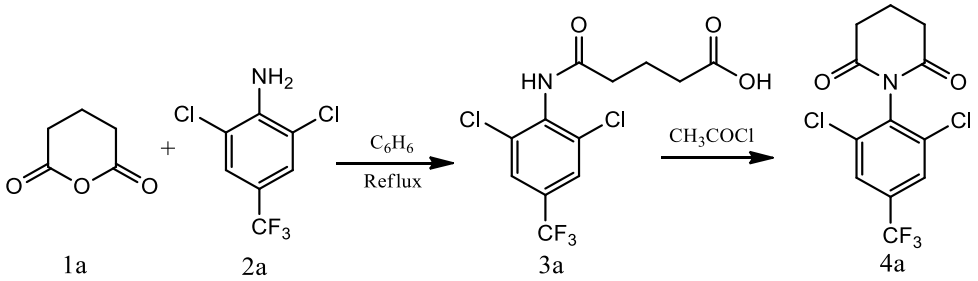
3.0 Experimental

3.1 General method for synthesis of cyclic imides

Synthesis of 1-(2, 6-Dichloro-4-triflouromethyl-phenyl)-piperidine-2, 6-Dione (4a):

Glutaric anhydride (0.01mol) was dissolved in benzene (20ml) and transferred to a round bottom flask. Then 2,6-dichloro-4-trifluoromethyl aniline (0.01mol) was dissolved in 5 ml

benzene and added to it vigorously. The 4-((2, 6-dichloro-4- (trifluoromethyl) phenyl) amino)-4-oxopentanoic acid was formed. This acid underwent cyclization by using (0.09mol) of acetyl chloride under refluxed condition for one hour at 60-70°C. The reaction was simultaneously monitored by TLC by using pre-coated silica gel aluminum plates with a mixture of n-hexane and ethyl acetate (8:2) as a solvent phase. The crude product (4a) was obtained and recrystallized from methanol (Scheme-1).



Scheme-1 Synthesis of 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-piperidine -2,6-Dione

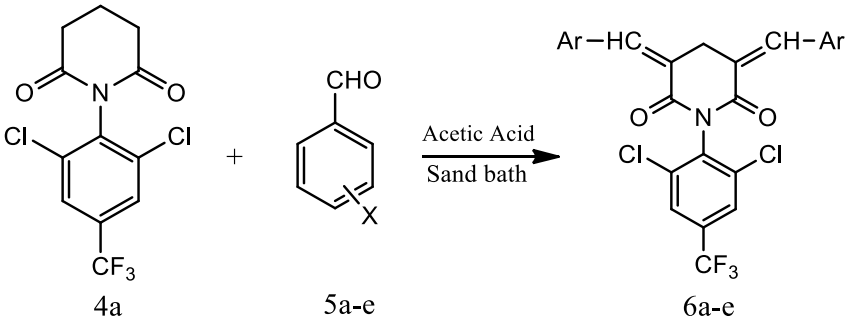
1-(2, 6-Dichloro-4-triflouromethyl-phenyl)-piperidine-2, 6-Dione (4a):

Molecular Formula: $C_{12}H_8Cl_2F_3NO_2$, **Molecular Weight (g/mol):** 326, **Melting Point (°C):** 70-72, **Physical Appearance:** Off white solid, **Percentage Yield (%):** 72
FT-IR (KBr) cm^{-1}: 3088 (C-H stretching), 2870 (C-H stretching of Ar-H), 1737 (C=O stretching), 1575 and 1531 (ArC=C), 1037 (C-F stretching), 886 (Cl stretching)
H^1-NMR (500 MHz, DMSO-d^6 δ ppm): 2.5 (s, 4H), 7.7 (s, 2H, Ar-H).

3.2 General methods for the synthesis chalcones using cyclic imide (4a) and aromatic aldehydes

Synthesis of 1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-3,4- bis(substituted-benzylidene) piperidine-2,6-dione (6a-e):

Cyclic imide 1-(2,6-dichloro-4-trifluoromethyl- phenyl)-piperidine-2,6-Dione (0.01 mol) and aromatic aldehyde (5a-e) (0.02 mol) was dissolved in glacial acetic acid (8 ml) and then concentrated on a sand bath with maintaining a low flame. The coloured solid product was obtained (6a-e) and recrystallized from ethanol (Scheme-1.1).



X= 6a = 4-Cl 6b = 4-Br 6c = 4-hydroxy
6d = 3-methoxy, 4-hydroxy 6e = 4-NO_2

Scheme-1.1 Synthesis of a novel series of Chalcones glutarimide and aromatic aldehydes

i) 6a- 3,5-bis (Z) (4-chlorobenzylidene)-1-(2,6 dichloro-4-(trifluoromethyl) phenyl)piperidine-2,6-dione (6a)

Molecular Formula: $C_{26}H_{14}Cl_4F_3NO_2$, **Physical Appearance:** Off-White solid, **Nature of compound:** Amorphous, **Percentage Yield (%):** 85, **Melting Point (°C):** 162-164, **Molecular Weight (g/mol):** 571.

C, H, N Ele. Analysis: Cal; C, 54.67; H, 2.47; N, 2.45. Obs; C, 54.61; H, 2.43; N, 2.41.
FT-IR (KBr) cm^{-1}: 2930 (C=C-H stretching), 1695 (N-C=O), 1591 (C=C Non aromatic), 1529, 1492 and 1425 (Aromatic C=C), 1321 (N-C stretching), 1014 (C-F stretching), 821 (C-Cl stretching).
^{1}H-NMR (500 MHz, DMSO-d^{6}, δ ppm): 8.004 (s, 2H, Ar-H, *J* = 2.3 Hz), 7.947 (m, 4H, Ar-H, *J* = 7.5 Hz), 7.582 (m, 4H, 2Ar-H, *J* = 7.5 Hz), 7.564 (s, 2H, =C-H), 2.507 (s, 2H, -CH_2).

ii) 6b- 3,5-bis (Z) (4-bromobenzylidene)-1-(2,6 dichloro-4-(trifluoromethyl) phenyl) piperidine-2,6-dione (6b)

Molecular Formula: $C_{26}H_{14}Br_2Cl_2F_3NO_2$, **Physical Appearance:** Off-White crystal, **Nature of compound:** Needle shape Crystals, **Percentage Yield (%):** 84, **Melting Point (ºC):** 162-164, **Molecular Weight (g/mol):** 660.
C, H, N Ele. Analysis: Cal; C, 47.31; H, 2.14; N, 2.12. Obs; C, 47.28; H, 2.11; N, 2.08.
FT-IR (KBr) cm^{-1}: 3010 (C=C-H stretching), 1695 (N-C=O), 1591 (C=C Non aromatic), 1510, 1465 and 1425 (Aromatic C=C), 1310 (N-C stretching), 1010 (C-F stretching), 828 (C-Cl stretching).
^{1}H-NMR (500 MHz, DMSO-d^{6}, δ ppm): 7.975 (s, 2H, Ar-H, *J* = 2.3 Hz), 7.839 (m, 4H, Ar-H, *J* = 7.5 Hz), 7.707 (m, 4H, *J* = 7.5 Hz, 2Ar-H), 7.690 (s, 2H, =C-H), 2.509 (s, 2H, -CH_2).
^{13}C-NMR (DMSO-d^{6}, δ ppm): 121.896 (s, 2C, Ar- C), 124.068 (s, 2C, C-Br), 125.982 (s, 1C, C-F), 127.274 (d, 2C, Ar- C), 130.615 (s, 1C, Ar- C-N), 131-135 (s, 13C, Ar-C), 137.707 (d, 2C, Ar-C), 168.995 (s, 2C, Ar-C=O), 33.189 (t, 1C, Ar-CH_2).

iii) 6c- 3,5-bis (Z) (4-hydroxybenzylidene)-1-(2,6 dichloro-4-(trifluoromethyl) phenyl)piperidine-2,6-dione (6c)

Molecular Formula: $C_{26}H_{16}Cl_2F_3NO_4$, **Physical Appearance:** Off-White solid, **Nature of compound:** Amorphous, **Percentage Yield (%):** 84, **Melting Point (ºC):** 82-84, **Molecular Weight (g/mol):** 534.
C, H, N Ele. Analysis: Cal: C, 58.45; H, 3.02; N, 2.62; Obs: C, 58.43; H, 3.01; N, 2.58.
FT-IR (KBr) cm^{-1}: 3184 (Ar-O-H stretching), 3020, 2924 and 2583 (C=C-H stretching), 1678 (N-C=O), 1591, 1535 and 1440 (Ar-C=C, ethylene), 1390 (O-H bending), 1323 (C-N stretching), 1286 (C-O Stretching), 1016 (C-F stretching), 850 (C-Cl stretching).
^{1}H-NMR (500 MHz, DMSO-d^{6}, δ ppm): 9.818 (s, 2H, Ar-O-H), 8.00 (s, 2H, Ar-H, *J* = 2.3 Hz), 7.776 (m, 4H, Ar-H, *J* = 7.5 Hz), 6.946 (m, 4H, Ar-H, *J* = 7.5 Hz), 6.929 (s, 2H, =C-H), 2.51 (s, 2H, -CH_2).
^{13}C-NMR (DMSO-d^{6}, δ ppm): 124.68 (d,4C, Ar-C), 125.93 (s, 1C, C-F), 123.55 (s, 2C, Ar-C), 127-134 (d,9C Ar-C), 137.70 (s, 1C, Ar- C-N), 140.46 (s, 2C, Ar- C), 151.94 (d, 2C, Ar=C), 174.70 (s, 2C, Ar- C-OH), 192.78 (s, 2C, Ar-C=O), 33.20 (t, 1C, Ar-CH_2).

iv) 6d-3,5-bis (Z) (3-methoxy, 4-hydroxybenzylidene)-1-(2,6 dichloro-4-(trifluoromethyl) phenyl)piperidine-2,6-dione (6d)

Molecular Formula: $C_{28}H_{20}Cl_2F_3NO_6$**, Physical Appearance:** Off white solid, **Nature of compound:** Amorphous, **Percentage Yield (%):** 80 **Melting Point (ºC):** 80-82, **Molecular Weight (g/mol):** 594
C, H, N Ele. Analysis: Cal: C, 56.58; H, 3.39; N, 2.36. Obs: C, 56.54; H, 3.33; N, 2.32.
FT-IR (KBr) cm^{-1}: 3320 (Ar-OH), 3010 (C=C-H stretching), 2910 (C-H stretching), 1520-1630 (C=C), 1678 (C=O stretching), 1425-1600 (ArC=C), 1210 (N-C=O stretching), 1280 (O-CH_3), 1286 (C-O Stretching), 1030 (C-F stretching), 835 (C-Cl stretching).
^{1}H-NMR (500 MHz, DMSO-d^{6}, δ ppm): 9.77 (s, 2H, Ar-O-H), 8.003 (s, 2H, Ar-H, *J* = 2.3 Hz), 7.41-7.43 (d, 2H, Ar-H, *J* = 7.5 Hz), 6.95 (s, 2H, Ar-H, *J* = 7.5 Hz), 6.97(d, 2H, Ar-H, *J* = 7.5 Hz), 7.39 (s, 2H, =CH), 3.847 (s, 6H, OCH_3), 2.50 (s, 2H, -CH_2).

v) 6e- 3,5-bis (Z) (4-nitrobenzylidene)-1-(2,6 dichloro-4-(trifluoromethyl) phenyl)piperidine-2,6-dione (6e)

Molecular Formula: $C_{26}H_{14}Cl_2F_3N_3O_6$, **Physical Appearance:** Off white solid, **Nature of compound:** Amorphous **Percentage Yield (%):** 82, **Melting Point (ºC):** 96-98, **Molecular Weight (g/mol):** 592

C, H, N Ele. Analysis: Cal: C, 52.72; H, 2.38; N, 7.09.Obs: C, 52.68; H, 2.35; N, 7.02.

FT-IR (KBr) cm^{-1}: 3040 (C=C-H stretching), 1665 (C=O stretching), 1520-1630 (C=C), 1425-1600 (ArC=C), 1550-1600 (N=O stretching), 1310 (N-C=O stretching), 1030 (C-F stretching), 835 (C-Cl stretching).

^{1}H-NMR (500 MHz, DMSO-d^6, δ ppm): 8.146 (d, 2H, Ar-H, *J* = 2.3 Hz), 7.956 (m, 4H, Ar-H, *J* = 7.5 Hz), 7.912 (m, 4H, 2Ar-H, *J* = 7.5 Hz), 7.889 (s, 2H, =C-H), 2.54 (s, 2H, -CH_2).

^{13}C-NMR (DMSO-d^6, δ ppm): 124.091-124.75 (d, 4C, Ar-C), 125.97 (s, 1C, C-F), 130-134 (d, 12C, Ar-C), 135 (d, 2C, Ar=C-), 137.794 (s, 2C, Ar-C), 149.55 (s, 2C, Ar- C-N), 168.55 (s, 2C, Ar-C=O), 33.219 (t, 1C, Ar-CH_2).

4.0 Biological Studies:

4.1 Antimicrobial activity:

All synthetically developed innovative compounds (6a-e) were investigated for their antimicrobial activities in vitro against two bacterial strains, Gram positive *Bacillus subtilis*, Gram negative *Escherichia coli* and two fungal strains, *Aspergillus niger* and *Candida albicans* respectively using disc diffusion method.

4.1.1 Antimicrobial Assay:

Stock solution (1000 microgram per ml) of the test sample was produced in DMSO solvent. The test was performed by the disc diffusion method using an appropriate volume of test samples. Hi-media antibiotics disc: Chloramphenicol and Amphotericin-B (100 microgram/disc), drizzled with deionized water were used as standard references to investigate the antimicrobial activity of synthetic compounds against bacteria and fungi respectively.

Microbial media used for bacteria is nutrient agar (Hi media) with composition (gL-1): Sodium chloride, 5.0; Beef extract 10.0; Peptone 10.0 (pH 7.2). However microbiological media utilized for fungi and yeast is Potato dextrose agar (all ingredients of Hi media) with composition (gL1): Potatoes infusion, 200; Dextrose, 20; Agar, 15; Final pH (at 25°C) 5.6±0.2.

Microbiological media was created under the guideline of high-media producers. Using sterile forceps, paper discs of 6 mm in diameter containing a set volume of test sample solution were placed on the surface of inoculated agar plates and simultaneously pushed down to ensure that discs and agar surface were in contact. In the same manner paper discs saturated with controls (DMSO and reference standard) were placed on agar plates and were placed for incubation at optimum growth temperature for 24 hours (for antibacterial activity investigation) and 3 to 7 days (for antifungal activity investigation) and ultimately, results were examined. The zone of inhibition around the disc has shown antimicrobial activity. This indicates that microbial growth has been inhibited by effective test samples. The diameter of the zone of inhibition was measured by Vernier Caliper in mm and tabulated in Table (1.0).

5.0 Result and Discussion:

We have synthesized cyclic imide 1-(2,6-dichloro-4-trifluoromethyl- phenyl)-piperidine-2,6-Dione (4a) as shown in (scheme-1.0) and this cyclic imide was confirmed by spectral analysis (H^1-NMR, FT-IR) and elemental analysis techniques. This imide and various benzaldehydes (5a-e) were used to synthesize multifarious chalcones (6a-e) as shown in (Scheme-1.1).

It has been observed that in the case of N-aryl halovinyl aldehydes having electron-donating effects on their phenyl ring, provides a high yield of product, while those having an electron-

donating, as well as electron-withdrawing effects on the phenyl ring, shows high to a mild yield of chalcone derivatives. All these newly developed chalcones were characterized by elemental analysis and spectral analysis techniques like FT-IR, ^{1}H-NMR, ^{13}C-NMR, and Mass spectroscopy. These compounds were also successfully investigated for their antimicrobial properties.

i) Biological activity:

A new bunch of compounds (6a-e) were evaluated for their antimicrobial activities against two bacterial strains such as gram-positive *"Bacillus subtilis",* gram-negative "*Escherichia coli"* and two fungal strains, *Aspergillus niger* and *Candida albicans* by disc diffusion method in vitro.

6 mm circular shaped cellular paper discs containing a fixed concentration of test sample solution (disc/sample) along with paper discs saturated by controls were placed on inoculated solid agar plates. These plates were kept in the incubator at optimum growth temperature for few days and the final consequences were monitored by observing zone of inhibition Table (1.0).

ii) Results:

All compounds were tested for their antimicrobial properties over bacterial and fungal strains. It was noted that few of them were observed potent and some were found mild antimicrobial agents. Compounds 6a and 6b were observed effective against *Bacillus stibillis* while compound 6d found to be a potent antibacterial agent against *Escherichia coli*.

Similarly these compounds were tested for their antifungal properties against two fungal strains. It was evaluated that compounds 6a and 6b were exhibited antifungal activity against *Aspergillus niger* and *Candida albicans* respectively. However compounds 6c and 6e were observed extremely effective over both fungal strains. It was also investigated that compound 6d was quite effective against *Aspergillus niger*.

Table 1.0 Antibacterial activity of compounds (6a-e)

Zone diameter in mm for 100 microgram per disk					
Sr. No.	**Compound**	***B. Stibillis***	***E. Coli***	***A. Niger***	***C.Albicans***
1	6a	9.98	-	-	8.73
2	6b	8.54	-	6.74	-
3	6c	-	-	11.74	8.90
4	6d	-	13.5	8.26	-
5	6e	-	-	8.74	8.99
Std-1	Chloramphenicol	17.87	21.79	NA	NA
Std-2	Amphotericin-B	NA	NA	16.35	12.21
Ctrl	DMSO	-	-	-	-

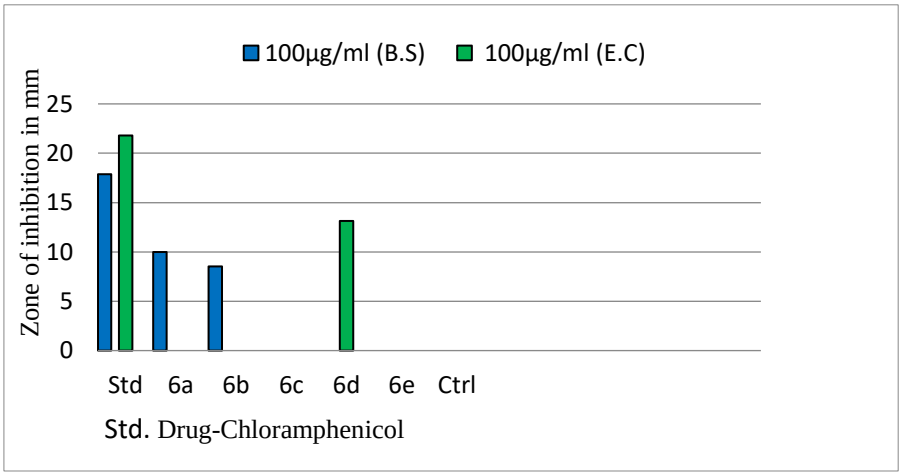


Chart-1.0 Antibacterial activity of compounds (6a-e)

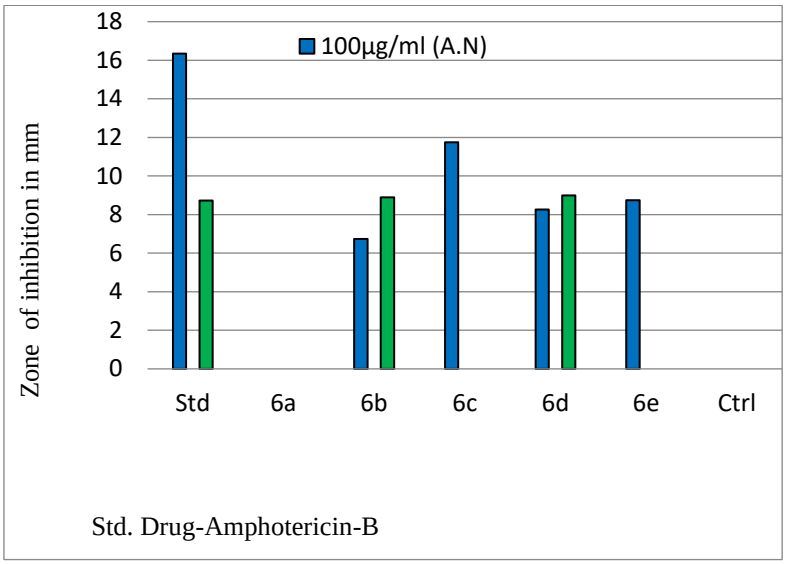


Chart-1.1 Antifungal activity of compound (6a-e)

6.0 Conclusion:

A novel series of Chalcones derived from several substituted aromatic aldehyde (5a-e), and succinimide have been reported by the most convenient method. All newly synthesized molecules were investigated by spectral analysis techniques and screened for their antimicrobial activity. It is concluded that among these compounds (6a-e) few were exhibited good to mild antibacterial activity while most of the compounds were recognized as antifungal agents. However, compounds 6c and 6d were observed as notably efficacious antimicrobial agents.

7.0 Acknowledgement:

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